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Journal article on the Internet

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Website

Cancer-pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources [updated 16 May 2002; cited 9 Jul 2002]. Available from: www.cancer-pain.org

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CASE REPORT

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Orjinal Araştırma / Original Article

Overview of Umbilical Cord Prolapse: Evaluation of Maternal and Neonatal Outcomes

Umbilikal Kord Prolapsusunun Değerlendirilmesi: Maternal ve Neonatal Sonuçları

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Abstract

Aim: Umbilical cord prolapse(UCP) is the presence of the umbilical cord preceding ahead of the fetal presenting part with absent membranes through the cervical canal. Despite improved obstetric care and liberal use of cesarean delivery, the incidence has not been decreased dramatically. The purpose of this study was to review the literature and represent clinical experience to improve neonatal outcomes.

Material and Method: A retrospective cohort study was conducted. Patients who experienced umbilical cord prolapse between October 2016 and December 2019 were evaluated in terms of antenatal care, risk factors, labor progress, and neonatal outcomes. Maternal and neonatal outcomes of these patients were compared with the women who underwent emergent cesarean delivery due to acute fetal distress.

Results: Forty-three pregnant women experienced umbilical cord prolapses with an incidence of 11/10.000. The mean cervical dilatation of the patients was 5,4 cm. None of the fetus' presenting part station was below zero. All patients underwent emergent cesarean delivery. The mean interval between UCP and fetal delivery was 16,7 minutes. All patients delivered live newborns. The number of women who underwent emergent cesarean was 255. The APGAR scores of newborns were similar, however admission to NICU differed statistically significant. Intra-operative or postoperative complications did not differ significantly.

Conclusion: Emergent cesarean delivery could improve neonatal outcomes in patients diagnosed with UCP. Fetal wellbeing monitorization, especially in the one hour from rupture of fetal membranes, provides remarkable clues for UCP diagnosis. To improve neonatal outcomes, there should be one available operating theatre for emergent circumstances and a pediatrician for neonatal resuscitation.

Keywords: Umbilical cord prolapse, emergent cesarean, stillbirth, acute fetal distress, diagnosis delivery interval

Öz

Amaç: Umbilikal Kord Prolapsusu (UCP) ,umbilikal kordun fetüsun prezente olan kısmının yanından kayarak servikal kanalın dışında membransız şekilde bulunmasıdır. Sezaryenin liberal kullanılması ve gelişen obstetrik bakıya rağmen insidansta dramatik bir düşüş saptanmamıştır. Bu çalışmada literatürün gözden geçirilmesi, ve neonatal sonuçları iyileştirmek için klinik tecrübenin sunulması amaçlanmıştır.

Gereç ve Yöntem: Retrospektif kohort çalışma planlandı. Ekim 2016-Aralık 2019 tarihleri arsında UCP tecrübe eden hastalar antenatal bakım, UCP risk faktörleri, doğum süreci ve neonatal sonuçlar açısından değerlendirildi. Bu hastaların maternal ve neonatal sonuçları, akut fetal distress(AFD) nedeniyle acil sezaryene alınan hastalarla karşılaştırıldı.

Sonuç: Kırk üç gebe, 11/10.000 insidans oranı ile UCP yaşamıştır. Teşhis anında hastaların ortalama servikal dilatasyon 5,4 cm idi. Hiçbir fetüsun prezente olan kısmının seviyesi '0' altında saptanmadı. Tüm hastalar acil sezaryen ile doğurtuldu. Tanı ile bebeğin doğumu arasındaki süre ortalama 16,7dk. Tüm fetüsler canlı doğurtuldu. Çalışmaya dahil edilen acil sezaryen uygulanan kadın sayısı 255. UCP tanısı ile doğan bebekler ile APGAR skorları benzer olsa dahi, yenidoğan yoğun bakıma kabulde istatistiki anlamlı fark saptandı. Per-operatif ve post-operatif komplikasyonlarda istatistiki farklılık saptanmadı.

Tartışma: UCP tanısı alan hastalarda acil sezaryen ile doğum neonatal sonuçları iyileştirebilmektedir. Fetal iyilik hali monitörizasyonu, özellikle fetal membran rüptüründen sonraki ilk bir saat içinde, UCP teşhisi için önemli ipuçları sağlar.Yenidoğan sonuçlarını iyileştirmek için, doğumhane koşullarında acil durumlar için kullanılabilecek uygun bir ameliyathane ve yenidoğan resüsitasyonu için bir pediatrist her daim ulaşılabilir olmalıdır.

Anahtar Kelimeler: Umblikal kord prolapsusu,acil sezaryen , ölü doğum, akut fetal distres, teşhis doğum aralığı

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INTRODUCTION

The World Health Organization (WHO) defines normal birth as spontaneous in onset, low- risk at the start of labor, and remaining so throughout labor and delivery. The infant is born spontaneously in the vertex position between 37 and 42 completed weeks of pregnancy. After birth mother and infant are in good condition.[1] Despite the normal birth definition, obstetric practice consists of emergent and abnormal events. Umbilical cord prolapse(UCP), which is identified as the presence of the umbilical cord preceding ahead of the fetal presenting part with absent membranes through the cervical canal, is one of the life- threatening conditions of the fetus. The true incidence is hard to consider due to infrequent occurrence; nonetheless, a population-based study revealed that the incidence is 1.6 cases in 1000 births.[2] Risk factors have properly ascertained like prematurity, malpresentation, multiple gestations, polyhydramnios, multiparity, prolonged labor, artificial rupture of membranes (ARM), external cephalic version, and induction of labor.[3-5] Diagnosis can be assessed by visualization or palpation of the umbilical cord in the cervical canal or vagina. No confirmation with any diagnostic tool is needed. Prompt delivery is obligatory to prevent neonatal mortality and adverse outcomes. The prolapsed umbilical cord through the cervical canal is vulnerable to mechanical compression, and cooler temperature. These effects trigger cord vasospasm, deterioration of fetal circulation, hypoxia, and asphyxia. Total compression of the umbilical cord could lead to fetal death. Fetal bradycardia or recurrent variable decelerations especially after artificial or spontaneous rupture of membranes are the clinical findings suggestive of UCP.[5-7] Delayed diagnosis and delivery are associated with perinatal mortality which could be as high as 36%.[8] Improved obstetrical care, liberal use of cesarean, and effective neonatal resuscitation have decreased the adverse outcomes. In cases of inability to perform emergent delivery, intrauterine resuscitation is essential. Some maneuvers have been suggested to decrease the compression on the umbilical cord such as placing the pregnant women in the knee-chest position, retro-filling the bladder with 500-700 cc of saline, and tocolytic utilization.[9-11] Manual elevation of the fetal presenting part until the delivery of the fetus is crucial if an emergency cesarean would be performed.The fetus should be delivered as quickly as possible. If the time interval between diagnosis and delivery is shorter than 30 minutes, better neonatal outcomes could be achieved.[9,12,13] The purpose of this present study was to review the literature about UCP while demonstrating the single center experience. Comparison of the maternal and neonatal outcomes were achieved with the women who underwent emergent cesarean delivery due to acute fetal distress.

MATERIAL AND METHOD

A retrospective cohort study was conducted at a single university-affiliated research and training hospital. This study was approved by the local ethics committeein Bursa Yuksek Ihtisas Training and Research Hospital, University of Health Sciences with a decision number 2011-KAEK-25 2020/03-14 and it was in accordance with the Declaration of Helsinki.

Outcomes of all deliveries were identified between October 2016 and December 2019 from the hospital registry database. Patients who experienced umbilical cord prolapse were extracted using the International Classification of Diseases (ICD) codes. Patients' hospital data file folders were reviewed. Patients' characteristics, ultrasonographic evaluations (fetal presentation, amniotic fluid volume), obstetric examinations, labor progress,utilization of labor induction, cervical dilatation, fetal presented part position at the time of UCP, the time interval between UCP diagnosis and delivery of the baby, complication during cesarean delivery. Neonatal parameters were reviewed as birth weight, 1st and 5th minute APGAR scores, admission to neonatal intensive care unit (NICU), and stillbirth. Postoperative events were recorded as any of the blood component transfusion, the need for critical care admission, need for re-laparotomy, thromboembolic events, wound site infection or dehiscence, endometritis, and febrile morbidity.

The maternal and neonatal outcomes were compared with the women who underwent emergent cesarean delivery due to acute fetal distress. Patients were randomly chosen from the delivery system and recruited in the study. These patients were admitted to the delivery unit without any obstetric problem and were supposed to have a vaginal birth. Acute fetal distress was diagnosed via continuous fetal monitoring withthe Non-Stress Test (NST). Montevideo units were calculated by subtracting the resting tone of the uterus from peak uterine pressure amplitude during contractions within 10 minutes. Labor progress was determined from patients' file as cervical dilation, presented part station, time of UCP diagnosis, time of fetal delivery which were recorded by resident physicians. All patients were administered antibiotic prophylaxis(the third-generation cephalosporin concomitant metronidazole in the umbilical cord prolapse group, and the second- generation cephalosporin in the acute fetal distress group), and postpartum thromboprophylaxis due to the guidelines.[14,15]

Statistical Analysis

Statistical analysis was performed using the SPSS 24.0 software for Windows (IBM Corp, Armonk, NY). Variables are described as frequencies, mean±standard deviation of the mean. The normal distribution of continuous variables was evaluated using the Shapiro- Wilk test. Paired Student's t-test, chi-square test, and Fisher's exact test were used as appropriate. An overall p-value of less than 0, 05 was considered a statistically significant result.

RESULTS

Approximately over the 3 years of the period, 37.536 women gave birth in Bursa Yüksek İhtisas Training and Research

Hospital. The number of patients who experienced UCP was 43 with an incidence of 11 cases in 10.000 births. Median gravidity and parity of the patients were 3 and 1 respectively. In **Table 1**, patients' labor progress characteristics and neonatal outcomes were summarized.The mean UCP diagnosis delivery interval (DDI) was 16.7 minutes with a range of 7-30 minutes.

All patients underwent emergency cesarean. Five of the patients had 10 cm dilation while the head was at -3 station. Two patients experienced cesarean complications such as uterine atony and inadvertent extension of uterine incision laterally. None of the patients underwent hysterectomy. The wound site infection occurred in one patient as a postoperative complication. The need for blood transfusion, thromboembolic event, endometritis, and febrile morbidity did not occur in any of the patients. All deliveries were concluded with live newborns.Thirty newborns were male (70%). The mean birth weight was 3035±885 gr. Nine babies had an Apgar 1st minute score of ≤7, and 2 had an Apgar 5th minute score of ≤7. The number of patients admitted to NICU was 11 with a rate of 25%. Of these, the mean birth weight was 1967 grams and 9 babies were weighted below 2500 grams. The mean DDI of the patients whose babies were admitted to NICU was 19.4 min. Only 1 patient's DDI was 30 minutes that the patient had overt umbilical cord prolapses in antenatal service which was 3 floors below the delivery unit. Apart from this patient, 6 women delivered over 20 minutes after the diagnosis. Four patients diagnosed UCP out of the delivery unit and transferred to operation theatre and prompt cesarean delivery was performed. Preterm deliveries accounted for 23 % of all cases. Seven of these preterm deliveries presented with a non-vertex presentation. Four patients had polyhydramnios at the admission to the delivery unit. Two of them had UCP after the spontaneous rupture of the membrane. The other two patients were utilized artificial rupture of membranes. The UCP was detected during the follow-up of the labor within one hour, not immediately after opening the membranes. Fetal bradycardia or severe recurrent decelerations in NST were detected before UCP diagnosis.

Five patients had oligohydramnios due to spontaneous rupture of the membranes before admission to the hospital. These patients experienced UCP during the hospitalization follow-up.

The number of women who were recruited in the study as a control group, underwent emergent cesarean delivery due to acute fetal distress was 255. The mean birth weight, mean APGAR 1st and 5th minute scores were 3174 gr, 8.65, and 9.65 respectively. Only the 1st min APGAR scores differed significantly comparing the groups (p:0.031). Twenty newborns with a percentage of 7% were admitted to NICU. Comparing the UCP and acute fetal distress group in terms of admission to NICU differed statistically significantly. Baby gender, complications during cesarean delivery, and post-partum complications did not differ statistically significantly. The comparison of the groups was demonstrated in **Table 2**.

Table 1. Patients who experienced umbilical cord prolapse were evaluated in terms of characteristics, labor situation before diagnosis, and postpartum features

Parity	Nulliparous N: 9 ,21%	Multiparous N: 29, 68%	Grand-Multiparous N: 5, 11%
Presentation	Vertex N: 36, 85%	Breech N:5, 11%	Transverse N:2, 4%
Gestation week	Term, n:33 77%	Preterm, n:10 23%	
Amniotic fluid index	Normal N: 34, 79%	Polyhydramnios N:4, 9%	Oligohydramnios N:5, 11%
Cervical dilation	0-6cm N: 25, 58%	6-9cm N: 13, 30%	9-10cm N: 5, 11%
Cervical effacement	0-20 % N:8, 18%	20-60 % N:9, 21%	60-100 % N: 26, 60%
Presented part Station	-3 / -2 N: 11, 26%	-1 / 0 N: 27, 63%	Above -3 N:5, 11%
Utilization of labor Induction	Yes N:16, 37%	No N:27, 63%	
Uterine Contraction Performance	> 200 Montevideo unit n:24 , 56%	< 200 Montevideo unit n:19, 44%	
Diagnose to Delivery time	<20 min n:36	20-30 min n:6	> 30 min n:1

Table 2. Comparison of the neonatal outcomes of the patients with Umbilical cord prolapse and acute fetal distress were demonstrated.

	Umbilical cord prolapse N:43	Acute Fetal Distress N:255	P value
Birth Weight (gr ±Std)	3035±896	3174±413	0.326
APGAR 1st minute	8.09 ±1.6	8.65±1.01	0.031
APGAR 5th minute	9.44±0.85	9.65±0.68	0.141
NICU admission	11 25%	20 7.8%	0.002
Complication in Cesarean (N)	2 4.6%	7 2.7%	0.623
Post-op complication	1 2.3%	11 4.3%	1.000
Baby Gender Male Female	30 (70%) 13 (30%)	144 (56%) 111 (44%)	0.102

DISCUSSION

A true obstetric emergency umbilical cord prolapse is a rare incident yet threatens the wellbeing of the fetus. The risk factors have been exposed particularly. Liberal performing of cesarean section was supposed to decrease the occurrence of UCP however the incidence is almost the same during the last decades which was about 0.1 to 0.18%.[2,16] The incidence of the UCP was 0.11% at this present study which was compatible with recent literature.Women who underwent emergent cesarean were included in the study as a control group to evaluate the maternal and neonatal outcomes. The results have depicted that maternal complications were approximately similar. The UCP was one of the crucial reasons for emergent cesarean delivery as acute fetal distress. Admission to NICU was higher in the UCP group however that could be occurred due to the high prematurity rates. The vaginal delivery could be more secure for maternal

outcomes if the delivery could occur immediately however, due to the results of that present study, women who were performed cesarean section did not have an increased risk of operational adverse outcomes comparing the women who underwent emergency cesarean for acute fetal distress. Additionally, there was no proper time for vaginal birth that could avoid adverse neonatal outcomes. Due to the results of this study, fetuses may benefit more from emergency cesarean delivery.

The point that should be paid attention to the high percentage of preterm deliveries which was not only the main determinant of neonatal morbidity and mortality[17] but also one of the major risk factorsfor UCP.[18] The emphasized issue for these patientscould be the examination with transvaginal ultrasound for funic presentation at the hospital admission, and speculum examination soon after ruptures of membranes.Fifteen percent of the cases were non-vertex presentation in our study. In a contemporary study, it was depicted that the incidence of UCP was 9.6% and 3.5% for transverse and breech presentations respectively.[19]

The most catastrophic event for the patient and the physician is the experience of intrapartum still birth. Most of the articles have referred to stillbirth related to UCP.[6,7,20] In the present study, stillbirth did not occur due to UCP. The major reason of this success was the immediate delivery of the fetuses. The mean diagnosis delivery interval (DDI) was 16 minutes which was quite shorter than similar studies.[7,9,21,22] The foremost determinant of this interval was the diagnose. Approximately 30 babies are born in a day in the hospital that the study presented. Intrapartum continuous fetal heart rate monitoring has been routinely performed on patients admitted to the delivery unit. If UCP occurs, an emergency cesarean is performed and the fetal presented part is elevated manually until the baby is born. A pediatrician attends to emergent cesareans, and also the cases if the obstetrician anticipates any possible neonatal adverse outcome. These managements and the interventions might be related to the success of neonatal outcomes.In some studies, about 50 percent of UCP was caused by iatrogenic interventions.[22,23] Murphy et al. declared that UCP occurred within 5 minutes after the ARM.[24] No UCP had occurred within 5 minutes after ARM at the present study. The physicians should be aware that opening the amniotic membrane should be performed after the engagement has occurred. Overlooking some factors may increase the risk of UCP, such as ARM which was performed by inexperienced resident trainees. It is also important that multiparity and utilization of labor induction would cause a late engagement.[25] Thus, we recommend that ARM ought to be performed by an experienced physicianafter the engagement had occurred. Before opening the membranes, the patient should have an active uterine contraction, minimal fundal pressure could be applied or the patient could push the baby. Patients should be monitored with NST for at least one hour after amniotomy due to the crucial findings of that study which was the occurrence of UCP during the labor fallow up occurred within one hour after spontaneous rupture of membranes. If the NST has not been utilized during labor continuously, patients ought to be monitored for at least one hour along after the spontaneous or artificial rupture of membranes.

Prompt cesarean delivery was performed at the present study even patient hasa 9-10 cm dilated cervix because each attempt for vaginal delivery would increase the compression on the umbilical cord and could increase the possibility of fetal morbidity or mortality. There is always one operating theatre at our delivery unit which can be used for emergency cesareans. Pediatricians are always informed before emergency cesarean delivery, and the pediatrician is ready for neonatal resuscitation in the operating room. The lack of these two conditions was inevitable to increase perinatal mortality.[2,8,9] Behbehani et al achieved a precious population-based study evaluating UCP.[2] They determined that vaginal birth causes less birth injury without increasing mortality. In our study, the birth injury did not occur in any patient even the cesarean had performed in the fully dilated cervix. They also determined that placental abruption, postpartum hemorrhage (PPH), meconium-stained amniotic fluid, and law APGAR scores had occurred more in emergency cesarean of UCP.[2] In the present study, only one patient experienced PPH treated with Bakri Balloon and one patient experienced inadvertent extension of uterine incision which was repaired without the need for any extra intervention. None of the patients needed blood component, transfusion. These low complications could be related to high experienced obstetricians. Simulation scenario programs have recommended for emergency cesarean to decrease complications and decrease perinatal comorbidities.[26,27] These programs are definitely useful,especially for the clinics performing the small number of emergency cesarean cases. If the emergency delivery was not possible, the aforementioned maneuvers could be utilized for intrauterine resuscitation.[9-11] Esau et al described that the knee-to-chest position is effective in reducing neonatal mortality for patients who experienced UCP outside the hospital.[9] We prefer to elevate the presenting part manually by a physician from vagina forumbilical cord decompression until the fetus was delivered.

WHO defines normal birth without any intervention.[1] Understanding labor progress is fundamental of obstetrics. Traditionally Friedman's curve has been used by health care providers to define the normal length of labor. Zhang et al have assessed the curve with larger sample participants.[28] Evaluating labor progress decreases maternal and neonatal adverse outcomes. The fact that every intervention could also cause more intervention. Multiparity and labor induction could increase UCP due to the cause of late engagement. We evaluated the cervical dilatation and station before UCP. About 60% of the patients were not in the active labor phase. Our findings were similar to Kawakita et al. They stated that any fetal position before 6 cm cervical dilation and fetal station

above station -3 at 6-10 cm cervical dilation was associated with UCP. It is obvious that if the fetal head is not engaged particularly; there is always a risk of UCP. The engagement of the presented part of the fetus is crucial for the artificial rupture of membranes however, the fact is that there is no possibility to predict the time of spontaneous rupture of membranes, and the relation with the engagement. Fetal gender was also defined as an independent risk factor of UCP.[2,7,29] Seventy percent of the newborn babies were male in our study which was compatible with literature.

Murphy and colleagues conducted a very remarkable definition that knowledge of UCP did not decrease the occurrence.[24] Thus, obstetricians should concentrate on the interventions to deliver the fetus with the minimum adverse consequences when the UCP occurred. The most crucial point is the prompt delivery and adequate neonatal resuscitation. There is always one operating theatre for the emergency cesarean section. These approaches ensured that there was no neonatal mortality in patients with umbilical cord prolapse.

The limitations of the present study were being a retrospective nature, small patient population (due to low incidence) and not having a proper control group and the data was obtained from patients' files which were filled by different resident physicians. The strengths of the study were unique literature investigating, presenting adequate suggestions for neonatal and maternal outcomes, and the study was carried out in a high- volume hospital with more than 13000 births each year.

CONCLUSION

As a true emergency, umbilical cord prolapse threatens neonates well being. Although approaches that reduce risk factors are important, the most precious intervention is prompt delivery. Each woman ought to be monitored continuously with NST for at least one hour after spontaneous or artificial rupture of membranes. There should be always a suitable operating theatre for emergency cesarean sections, and a pediatrician who can perform adequate neonatal resuscitation.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the local ethics committeein Bursa Yuksek Ihtisas Training and Research Hospital, University of Health Sciences with a decision number 2011-KAEK-25 2020/03-14.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Orjinal Araştırma / Original Article

Frequency of Vitamin D Deficiency in Children: A Single-Center Cross-Sectional Study in Istanbul

Çocuklarda D Vitamini Eksikliğinin Sıklığı: İstanbul'da Tek Merkezli Kesitsel Bir Çalışma

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Abstract

Aim: Vitamin D deficiency is highly prevalent among children worldwide. This study aims to assess the frequency of vitamin D deficiency in children and how it varies according to gender, age, and season in Istanbul.

Material and Method: The study included 3096 children aged 0-18 admitted to the pediatric outpatient clinic in Istanbul. The serum 25 hydroxyvitamin D concentration was analyzed by the High-Performance Liquid Chromatography method using HPLC systems analyzers, and the results were categorized into four groups: deficiency (<20 ng/mL), insufficiency (20–30 ng/mL), sufficiency (30-100 ng/mL), and toxicity (>100 ng/mL). Descriptive methods, Chi-square, Independent Samples T-Test, ANOVA, and correlation test were used in the statistical analysis of the data.

Results: Of children, 52% were girls and 48% boys. The mean serum 25 hydroxyvitamin D concentration was 21.8±15.8 ng/mL, and the frequency of vitamin D deficiency was 53.1%. There was a different distribution of vitamin D status between age groups. Vitamin D deficiency was more common in older children. The frequency of vitamin D deficiency was significantly higher in girls than boys (57.6% versus 48.3%). The mean serum 25 hydroxyvitamin D concentration was significantly lower in winter and spring. A moderate negative correlation was found between age and serum 25 hydroxyvitamin D concentration (correlation coefficient:-0.36).

Conclusion: This study showed that female sex, older children, and the winter/spring seasons were significantly associated with a higher frequency of vitamin D deficiency and a lower mean serum 25 hydroxyvitamin D concentration.

Keywords: Vitamin D deficiency, children, outpatient clinic, frequency

Öz

Amaç: D vitamini eksikliği dünya çapında çocuklar arasında oldukça yaygındır. Bu çalışmada, İstanbul Tıp Fakültesi çocuk polikliniğine başvuranlarda D vitamini eksikliği sıklığının cinsiyet, yaş ve mevsime göre nasıl değiştiğinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Araştırmaya İstanbul'da çocuk polikliniğine başvuran 0-18 yaş arası kronik hastalığı olmayan 3096 çocuk dahil edildi. HPLC sistem analizörleri kullanılarak Yüksek Performanslı Sıvı Kromatografi yöntemiyle analiz edilen Serum 25 hidroksivitamin D konsantrasyonu dört grupta değerlendirildi; eksiklik (<20 ng/mL), yetersizlik (20-30 ng/mL), yeterlilik (30-100 ng/mL) ve toksisite (>100 ng/mL). Verilerin istatistiksel analizinde tanımlayıcı yöntemler, Ki-kare, Bağımsız Örneklem T-Testi, ANOVA ve korelasyon testi kullanıldı.

Bulgular: Çocukların %52'si kız, %48'i erkekti. Ortalama serum 25 hidroksivitamin D konsantrasyonu 21,8±15,8 ng/mL ve D vitamini eksikliği sıklığı %53,1 idi. Yaş grupları arasında D vitamini eksikliği anlamlı olarak farklıydı. Yaş ilerledikçe eksikliğin arttığı görüldü. D vitamini eksikliğinin sıklığı kızlarda erkeklere göre anlamlı olarak daha yüksekti (%57,6'ya %48,3). Ortalama serum 25 hidroksivitamin D konsantrasyonu kış ve ilkbaharda önemli ölçüde daha düşüktü. Yaş ile serum 25 hidroksivitamin D konsantrasyonu arasında orta derecede negatif korelasyon bulundu (korelasyon katsayısı: -0,36).

Sonuç: Bu çalışma, kadın cinsiyetin, yaşı büyük çocukların ve kış/ilkbahar mevsimlerinin, daha yüksek D vitamini eksikliği sıklığı ve daha düşük bir ortalama serum 25 hidroksivitamin D konsantrasyonu ile önemli ölçüde ilişkili olduğunu gösterdi.

Anahtar Kelimeler: D vitamini eksikliği, çocuk, poliklinik, sıklık

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INTRODUCTION

Vitamin D is a steroid hormone that plays a vital role in human physiology and is mainly synthesized in the skin by sunlight. Humans also obtain vitamin D from foods and supplements.[1] Vitamin D is necessary for calcium homeostasis, bone mineralization, and providing the intestinal absorption of calcium and phosphorus.[1] Vitamin D also has extra-musculoskeletal roles. Evidence shows that vitamin D deficiency is related to autoimmune disorders, cardiovascular disease, diabetes, and immune deficiency, in addition to rickets and other musculoskeletal disorders.[2-5]

Vitamin D deficiency is highly prevalent among children worldwide.[2] Similarly, vitamin D deficiency was commonly reported in studies conducted in different regions of Turkey.[6-10] In most studies, vitamin D deficiency prevalence estimates vary due to deficiency definitions, assessed areas, and considered risk factors. Primary causes of vitamin D deficiency are inadequate vitamin D intake by nutrition and insufficient sunlight exposure.[4] However, vitamin D metabolism is affected by many factors. Wearing sun-protective clothes, living at a northern latitude, winter season, dark skin or race, female gender, and sunscreen creams reduce vitamin D synthesis in the skin.[4] In addition, obesity, fat malabsorption syndromes, hyperparathyroidism, some medications such as anticonvulsants and anti-HIV drugs are associated with vitamin D deficiency.[2]

The present study objective was to investigate the rate of vitamin D deficiency and investigate the effects of age, gender, and season in children with similar living conditions by using data available on vitamin D in a large sample in Istanbul.

MATERIAL AND METHOD

Study design: The study was designed as a single-center and cross-sectional observational study. The study period is between February 2020 and February 2021.

Participant and data collection: A total of 3096 children aged 0 to 18 years admitted to the pediatric outpatient clinic in Istanbul Medical Faculty were enrolled. Subjects who had any chronic diseases such as skeletal diseases, genetic syndromes, or malabsorptive disorders were excluded from the study. Data were obtained from the hospital database. Demographic features and serum vitamin D levels of participants were enrolled. Age was divided into four groups: infantile period (0 days–1 year), toddler period and preschool age (2–7 years), puberty period (8–13 years), and adolescence (14–18 years).

Laboratory assessment: The serum 25 hydroxyvitamin D concentration was analyzed by the High-Performance Liquid Chromatography method using HPLC systems analyzers. Vitamin D status was categorized into four groups: deficiency (<20 ng/mL), insufficiency (20–30 ng/mL), sufficiency (30-100 ng/mL), and toxicity (>100 ng/mL)(2).

Statistical analyses: Data were evaluated using IBM SPSS 21 for Windows. Equality of variances was checked with Levene's Test for Equality of Variances, and normality of distribution was examined with the Kolmogorov-Smirnov test. Descriptive statistical analyses were used to obtain the means and standard deviations of continuous variables. Independent Sample T-Test and One-way ANOVA were used to compare variables between the separate groups. In addition, the Chi-square test was used to compare frequencies. P values <0.05 were accepted as significant.

Ethical approval: The study was carried out with the permission of İstanbul University Faculty of Medicine Department of Child Health and Diseases Ethics Committee (Date: 10.09.2021, Decision No: 2021/1482-16).

RESULTS

Of a total of 3096 children, 52% were girls and 48% boys. The mean serum 25(OH) D concentration was 21.8±15.8 ng/mL, and the frequency of vitamin D deficiency was 53.1%. There was a different distribution of vitamin D status between age groups. The frequency of vitamin D deficiency in the infantile age group was found at 9%. However, the frequency in the adolescent group was 70.1%. Demographic properties and serum vitamin D status according to sex and age group are summarized in **Table 1**.

A significant difference in serum 25(OH)D concentration was found between girls (20.6±15.5 ng/mL and boys (23.1±16.0 ng/mL). There was also a significant difference between girls and boys in the frequency of vitamin D deficiency (57.6% versus 48.3%) (**Table 2**).

Table 1. Demographic properties and serum vitamin D status according to sex and age group

	n, %	Age, year	Serum Vitamin D (ng/mL)	Deficiency %	Insufficiency %	Sufficiency %	Toxicity %
Sex							
Girl	1599.52	8.8±5.4	20.6±15.5	57.6	23.1	18.9	0.3
Boy	1497.48	7.9±5.1	23.1±16.0	48.3	26.9	24.6	0.3
Age group							
0-1 y	199.6	0.6±0.2	44.0±30.3	9.0	14.1	75.4	1.5
2-7 y	1160.37	3.7±1.8	24.5±13.2	41.3	28.6	29.9	0.2
8-13 y	975.31	10.0±1.8	18.2±11.2	62.9	26.1	11.0	0.1
14-18 y	762.25	15.5±1.5	16.5±12.8	70.1	20.7	8.8	0.4
Total	3096	8.4±5.3	21.8±15.8	53.1	24.9	21.7	0.3

y: year, Age and serum vitamin D parameters presented as mean±standard deviation, Serum vitamin D values <20 ng/mL were accepted as a deficiency, 20-30 ng/mL as insufficiency, 30-100 ng/mL as sufficiency and >100 ng/mL as toxicity.

Table 2. Serum vitamin D status by sex

	All cases n=3096	Girl n=1599	Boy n=1497	p
Serum vitamin D	21.8±15.8	20.6±15.5	23.1±16.0	<0.05
Vitamin D status, n (%)				
Deficiency	1644 (53.1)	921 (57.6)	723 (48.3)	<0.05
Insufficiency	772 (24.9)	370 (23.1)	404 (26.9)	<0.05
Sufficiency	671 (21.7)	303 (18.9)	368 (24.6)	<0.05
Toxicity	9 (0.3)	5 (0.3)	4 (0.3)	>0.05

Serum vitamin D parameters presented as mean±standard deviation, Serum vitamin D values <20 ng/mL were accepted as a deficiency, 20-30 ng/mL as insufficiency, 30-100 ng/mL as sufficiency and >100 ng/mL as toxicity.

There were also significant differences in mean serum 25(OH)D levels between seasons. Mean serum 25(OH) D concentration was the lowest in winter and the highest in summer. The mean serum 25(OH) D concentration was significantly lower in winter and spring (**Table 3**).

Table 3. Serum vitamin D status by season

	Allcases n=3096	Winter n=1201	Spring n=268	Summer n=843	Fall n=784
Serum vitamin D	21.8±15.8	17.6±15.4	19.8±12.7	26.3±17.1	24.2±14.0
Vitamin D status, n (%)					
Deficiency	1644 (53.1)	842 (70.1)	163 (60.8)	303 (35.9)	336 (42.9)
Insufficiency	772 (24.9)	204 (17.0)	65 (24.3)	266 (31.6)	237 (30.2)
Sufficiency	671 (21.7)	152 (12.7)	40 (14.9)	270 (32.0)	209 (26.7)
Toxicity	9 (0.3)	3 (0.2)	0 (0.0)	4 (0.5)	2 (0.3)

Serum vitamin D parameters presented as mean±standard deviation, Serum vitamin D values <20 ng/mL were accepted as a deficiency, 20-30 ng/mL as insufficiency, 30-100 ng/mL as sufficiency and >100 ng/mL as toxicity.

Chi-square test results showed significant differences in the frequency of vitamin D deficiency, insufficiency, and sufficiency in different sex, ages, and seasons. In addition, One-way ANOVA with post hoc analysis showed significant differences in the mean serum 25(OH) D concentration in different age groups and seasons. Among children, female sex, older children, and the winter/spring seasons were significantly associated with a higher frequency of vitamin D deficiency and a lower mean serum 25(OH) D concentration.

A moderate negative correlation was found between age and serum 25(OH) D concentration (correlation coefficient:-0.36).

DISCUSSION

We conducted a cross-sectional observational study with a large sample to investigate the rate of vitamin D deficiency and insufficiency in the pediatric outpatient clinic and evaluated demographic features and laboratory data of 3096 children aged 0-18. The results showed that Vitamin D deficiency (53.1%) and insufficiency (24.9%) were highly prevalent in children living in Istanbul. In particular, the rate of vitamin D deficiency was significantly higher in girls and adolescents. Besides, vitamin D deficiency was most common in winter.

Vitamin D deficiency is a global problem, varying in frequency in different populations.[1] In recent studies conducted in Turkey, the prevalence of vitamin D deficiency has been reported from 16.5% to 89.6% (**Table 4**).[6-17] Among these studies, the highest rate of vitamin D deficiency was found in the study included pubertal children and adolescents.[11] The lowest deficiency rate was shown in a study conducted on children younger than 10 years old.[15] However, the studies with all pediatric age groups reported that vitamin D deficiency was in the range of 35.1% to 65.0%.[7,8,13,14,16,17] In a study with more than ninety thousand participants, Sahin et al.[6] found that vitamin D deficiency was 45-50% in children younger than 10 and 80-90% older than 10. The results of this study were significant due to the high number of participants. In another study conducted by Yetim et al.[10], the rate of vitamin D deficiency in children older than 10 was reported as 56%. Many studies also showed this relationship, as in the present study (**Table 5**).[9,13,16,18-20] In contrast, some studies found a lower frequency of vitamin D deficiency in adolescents.[8,21]

A cohort study of neonates performed by Kanike et al.[22] reported a high prevalence of vitamin D deficiency (31%) and insufficiency (49%) at birth. Similarly, a multicenter study in China conducted by Yang et al.[19] reported that vitamin D deficiency was seen most commonly in neonates. These two studies pointed to maternal vitamin D deficiency as the cause of vitamin D deficiency in infants. Similar studies also showed this relationship.[23-25] However, this study was unable to analyze this due to the small number of neonates.

Some studies found that the frequency of vitamin D deficiency was higher in girls as in the present study.[9,16] However, some studies reported no difference.[18,26] Cultural factors also have an essential role in vitamin D levels. In particular, traditional dress-style limits sun exposure and decreases vitamin D production. Therefore, vitamin D deficiency prevalence was reported higher among girls in Muslim countries.[20,27-29]

Many studies reported that vitamin D levels were at the lowest in spring and winter.[16,19] Sunlight exposure is the main factor in vitamin D synthesis. High latitudes are associated with inadequate levels of vitamin D. However; vitamin D insufficiency is not explained only by season and latitude. Recently, vitamin D insufficiency and deficiency are reported commonly in sunny countries.[30-33]

The present study assessed the role of age, sex, and season on vitamin D deficiency. A large sample of participants was the strong aspect of our research. However, there were a few significant limitations to this study. First of all, it was a cross-sectional design study and could not reflect the cause-effect relationship. Secondly, some important factors affecting vitamin D concentration, such as body composition and physical activity, skin pigmentation and sun exposure time, vitamin D intake, and socioeconomic status, could not be evaluated.[1] Many studies have established the relationship between obesity and lower serum vitamin D concentrations.[18,27,34-36] Vitamin D deficiency related to obesity is likely due

to the deposition of vitamin D in body fat tissues and the decreased bioavailability.[36] It has long been known that ethnicity and darker skin can greatly reduce vitamin D synthesis.[37]

Low vitamin D intake and breastfeeding were other important causes of vitamin D deficiency.[1,23] In addition, many study results showed that vitamin D deficiency was more prevalent among populations with lower socioeconomic status.[18,27,38,39]

Table 4. Studies on the prevalence of vitamin D deficiency in Turkey

Study	Year	n	Age	Mean Serum Vitamin D (ng/mL)	Deficiency %	Insufficiency %
Dogan et al.[13]	2015	2909	0-18 y	28.0±15.5	35.1	61.2
Ozhan et al.[14]	2016	556	0-18 y	27.2±15.9	39.3	24.1
Demiral et al.[9]	2016	171	3-18 y	-	86.6	-
Bucak et al.[15]		775	0-10 y		16.5	25.3
Girl	2016	335	-	32.9±13.9	-	-
Boy		440	-	34.4±14.6	-	-
Yetim et al.[10]		187	10-20 y	-	56	36
Girl	2017	103	-	18.7±8.9	-	-
Boy		84	-	19.2±9.3	-	-
Topal et al.[16]		2346	0-18 y	-	42.3	27.3
Girl	2018		-	21.3±15.0	-	-
Boy			-	22.5±13.9	-	-
Acik et al.[17]		417	0-17 y	-	51.7	16.7
Case-ICU	2018	327	-	-	55	16
Control		90	-	25.9±14.4	40	20
Sahin et al.[6]		90042	0-18 y	-	-	-
Girl		47928		22.3±14.0	-	-
Boy	2018	42114		25.3±13.4	-	-
<10 y		-		-	45-50	-
>10 y		-		-	80-90	-
Coskun et al.[7]	2018	346	0-18 y	-	49.1	27.5
Atasoy et al.[11]	2019	77	6-18 y	-	89.6	10.4
Naiboglu et al.[12]	2019	103	0-14 y	23.9±13.7	49	-
Ture et al.[8]	2020	4153	0-17 y	18.1±11.2	65.0	23.1
Varkal MA*	2021	3096	0-18 y	21.8±15.8	53.1	24.9

y: year, Serum vitamin D parameters presented as mean±standard deviation, Serum vitamin D values <20 ng/mL were accepted as a deficiency and 20-30 ng/mL as insufficiency.
* The present study

Table 5. Studies on the prevalence of vitamin D deficiency

Study	Year	n	Age	Mean/Median Serum Vitamin D (ng/mL)	Deficiency %	Insufficiency %
Turer et al.[35]	2013	12292	6-18 y			
Healthy-Weight		7728		-	21	-
Overweight		2086		-	29	-
Obese		1897		-	34	-
Severely obese		581		-	49	-
Zhang et al.[34]	2014	1488	7-11 y	18.4 (6.7-33.1)	56.4	23.3
Moore et al.[18]	2015	2492	6-18 y	-	26.8	46.7
Al-Sadat et al.[27]	2016	1361	13-15 y	-	92.6	-
Beer et al.[21]*	2020	2104	1-2 y	23.0±16	42.5	-
		6813	2-5 y	26.1±19	27.7	-
		16454	5-13 y	26.4±23	21.8	-
		6470	13-18 y	26.9±19	20.4	-
Kanike et al.[22] †	2020	1517	newborn	19.0 (3-223)	31	49
Yang et al.[19]	2020	460537	0-18 y	28.9±12.0	22.6	-
Chen et al.[26]	2021	1510	2-6 y	28.0±7.3	11.4	52.6
Varkal MA‡	2021	3096	0-18 y	21.8±15.8	53.1	24.9

y: year, Serum vitamin D parameters presented as mean±standard deviation or median (minimum-maximum), Serum vitamin D values <20 ng/mL were accepted as a deficiency and 20-30 ng/mL as insufficiency.
* In the study, standard errors were converted to standard deviation, and serum vitamin D values <20 ng/mL were shown in the deficiency column. †In the study, serum vitamin D values <15 ng/mL were accepted as a deficiency and 15-30 ng/mL as insufficiency. ‡The present study

CONCLUSION

This study showed that female sex, older children, and the winter/spring seasons were significantly associated with a higher frequency of vitamin D deficiency and a lower mean serum 25 hydroxyvitamin D concentration. The study findings suggest the need for caution in vitamin D supplementation of girls and older children. These children may require additional vitamin D supplementation to prevent vitamin D deficiency.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul University Faculty of Medicine Department of Child Health and Diseases Ethics Committee (Date: 10.09.2021, Decision No: 2021/1482-16).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Orjinal Araştırma / Original Article

CagA Positive *Helicobacter pylori* Infection in Coronary Atherosclerosis: Discriminative Value of Lymphocyte to Mean Platelet Volume Ratio

Koroner Aterosklerozda CagA Pozitif *Helicobacter pylori* Enfeksiyonu: Lenfosit Sayısının Ortalama Trombosit Hacmine Oranının Tanısal Değeri

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Abstract

Aim: Potent combined and long-term antithrombotic therapies that predispose to gastric injury are the mainstay of treatment in acute coronary syndromes (ACS). Severe chronic gastric mucosal inflammation due to the *Helicobacter pylori* (*H. pylori*) infection was shown to be associated with higher peripheral blood lymphocytes and lower blood mean platelet volume (MPV) levels. We aimed to investigate the discriminative usefulness of blood lymphocyte to MPV ratio as a simple premise marker for CagA positive *H. pylori* infection before the required advanced diagnostic tests in patients with coronary arterial disease (CAD).

Material and Method: A total of 293 patients' who had undergone elective and urgent coronary angiography due to CAD were included in the study. Serologic *H. pylori* infection status and hematological parameters were determined. Two groups were compared according to CagA serology status. Confounding factors were adjusted by propensity score matching and multivariate logistic regression analysis.

Results: Rates of ACS, male gender, diabetes mellitus, family history of CAD, current smoking and lymphocyte to MPV ratio were higher in seropositive patients according to seronegative patients ($p<0.05$). The ROC curve analysis showed that the lymphocyte to MPV ratio at a cut-off point of 165 had 71% sensitivity and 60% specificity for discriminating patients with positive *H. pylori* serology (AUC=0.71, $p<0.0001$). Lymphocyte to MPV ratio was independently associated with positive *H. pylori* serology.

Conclusion: Lymphocyte to MPV ratio can be helpful for discriminating CagA positive *H. pylori* infected CAD patients requiring advanced confirmatory tests.

Keywords: CagA, coronary arterial disease, *H. Pylori,* lymphocytes, mean platelet volume

Öz

Amaç: Akut koroner sendromlarda (AKS) mideye hasar verebilen uzun süreli güçlü-ikili antitrombotik tedavi kullanılmaktadır. *Helicobacter pylori* (*H. pylori*) enfeksiyonuna bağlı şiddetli kronik gastrik mukozal inflamasyonun, daha yüksek sayıda periferik kan lenfositleri ve daha düşük kan ortalama trombosit hacmi (MPV) seviyeleri ile ilişkili olduğu gösterilmiştir. Koroner arter hastalığı (KAH) olan hastalarda gerekli ileri tanı testlerinden önce CagA pozitif *H. pylori* enfeksiyonu varlığını belirlemede kan lenfosit/MPV oranının öncül belirteç olarak ayırt edici yararlılığını araştırmayı amaçladık.

Gereç ve Yöntem: KAH nedeniyle elektif ve acil koroner anjiyografi yapılan toplam 293 hasta çalışmaya dahil edildi. Serolojik *H. pylori* enfeksiyon durumu ve hematolojik parametreler belirlendi. CagA seroloji durumuna göre iki grup karşılaştırıldı. Etkin faktörler, eğilim skoru eşleştirmesi ve çok değişkenli lojistik regresyon analizi ile ayarlandı

Bulgular: AKS, erkek cinsiyet, diabetes mellitus, ailede KAH öyküsü, halen sigara kullanımı ve lenfosit/MPV oranı seropozitif hastalarda seronegatif hastalara göre daha yüksekti ($p<0.05$). ROC eğrisi analizi, lenfosit/MPV oranının 165 kestirim noktası için pozitif *H. pylori* serolojisi olan hastaları ayırt etmede %71 duyarlılığa ve %60 özgüllüğe sahip olduğunu göstermiştir (AUC=0.71, $p<0.0001$). Lenfosit/MPV oranı bağımsız olarak pozitif *H. pylori* serolojisi ile ilişkiliydi.

Sonuç: Lenfosit/MPV oranı, CagA pozitif *H. pylori* açısından İleri yöntemler ile taranması gereken KAH hastalarını ayırt etmede yardımcı olabilir.

Anahtar Kelimeler: CagA, Koroner Arter Hastalığı, *H. Pylori*, lenfositler, ortalama trombosit hacmi

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is common everywhere in the world, and it affects more than 50% of the world's population.[1] *H. pylori* infection causes variable degrees of mucosal damage in sensitive persons varying from mild gastritis to ulcer, gastrointestinal bleeding and gastric carcinoma.[2,3] Although association between coronary arterial diseases (CAD) and *H. pylori* infection is controversial, factors such as diabetes mellitus and smoking that predispose to both of these diseases, are frequently observed in both CAD and *H. pylori* infection.[3,4] Suggested explanations for the pathogenesis include direct cytotoxic effect and persistent local or systemic inflammatory response due to the microorganism.[2,5] Leukocyte and platelet activation occurs during an inflammatory reaction and mean platelet volume (MPV) is the indicator of platelet reactivity. Recently, MPV has been started to be used as a simple inflammatory indicator in some diseases such as diabetes mellitus, hypertension, atherosclerosis and other inflammatory disorders.[6,7] Also, severe chronic gastric mucosal inflammation due to the *H. pylori* infection was shown to be associated with higher peripheral blood lymphocytes and lower blood MPV levels.[2,8] Besides, positive *H. pylori* CagA serology, accepted as a potent systemic immune-inflammatory response marker, was associated with higher prevalence of acute coronary syndromes (ACS).[9,10]

Potent combined and long-term antithrombotic therapies that predispose to gastric injury are the mainstay of treatment in ACS.[11] Gastrointestinal bleeding after ACS is associated with increased mortality and the role of *H. pylori* infection in gastrointestinal bleeding is well established.[3] Tests required for the diagnosis of the infection; such as endoscopic biopsies, blood serology of *H. pylori* infection or urea breath tests are expensive and are not available everywhere. Therefore especially in CAD patients; a simple, minimally invasive, inexpensive, and widely available diagnostic marker for detecting *H. pylori* infection can be important for clinical practice.

Correlation between inflammatory mediators and the presence of *H. pylori* infection has been determined but the ability of these indicators for discriminating patients with *H. pylori* infection is uncertain.[2,12-15] As *H. pylori* infection was shown to be associated with higher peripheral blood lymphocytes and lower blood MPV levels; we therefore sought to investigate the discriminative usefulness of blood lymphocyte to MPV ratio as a simple premise marker for CagA positive *H. pylori* infection before the required advanced diagnostic tests in patients with CAD.

MATERIAL AND METHOD

Study population

After exclusion of unsuitable patients, a total of 293 subjects undergoing elective and urgent coronary angiography in our Cardiology clinic with various manifestations of ischemic heart disease were included. All of the patients were suspected of having CAD due to clinical symptoms or the results of clinical tests. Subjects with normal coronary arteries and with a disorder associated with acute or chronic infection/inflammation were excluded. None of the subjects included in the study had clinical evidence of connective tissue disease, liver dysfunction, hypothyroidism, severe chronic heart failure (NYHA class III-IV), moderate-severe renal dysfunction (eGFR<60 mL/min/1.73 m^2) and malignant diseases. Additionally, patients with any surgery within the previous 4 weeks, prior upper gastrointestinal tract and coronary arterial bypass surgery, use of nonsteroid anti-inflamatory drugs, blood transfusion during the last three months and incomplete data were excluded. Also none of the 293 individuals recruited had a history of eradication therapy for *H. pylori* infection or had received any antibiotic treatment during the study.

All subjects were screened with a questionnaire. Demographic data and risk factors for CAD were recorded in all participants. Individuals whose income was lower than at least two times of the minimum wage in our country were defined as lower socioeconomic status. The education level was divided into <10 years and ≥10 years. Among the main cardiovascular risk factors, the presence of family history of CAD (in a first-degree relative <55 years of age), hypertension (systolic or diastolic blood pressure >140 and 90 mm Hg, respectively, or pharmacological therapy with antihypertensive drugs), diabetes mellitus (fasting glucose plasma concentrations >126 mg/dL or pharmacological therapy with antidiabetic drugs or insulin), hyperlipidemia (low-density lipoprotein (LDL) cholesterol levels ≥ 130 mg/dl or being treated with lipid-lowering medication) were considered definitions. Current smoking was defined as at least 20 cigarettes per month for more than 6 months. Effort angina was defined by the presence of chest pain on walking that was relieved within 10 minutes after stopping or by ST segment of ECG down-sloping in a standard 12-lead electrocardiogram during chest pain or by positive stress testing. The diagnosis of AMI was established by using American College of Cardiology/European Society of Cardiology criteria.[16] Participation was voluntary, and written, informed consent was obtained from each subject. The study protocol was approved by the ethics committee of our hospital. The inclusion period was from March to September of 2013.

Laboratory Methods

All blood samples were drawn before the procedure after an overnight fasting under standardized conditions. Hematological parameters were measured using a Beckman Coulter LH780 Hematology Analyzer (Beckman Coulter, Inc). Lymphocyte to MPV ratio had calculated from the measurements in the peripheral blood. HsCRP (Siemens BN-II kinetic nephelometry analyzer) was used as a marker of inflammation.

Specific *H. pylori* anti-CagA IgG antibodies were measured by use of a commercial Enzyme-linked immune-sorbent assay (ELISA) (Radim Diagnostics, Rome, Italy) according to

manufacturer's instructions. Titers were defined as positive or negative according to a cutoff value of 30 UR/mL. The sensitivity and specificity of the tests of Radim (TM was 88% and 93.8%, respectively.[17] Patients were divided into 2 groups according to CagA IgG serostatus. All measurements were processed according to standard laboratory practice in a blinded fashion.

Determination of Coronary Arterial Disease

Coronary angiography was performed by a femoral approach using the standard Judkins technique (Axiom Artis zee 2011; Siemens, Munich, Germany). Coronary arteries were opacified with manual injections of 6–8 mL of Iohexol (Omnipaque, Nycomed Ireland, Cork, Ireland) at each position. Coronary artery disease has been defined as stenosis of at least one major epicardial coronary vessel at any degree. Two independent cardiologists who were unaware of the *H. pylori* status of the patients performed visual analysis of the coronary angiograms.

Statistical Analysis

We used the Kolmogorov-Smirnov test to assess the normality of numeric variables and analyzed homogeneity of numeric variables using the Levene test. Continuous variables with a normal distribution were expressed as means with standard deviations. Continuous variables with a skewed distribution (Neutrophils, Lymphocytes, MPV, RDW and Lymphocyte to MPV ratio) were expressed as medians with lower and upper quartiles. The categorical variables were expressed as numbers with percentages. The Student t test, the Mann–Whitney U test and the chi-square ($\chi 2$) tests (or Fisher's exact test if any expected cell count was <5) were used to compare baseline characteristics according to *H. pylori* serology.

Our study groups exhibited significant demographic and atherosclerotic risk factor differences (**Table 1**). To minimize the confounding effect of these factors and to obtain the best balance among groups, we performed a multivariate logistic regression model based on the significant variables.[18] Furthermore, in order to estimate the ability of lymphocyte to MPV ratio for predicting the presence of positive *H. pylori* serology, the receiver–operating characteristic (ROC) curve analysis was done to estimate area under curve (AUC).

Univariate logistic regression was used to investigate the relation between *H. pylori* serologic status and confounding parameters in our entire sample. After performing univariate analysis, significantly obtained variables (female gender, family history of CAD, diabetes mellitus, current smoking, presence of acute coronary syndromes and lymphocyte to MPV ratio higher than 165 (10^3 /μL fL)) were included in multivariate logistic regression analysis. Results were expressed as odds ratio (OR) with 95% confidence intervals (CI).

Table 1. Demographic, clinical and laboratory characteristics of our entire study group according to *Helicobacter pylori* CagA serology.

	Overall Group n=293	CagA IgG seronegatif n=55	CagA IgG seropositive n=238	p-value
Age, (years)	60±14	60±16	60±14	0.9
Female, n (%)	169 (58)	44 (88)	125 (51)	<0.0001
Family history of CAD, n (%)	174 (59)	22 (44)	152 (63)	0.01
Socioeconomic status, n (%)				
Low	112 (38)	16 (32)	96 (39)	0.32
Middle-High	181 (62)	34 (68)	147 (61)	
School education <10 years, n (%)	140 (48)	27 (54)	113 (46)	0.33
Diabetes, n (%)	129 (44)	10 (20)	119 (49)	<0.0001
Hypertention,n (%)	188 (64)	33 (66)	155 (64)	0.77
Dyslipidemia, n (%)	153 (52)	26 (52)	127 (52)	0.97
Current smoker, n (%)	130 (44)	10 (18)	120 (50)	<0.0001
Dyspepsi, n (%)	172 (59)	30 (54)	142 (60)	0.49
White blood cell count (10^3 /μL)	9.4±3.1	10.2±3.8	9.3±2.9	0.07
Platelets (10^3 /μL)	228±61	211±56	231±62	0.03
Neutrophils (10^3 /μL)	6.3 (4.8-7.9)	7.4 (5.0-8.1)	5.6 (4.8-7.8)	0.04
Lymphocytes (10^3 /μL)	1.8 (1.3-2.4)	1.4 (1.2-1.8)	1.9 (1.4-2.7)	<0.0001
MPV, fL	8.8 (7.8-9.4)	9.1 (8.2-9.3)	8.6 (7.7-9.5)	0.20
RDW, %	14.0 (13.4-15.1)	14.1 (13.2-15.1)	13.9 (13.4-15.0)	0.83
HsCRP,	5.9±4.0	6.7±4.2	5.8±4.0	0.13
Haemoglobin, g/dL	13.9±1.7	14.1±1.6	13.8±1.8	0.29
Creatinine, mg/dL	1.0±0.3	1.1±0.3	1.0±0.3	0.23
Lymphocytes/MPV (10^3 /μL fL)	214 (140-307)	154 (123-197)	228 (147-307)	<0.0001
Lymphocytes/MPV>165 (10^3 /μL fL)	190 (65)	22 (40)	168 (71)	<0.0001
CagA IgG titer UR/mL	115±91	8±7	137±85	<0.0001
CAD type, n (%)				
Stable CAD	213 (73)	48 (87)	165 (69)	0.02
ACS	80 (27)	7 (13)	73 (31)	

ACS, acute coronary syndrome; CAD, coronary arterial disease; Cag A, cytotoxin-associated gene product; HsCRP, high sensitive C-reactive protein; IgG, immunoglobulin G; MPV, mean platelet volume; RDW, red cell distribution width.

The sample size was sufficient to detect odds ratios for an association between the *H. pylori* serology and confounding parameters with 80% power at the 5% level of significance. A P-value ≤0.05 was considered statistically significant. Statistical tests were two-sided. All analyses were performed with IBM SPSS 15 software (SPSS version 15.0, SPSS, Chicago, IL, USA).

RESULTS

Clinical variables, coronary atherosclerotic disease and *H. pylori* infection.

The general features of patients according to *H. pylori* serology status for both entire and matched samples are summarized in **Table 1** and **2.** Tests for CagA-positive strains of *H. pylori* infection were performed in all subjects with positive results in 81.2%. Prevalence of male gender, diabetes mellitus, family history of CAD and current smoking was higher in seropositive patients than the seronegative ones (p<0.05). Also presence of acute coronary syndromes, lymphocyte counts and lymphocyte to MPV ratio were higher in patients with positive serology according to seronegative patients (p<0.05). The odds ratio of positive serology for the presence of acute coronary syndromes was 3.0 (95% CI (1.3-7.0); p=0.007).

The ROC curve analysis showed that the lymphocyte to MPV ratio at a cut-off point of 165 had 71% sensitivity and 60% specificity to determine positive *H. pylori* serology (AUC=0.71, p<0.0001).

After balancing the groups for significant confounding CAD risk factors and coronary syndrome type; higher lymphocyte to MPV ratio, higher rates of male gender and current smoking remained significant in seropositive subjects compared to seronegatif ones (p<0.05) (**Table 2**).

Medical treatments

Treatment rates with ACEİ, beta-blocker, calcium channel blocker and statin were similar between the groups according to *H. pylori* CagA serology (p>0.05). Only rate of treatment with angiotensin converting enzyme blockers differed between the groups in our matched samples (79% vs. 54%; p<0.02; for negative and positive serology respectively).

Regression analysis

After univariate analysis, independent association of *H. pylori* serology with significant confounding clinical features was investigated by multivariate analyses. In our entire sample after controlling for female gender, family history of CAD, diabetes mellitus, current smoking and presence of acute coronary syndromes; lymphocyte to MPV ratio higher than 165 (10^3 /μL fL) remained positively associated with *H. pylori*

Table 2. Demographic, clinical and laboratory characteristics of our matched study group according to *Helicobacter pylori* CagA serology.

	Overall Group n=78	CagA IgG seronegatif n=39	CagA IgG seropositive n=39	p-value
Age, (years)	61±15	60±17	58±13	0.67
Female, n (%)	72 (92)	39 (100)	33 (85)	0.03
Family history of CAD, n (%)	32 (41)	15 (38)	17 (44)	0.64
Socioeconomic status, n (%) Low Middle-High	 31 (40) 47 (60)	 12 (31) 27 (69)	 19 (49) 20 (51)	 0.10
School education <10 years, n (%)	33 (42)	16 (41)	17 (44)	0.82
Diabetes, n (%)	11 (14)	5 (13)	6 (15)	0.74
Hypertention,n (%)	49 (63)	28 (72)	21 (54)	0.10
Dyslipidemia, n (%)	43 (55)	21 (54)	22 (56)	0.82
Current smoker, n (%)	9 (12)	1 (3)	8 (21)	0.03
Dyspepsi, n (%)	43 (55)	19 (49)	24 (61)	0.25
White blood cell count (10^3 /μL)	10.3±3.6	10.7±3.8	9.5±3.0	0.14
Platelets (10^3 /μL)	221±70	215±61	225±72	0.53
Neutrophils (10^3 /μL)	7.1 (5.4-8.1)	7.7 (6.5-9.2)	6.6 (4.7-7.9)	0.013
Lymphocytes (10^3 /μL)	1.8 (1.3-2.3)	1.4 (1.1-2.1)	2.1 (1.4-2.7)	0.002
MPV, fL	8.8 (7.5-9.1)	9.1 (7.8-9.1)	8.2 (7.2-9.1)	0.07
RDW, %	14.1 (13.4-15.0)	14.1 (13.1-15.1)	14.1 (13.6-15.0)	0.57
HsCRP,	6.8±3.9	6.9±4.1	6.5±3.6	0.65
Haemoglobin, g/dL	14.7±1.4	14.6±1.2	14.8±1.5	0.52
Creatinine, mg/dL	1.1±0.2	1.1±0.2	1.1±0.2	0.87
Lymphocytes/MPV (10^3 /μL fL)	191 (140-307)	154 (134-261)	247 (154-325)	0.005
Lymphocytes/MPV>165 (10^3 /μL fL)	44 (56)	16 (41)	28 (72)	0.006
CagA IgG titer UR/mL	49±60	7±5	118±74	<0.0001
CAD type, n (%) Stable CAD ACS	 64 (82) 14 (18)	 32 (82) 7 (18)	 32 (82) 7 (18)	 1

ACS, acute coronary syndrome; CAD, coronary arterial disease; Cag A, cytotoxin-associated gene product; HsCRP, high sensitive C-reactive protein; IgG, immunoglobulin G; MPV, mean platelet volume; RDW, red cell distribution width.

Table 3. Multivariable regression analysis of *Helicobacter pylori* CagA serology and potential associated variables in our entire and matched sample groups.

Variables	Entire sample n=293		Matched Sample n=78	
	Multivariate OR (95% CI)	P value	Multivariate OR (95% CI)	P Value
Male gender	4.3 (1.7-10.8)	0.002	-	-
Family history of CAD	2.7 (1.3-5.7)	0.010	-	-
Diabetes mellitus	2.5 (1.1-5.7)	0.037	-	-
Current smoker	4.3 (1.8-10.3)	0.001	4.8 (0.4-55.1)	0.20
Acute coronary syndromes	6.8 (2.5-18.7)	<0.0001	-	-
Lymphocytes/MPV>165 (10^3 /μL fL)	3.8 (1.9-7.8)	<0.0001	4.1 (1.5-11.2)	0.007

*Adjusted for Lymphocytes/MPV>165 (10^3 /μL fL), female gender and current smoking CAD, coronary arterial disease; CI, confidence interval; MPV, mean platelet volume; OR, odds ratio.

serology (OR:3.8; 95% CI (1.9-7.8); p<0.0001). İn our matched sample, after controlling for female gender and current smoking, multivariable regression analysis showed the independent association of lymphocyte to MPV ratio higher than 165 (10^3 /μL fL) with *H. pylori* serology (OR:4.1; 95% CI (1.5-11.2); p<0.007) (**Table 3**).

DISCUSSION

This propensity score match observational study has confirmed that in CAD patients, CagA positive *H. pylori* infection prevalence is high. Also positive *H. pylori* CagA serology is found to be associated with higher prevalence of diabetes mellitus, current smoking, family history of CAD and acute coronary syndromes. The major and novel finding of this study is the independent positive association of lymphocyte to MPV ratio with CagA positive *H. pylori* infection in CAD patients.

H. pylori infection is common everywhere in the world, and it affects more than 50% of the world's population.[1] Association between CAD and *H. pylori* infection is suggested to be effected by factors predisposing to both of these diseases.[3,4] Major factors responsible for increasing rate of CAD occurrence like diabetes mellitus and smoking were linked with higher prevalence of *H. pylori* infection.[4] Therefore, investigating the relation between *H. pylori* infection and stable or unstable forms of cardiac syndromes is complicated and related trials are controversial.[9,10,19-23] Population-based cohort studies have not observed a significant association of *H. pylori* infection and CAD.[20,21] However, such a significant, positive association between positive anti-CagA IgG serology and the occurrence of ACS was concluded in a meta-analysis and in a prospective, case-control study with a 12-year follow-up period.[9,10,21] In line with these studies ACS was associated with positive CagA *H. pylori* serology in our study. Reasons for the differences with the previous reports may be due to study designs, heterogeneous patient populations, validity of exposure information and differences in treatment modalities. Our study tried to solve these limitations at least partly by balancing the groups. Similar to the literature, female gender, family history of CAD, history of diabetes mellitus and current smoking were the covariates associated with positive anti-CagA IgG serology in our study. Also, positive *H. pylori* CagA serology, a potent systemic immune-inflammatory response marker, was associated with higher prevalence of acute coronary syndromes. The induction of thrombotic processes by the maintenance of a low grade general inflammatory response is recognized as one of the potential mechanisms linking *H. pylori* infection to ACS occurrence.[5] By observing a positive association between CagA IgG seroprevalence and lymphocyte count, we have supported this finding.

Gastrointestinal bleeding after ACS is associated with increased mortality and the role of *H. pylori* infection (especially CagA positive strains) in the pathogenesis of gastrointestinal bleeding is well established.[3] Also, potent combined and long-term antithrombotic therapies that predispose to gastric injury are the mainstay of treatment in ACS. When the frequent association of CAD risk factors with *H. pylori* infection and the high serologic prevalence of virulent *H. pylori* infection are taken into account, the necessity of diagnosis and treatment of infection should be emphasized in patients with CAD; especially in subjects with ACS. Currently *H. pylori* testing and eradication therapy for gastrointestinal primary bleeding prevention is recommended for patients at risk.[11,24] In addition, tests required for the diagnosis of the infection; such as endoscopic biopsies, blood *H. pylori* serology or urea breath tests are expensive and are not available everywhere. Therefore, a simple, minimally invasive, inexpensive, and widely available diagnostic marker for *H. pylori* infection can be important for clinical practice especially in CAD patients. As the appropriate markers; leukocytes, platelets and MPV levels, that are routinely reported during a complete blood count analysis, were investigated regarding the intensity and severity of inflammation in patients with *H. pylori* infection.[2,12]

Leukocyte and platelet activation occurs during an inflammatory reaction and MPV is the indicator of platelet reactivity.[7] Recently, MPV has been started to be used as a simple inflammatory indicator in some diseases such as diabetes mellitus, hypertension, atherosclerosis and other inflammatory disorders.[6] Few studies have also shown a correlation between inflammatory mediators and the presence of *H. pylori* infection.[2,12-15] Particularly, CRP levels were observed to be increased in *H. pylori* infection.[15] Also, value of neutrophil to lymphocyte ratio and MPV levels for the detection of *H. pylori* were reported.[2,12-14] The results of these studies were different from our findings. Farah et al.[12] determined the clinical importance of lower lymphocyte

counts and Topal et al.[2] demonstrated the impracticability of MPV levels for detecting *H. pylori* infection and severity of inflammation. In our study, lymphocyte to MPV ratio higher than 165 (10^3 /µL fL) detected positive *H. pylori* CagA serology with 71% sensitivity and 60% specificity. These conflicting results about inflammatory parameters in *H. pylori* infected patients might be partially explained by different patient selections (such as age, sample size, inclusion of patients with comorbidity) and different diagnostic criteria. In contrast to mentioned studies; in the present study, sample size was larger, all of the patients had CAD, detection of *H. pylori* was by serology and only CagA positive strains were evaluated. Actually, presence of lymphoid follicles in patients with *H. pylori* infection related chronic mucosal inflammation was shown to be associated with higher peripheral blood lymphocytes and lower blood MPV levels.[2,8] This finding suggests that, agent accepted to be responsible for more severe inflammation, can be important by influencing mirror indicators of advanced inflammatory status in blood. But due to the study designs, the rate of patients infected with pathogenic CagA strain was obscure in those studies.

Strengths of our study include the large sample size relative to similar studies and fully matched compared samples for probable confounders. Limitations are *H. pylori* diagnosis based on serology, which may reflect not only present but also recent or past *H. pylori* infection. So, association of acute *H. pylori* infection with the presence of acute coronary syndromes is uncertain. On the other hand, *H. pylori* status was determined among all cases with the same method reducing internal variability, and, although the test showed good correlation with previous *H. pylori* tests used in former studies, no specific local validation was performed. Our measurements of subsequent markers were based on a single determination and the time-course alterations cannot be extrapolated from the study. Observational studies are always open to residual confounding that cannot always be completely controlled. Here, we reported estimates of OR adjusted by most widely recognized independent risk factors.

CONCLUSION

We suggest that lymphocyte to MPV ratio can be an inexpensive premise test for the classification of CagA positive *H. pylori* infected patients with CAD who require advanced confirmatory tests. Nevertheless, future studies going deeper in this discussion are required for investigating the importance of the blood lymphocyte to MPV ratio.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ministry of Health and the ethics committee of Ankara Training and Research Hospital institution, and our study was carried out in accordance with Principles of the Helsinki Declaration (Decision no:4123 13/03/2013).

Informed Consent: Written consent was obtained from all patients who participated in the study and their relatives.

Referee Evaluation Process: Externally peer-reviewed.

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Pain Assessment in Patients Who Receive Hemodialysis Treatment

Hemodiyaliz Tedavisi Gören Hastalarda Ağrı Değerlendirmesi

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Abstract

Aim: Pain is an important health issue that is common among patients who receive hemodialysis treatment and greatly affects the patients' quality of life. This study aims to assess the qualitative pain characteristics of patients who receive hemodialysis treatment using the McGill Pain Questionnaire.

Material and Method: This descriptive and cross-sectional study included 87 patients who received HD treatment. Data were collected using an information form and the McGill Pain Questionnaire in the HD clinic of a training and research hospital in Turkey between 01.04.2019 and 31.09.2019.

Results: The study is found that the mean current pain scores of the HD patients were moderate (2.13±0.56). The study is determined that the patients experienced pain most often in the lower extremity (36.8%) and head region (29.9%) and least in the upper extremity (11.5%). The hemodialysis procedure (44.8%), not following the diet (23%), fatigue (16.1%) and stress (16.1%) were found to intensify the pain. The study is found that analgesics (36.8%), resting (31%), complementary approaches (17.2%) and other practices (14.9%) relieved pain when patients were in pain. The study is also found that the patients often used the words tiring (n=47), sickening (n=42), fearful (n=41), and wretched (n=38) to define the pain they felt.

Conclusion: Measuring pain are greatly important to increase the quality of life. The results obtained indicate that assessment of the pain individualistically will be a guide to provide a holistic approach in HD patients.

Keywords: Pain, pain measurement, hemodialysis, McGill Pain Questionnaire

Öz

Amaç: Hemodiyaliz (HD) tedavisi gören hastalarda ağrı sık görülen ve büyük ölçüde yaşam kalitesini etkileyen önemli bir sağlık problemidir. Bu araştırma, McGill Ağrı Anketi ile hemodiyaliz tedavisi gören hastaların kalitatif ağrı özelliklerini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Araştırma, hemodiyaliz tedavisi gören 87 hasta ile gerçekleştirilen tanımlayıcı ve kesitsel bir çalışmadır. Veriler bilgi formu ve McGill Ağrı Anketi aracılığıyla 01.04.2019-31.09.2019 tarihleri arasında Türkiye'de bir eğitim araştırma hastanesinin hemodiyaliz kliniğinde toplandı.

Bulgular: Çalışmada HD hastalarının var olan ağrı şiddeti puan ortalamalarının orta düzeyde (2,13±0,56) olduğu belirlendi. Katılımcıların en sık alt ekstremite (%36,8), ve baş bölgesinde (%29,9) en az üst ekstremitede (%11,5) ağrı deneyimlediği saptandı. Hemodiyaliz işlemi (%44,8), diyete dikkat etmemek (%23), yorgunluk (%16,1) ve stresin (%16,1) ağrıyı artırdığı belirlendi. Hastaların ağrısı olduğunda ise sırası ile analjeziklerin (%36,8), istirahat etmenin (%31), tamamlayıcı yaklaşımların (%17,2) ve diğer uygulamaların (%14,9) ağrıyı azalttığı belirlendi. Hastaların hissettikleri ağrıları tanımlarken sıklıkla yorucu (n=47), tiksindirici (n=42), korku veren (n=41) ve sefil eden (n=38) ifadelerini kullandığı görüldü.

Sonuç: Yaşam kalitesinin artırılmasında ağrıyı değerlendirmek son derece önemlidir. Elde edilen sonuçların hemodiyaliz hastalarında, ağrıyı bireye özgü değerlendirerek bütüncül bir yaklaşımın sunulmasında yol gösterici olacağı düşünülmektedir.

Anahtar Kelimeler: Ağrı, ağrı ölçümü, hemodiyaliz, McGill Pain Questionnaire

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INTRODUCTION

Kidney diseases are a global health issue that affects more than 750 million people worldwide.[1,2] While the symptoms and findings induced by kidney failure are brought under control with hemodialysis treatment, the treatment process and maintaining a life depending on the hemodialysis machine may cause different problems.[3] Patients who receive hemodialysis treatment struggle against significant health problems such as sleep disorder, depression, fluctuations in vital signs and pain.[4] Acute and chronic pain is an important health problem common among especially the population of patients who receive hemodialysis treatment that significantly affects their quality of life.[5] Pain negatively affects the coping process, functional capacity and direct quality of life.[6]

Pain is an experience that affects the individual with all dimensions and it is quite common among hemodialysis patients.[7] The International Association for the Study of Pain (IASP) defines pain as an unpleasant sensory and emotional experience associated with real or possible tissue damage.[8] Personal experiences and their responses change in every person; thus, pain is a subjective concept. However, reasons such as the patient's fear of disrupting the healthcare staff, belief that nothing will reduce the pain, fear of disbelief, and lack of a common language to discuss pain cause patients to be reluctant to communicate about their pain levels.[9] Additionally, since the priority is generally given to the treatment of the current disease in hemodialysis patients, the number of approaches related to the existence, etiology and management of pain is limited.[10]

The increasing incidence frequency, morbidity, mortality rates of kidney diseases and costly treatments make kidney diseases an important public health problem.[2] Considering that the pain incidence of patients who receive hemodialysis treatment due to kidney failure are high, it is also an important necessity to examine the existence, intensity, frequency, duration of pain and increasing/decreasing factors. The pain must be defined accurately to provide individualistic and holistic care regarding the concept of pain that is perceived differently by everyone and affected by personal factors. Pain assessment is important for healthcare personnel to provide effective pain management with accurate knowledge, behavior, attitude, assessment and clinical decision-making skill to increase the patients' quality of life.[11,12] Therefore, the results obtained in this study are considered to be guiding in the clinical area.

Research Question

What are the pain levels of hemodialysis patients?

MATERIALS AND METHOD

Design and Setting

This descriptive and cross-sectional study was carried out to determine the pain conditions of patients who received hemodialysis treatment.

Sample

The population of the study is included the patients who applied to the hemodialysis clinic of a training and research hospital in Turkey for treatment between 01.04.2019 and 31.09.2019. The aim was to reach all registered chronic regular hemodialysis patients in the service between these dates. A total of 230 individuals applied to the hemodialysis service of the hospital where the study was conducted as hemodialysis patients between the specified dates. While approximately 98 of these patients were registered chronic regular hemodialysis patients in the service, the rest were acute and temporary patients. The sample of the study included 87 patients who met the inclusion criteria and who agreed to participate in the study voluntarily.

Sample Selection Criteria of the Study;

- Being 18 or older.
- Receiving hemodialysis treatment in the relevant hospital.
- Receiving hemodialysis treatment for at least one year.
- Having pain.
- Knowing Turkish.

Data Tools

The data were collected using an information form and the McGill Pain Questionnaire.

Information Form

The structured information form used to collect data was formed by the researchers in line with the knowledge of literature.[6,10,15] This form questioned the descriptive characteristics of the patients and included 13 questions related to demographic characteristics (age, sex), socioeconomic characteristics (education level, employment status) and disease history (the date of the first dialysis, frequency of dialysis, comorbid disease).

The McGill Pain Questionnaire (MPQ)

The McGill Pain Questionnaire (MPQ) was developed by Melzack in 1975.[13] The MPQ is the most commonly used survey for the multidimensional assessment of pain. It provides information about the sensory characteristics, intensity and effect of pain. The Turkish validity and reliability of it was conducted by Kuguoglu, Aslan and Olgun (2003).[14] The coefficient reliability measured with the Cronbach's alpha was found as 0.98. The item reliability coefficients of the form parts were between 0.52 and 0.72 in the second part, between 0.50 and 0.70 in the third part and between 0.50 and 0.58 in the fourth part. The scale consists of four parts. The first part of the form includes information about the patient's age, medical diagnosis-problem, type and dosage of analgesics if used, as well as descriptive information about the patient's level of perception. In summary, the location of the pain, its relationship with time, its intensity, the feeling it creates in the patient and the livable pain for the patient are determined in the measurement made using the McGill Pain Questionnaire. Evaluation is made on an assessment scale consisting of words used to describe the pain intensity.

Data Collection

Data were collected using the face-to-face interview technique. The data were collected by the researchers in the hemodialysis service or in the waiting area within 15-20 minutes without hindering the patient's treatment protocol and the functioning of the service. It is seen in the literature that most patients who receive dialysis treatment and have chronic kidney problem experience pain.[6] It is also seen that the location and intensity of pain experienced before, during and after hemodialysis change. The patients' data were collected during the dialysis process in this study.

Ethical Considerations

Approval from the ethics committee (2011-KAEK-25 2019/02-02) and the hospital was obtained before the study was conducted. All persons included in the study signed the Informed Consent Form. The design and conduct of the study was in accordance with the general principles outlined in the Declaration of Helsinki and adhered to principles of Good Clinical Practice.

Statistical Analysis

Data analysis was performed through SPSS for Windows (Statistical Package for the Social Science for Windows, Version 24.0). The arithmetic mean, standard deviation, minimum and maximum values were adopted in the assessment of the numeric variables whereas in the assessment of the categorical variables, frequency and percentage were employed.

RESULTS

The demographic characteristics of the patients are presented in **Table 1**. The mean age of the patients included in the sample was 51.63±18.84. Of the participants, 52.9% were male, 81.6% were married, 62.1% were primary school graduates, 93.1% were unemployed and 52.9% defined their economic state as good. Of the patients, 70.1% had at least one comorbid disease besides kidney failure, 58.6% had been receiving dialysis treatment for 1-5 years, and 80.4% received hemodialysis treatment three days a week. Considering the BMI values of the patients, most of them (57.5%) had normal body weight. The number of patients who did not have any harmful substance abuse was determined to be n=62 (71.3%).

The mean level of perception of the patients was found to be moderate (3.49±1.07). The patients' mean current pain intensity score was 2.13±0.56 and the worst pain intensity was at the level of 3.28±0.98 points. Considering the analgesics the patients prefer when in pain, it was found that most of them (86.2%) used paracetamol. Also, the remaining 13.8% used nonsteroidal analgesics. The most commonly reported region among aching body parts of the participants was lower extremity (36.8% followed by head region (29.9%). The least pain was detected in the upper extremity region (11.5%). Of the participants, 67.8% described their pain as superficial and 54% described the pain's relationship with time as brief, momentary and transient .The conditions that intensify and reduce the pain were examined in this study. The hemodialysis procedure (44.8%), not following the diet (23%), fatigue (16.1%) and stress (16.1%) were found to intensify the pain. The study found that analgesics (36.8%), resting (31%), complementary approaches (17.2%) and other applications (14.9%) relieved pain when patients were in pain (**Table 2**).

Table 1. Distribution of the patients' demographic characteristics

Variables	Min-Max.	Mean±Sd
Mean Age	18-96	51.63±18.84
Weight	30-122	64.37±15.20
Height	140-183	163.87±8.98
	n	**%**
Age Groups		
18-43	31	35.6
44-70	42	48.3
71-96	14	16.1
Body Mass Index		
*Lower than 18.5 kg/m²	10	11.5
†Between 18.5-24.9 kg/m²	50	57.5
‡Higher than 25 kg/m²	27	31
Gender		
Female	41	47.1
Male	46	52.9
Marital status		
Married	71	81.6
Single	16	18.4
Educational Level		
Literate	19	21.8
Primary school	54	62.1
High school	11	12.6
University	3	3.4
Employment Status		
Employed	6	6.9
Unemployed	81	93.1
Economic Status		
Good	46	52.9
Moderate	37	42.5
Bad	4	4.6
Duration of Hemodialysis (year)		
Between 1-5 years	51	58.6
Between 6-10 years	26	29.9
More than 11 years	10	11.5
Frequency of Undergoing Dialysis (week)		
2	17	19.5
3	70	80.5
Using Harmful Substances		
Yes	25	28.7
No	62	71.3
Comorbid Disease		
Yes	61	70.1
No	26	29.9

*Underweight †Normal ‡Overweight

Table 2. Pain characterization in hemodialysis patients

Variables	Min-Max.	Mean±Sd
Level of Perception	1-5	3.49±1.07
Pain intensity		
Current Pain Score (0-5)	1-4.33	2.13±0.56
Worst Pain Score (0-5)	1-5	3.28±0.98
	n	**%**
Analgesic Used		
Paracetamol	75	86.2
Nonsteroidal	12	13.8
Pain Location		
Head Region	26	29.9
Abdominal Region	19	21.8
Lower extremity	32	36.8
Upper extremity	10	11.5
Deep/Superficial		
Deep	22	25.3
Superficial	59	67.8
Deep and Superficial	56	6.9
The Relationship of Pain with Time		
Continuous, steady, constant	18	20.7
Rhythmic, periodic, intermittent	22	25.3
Brief, momentary, transient	47	54.0
What relieves the pain		
Analgesics	32	36.8
Resting	27	31
Complementary Approaches*	15	17.2
Other Applications†	13	14.9
What intensifies the pain		
Fatigue	14	16.1
Stress	14	16.1
Not following the diet	20	23
Dialysis	39	44.8

*Massage, hot/cold applications †Walking, some nutrition

In **Table 3**, the word sets that describe pain in individuals who receive hemodialysis treatment in terms of sensory, affective, miscellaneous and evaluative classes. The patients used the following words most commonly to describe pain; "wretched" in the sensory class (n=38), "tiring" in the affective class (n=47), "numb" in the evaluative class (n=14), and "fearful" in the miscellaneous class (n=41).

Table 3. Descriptors of pain reported by the participants of the study

Descriptors*	Frequencies	%
Sensory		
Wretched	38	4.4
Flickering	36	4.1
Spreading	36	4.1
Tugging	34	3.9
Hot	33	3.8
Affective		
Tiring	47	5.4
Sickening	42	4.8
Tight	25	2.9
Grueling	19	2.2
Nauseating	19	2.2
Evaluative		
Numb	14	1.6
Squeezing	13	1.5
Tight	12	1.4
Drawing	8	0.9
Tearing	6	0.7
Miscellaneous		
Fearful	41	4.9
Cool	34	3.9
Cutting	31	3.6
Jumping	23	2.6
Flashing	21	2.4

* This descriptors were most reported

DISCUSSION

It is necessary to determine the perception levels of individuals who are in pain for the accurate description and effective management of pain. Therefore, the study was determined that the patients' perception level. The patients' perception levels were examined with a Likert-evaluation between 1-5 in the McGill pain questionnaire. Individuals' perception levels are important in interpreting their environment and themselves by understanding them. The study is found that the patients' perception levels were moderate. Cognition and perception are of great importance for the individual to interact with their environment purposefully and successfully. Cognition enables the individual to process, store and manage the information while perception enables the integration of sensations with meaningful information. On the other hand, cognitive and perceptive impairment affects self-care and conscious decision-making capacity.[15] Some diseases (paralysis), treatments (chemotherapy) and physiological changes (increasing age) increase the risk of cognitive decline.[16] Especially the negative effects of pain experienced on sleep, focus, memory, physical and social activities are known.[6] The fact that the participants' perception levels were moderate in this study makes it important to describe and express pain perceptions accurately.

The study is determined that the patients' perception level. The study is determined that the patients' mean current pain intensity score was 2.13 out of 5 and the worst pain intensity was at the level of 3.28 points. The study is found that the worst pain intensity was higher than the current pain intensity and a bit over moderate intensity. Kafkia et al. (2014) found that the patients scored the pain they experienced as 6 out of 10.[17] Özyiğit et al. (2016) found that the lowest pain score of the individuals who received hemodialysis treatment was 1.35 (mild) and the most intense pain score was 4.25 points out of 5.[6] In the same study, 51.4% of the patients stated that the pain they experienced was mildly intense. Ghonemy et al. (2016) found that 52% of the patients were in pain and 48% of those in pain stated that their pain intensity was high. In the comparison with the literature, the patients in this study experienced a slightly lower level of pain.[18] This result might be related to the population (sex) with whom the study was conducted and the time of pain inquiry (during/after dialysis).

Considering the types of analgesics the patients prefer when in pain, it was found that most of them used paracetamol while some used nonsteroidal analgesics. Similarly, Caravaco et al. (2016) found that majority of patients with chronic kidney disease used paracetamol or metamizole as analgesic and more than 20% of the patients with muscle pain meticulously took nonsteroidal anti-inflammatory drugs.[19] Sadigova et al. (2020) found that only 36.4% of patients who received hemodialysis treatment used analgesics, and the reasons why they did not want to use analgesics even though they were in pain might be the patients' concerns about the side effects of the drug, drug overload and addiction risks.[12] Özer et al. (2020) determined that the hemodialysis patients' psychological pain beliefs were higher, pain coping methods were insufficient,

and that as the patients' belief that psychological reasons are effective in the development of pain increases, the methods of seeking medical remedies decrease.[20] The present study found that all participants used analgesics, although not regularly, and they often preferred paracetamol group. This indicates that it is necessary to examine the factors (doctor's suggestion, prejudices, friend's recommendation, experience, etc.) that affect the analgesics preference of hemodialysis patients in detail.

The most commonly reported region among the body parts where the participants perceived pain was lower extremity and head regions. The least pain was detected in the upper extremity region. In the study by Yeşil et al. (2015) conducted with hemodialysis patients, it was found that the patients' pain complaints were mostly headache (31 patients, 58.5%), lower extremity pain (21 patients, 39.6%) and pain induced by cramp-like contractions (28 patients, 52.8%).[10] Low back pain is common among hemodialysis patients. Old age, increased body mass index and smoking are the main risk factors for low back pain. The existence of low back pain is also associated with bad quality of life related to health.[21,22] In the study by Özyiğit et al. (2016), it was found that individuals who receive hemodialysis treatment often experience pain in the head, abdomen, and musculoskeletal areas.[6] It was thought that the high rate of pain in the head area may be due to hemodialysis procedure. Caravaca et al. (2016) found that 38% of 1169 patients with chronic kidney disease had chronic musculoskeletal pain.[19] In a systematic review addressing the hemodialysis patients, most of the patients stated to experience pain as arteriovenous access (AVF), headache and musculoskeletal pain.[5] Sadigova et al. (2020) found that the most common pain region in patients who received hemodialysis treatment was lower extremity and that the patients with upper extremity pain had high AVF usage rates.12 of the patients, 55.4% experienced pain during the day and 16.3% stated that they experience headache the most.[20] Ghonemy et al. (2016) stated that patients experience muscle, skeleton and headache the most.[18] In a study which examined the problems experienced by patients after hemodialysis, it was found that 63.4% of the patients had headache.[23] The results of the present study are similar to the studies in the literature, and the pain experienced appears to be in the musculoskeletal system[18,19] and often in the lower extremities.[12]

While most of the hemodialysis patients in this study described their pain as superficial, they stated the relationship of their pain with time as brief, momentary and transient. Unlike the results obtained from this study, the patients in the study by Yeşil et al. (2015) described the nature of their pain as blunt, tingling and constant.[10] Most patients reported that the pain started slowly. Similarly, it was found in another study that the pain experienced by patients was mild and deep.[6] Different results obtained from the study might be related to the sample (age, sex) on which the study was conducted and the time of pain inquiry.

The study is examined the factors that intensify the pain in hemodialysis patients. Hemodialysis process, not following the diet, fatigue and stress were found to intensify the pain, respectively. Similar to the results obtained in this study, in the study by Sadigova et al. (2020) conducted with patients who receive hemodialysis treatment, the patients who experience pain had a longer duration of dialysis than patients who do not experience pain.[12] It is stated that hemodialysis process and stress increase the pain.[6] Following the therapeutic diet determines treatment success, quality of life and survival rates in hemodialysis patients. However, noncompliance with the diet continues to be serious health problem.[24] The results obtained from the study are similar to the literature.

The study is found that analgesics, resting, complementary approaches (massage, hot/cold applications, etc.) and other applications (walking, eating certain food, etc.) reduce pain in hemodialysis patients, respectively. Özyiğit et al. (2016) found that more than half of the hemodialysis patients used pharmacological treatments for pain relief and almost half of them used nonpharmacological methods such as massage, hot application, position changing.[6] Reiki, one of the complementary approaches, is known to provide symptom relief for individuals who receive hemodialysis.[25] The study is found that the patients did not primarily use complementary approaches, preferred analgesics and expected pain relief with rest. Although pain is one of the most common symptoms in patients with kidney problem, it is not recognized enough, its severity is underestimated and its treatment is inadequate.[26] The way followed in pain management in the study supports this information.

The patients who received hemodialysis treatment used the words "wretched" in the sensory class, "tiring" in the affective class, "numb" in the evaluative class, "fearful" in the miscellaneous group the most in this study. In a study which questioned the nature of pain in hemodialysis patients, the pain was described as blunt and tingling.[10] In the study by Ruela et al. (2018), the following pain descriptions were reported by patients who received chemotherapy; burning and sore as the sensorial descriptor, tiring and sickening as the emotional descriptor, troublesome and annoying as the evaluative descriptor, radiating and nauseating as the miscellaneous group descriptors.[27] Barbosa et al. (2016) found that the following words were preferred by onco-hematological patients the most; jumping, tugging and throbbing in the sensory category, exhausting, punishing and cruel in the affective category, troublesome, intense and miserable in the evaluative category, and penetrating, tight and dreadful in the miscellaneous category.[28] Pain is a subjective and highly personal experience. The subjective nature of pain requires us to rely on individuals' self-expression and to some extent their behavior in pain assessment.[29] Determining the perception differences in pain experience will affect the approaches in pain management. Therefore, the pain descriptions obtained in this study are important to reflect the pain perceptions of hemodialysis patients.

CONCLUSION

In conclusion, the fact that pain is a personal sensation makes it necessary for us to consider that the one who can describe the pain in the most reliable way is the patient itself. This study determined and revealed the type, frequency, localization, intensity and characteristics of pain experienced by patients who receive dialysis treatment. Healthcare personnel should assess pain in hemodialysis patients using suitable tools to strengthen their communication with the patients. The results to be obtained are considered to be a resource for future studies and practices of healthcare personnel

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval from the ethics committee (2011-KAEK-25 2019/02-02) and the hospital was obtained before the study was conducted.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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Orjinal Araştırma / Original Article

Neutrophil-Lymphocyte ratio and C-Reactive Protein Levels in Acne Vulgaris Patients Treated with Systemic Isotretinoin

Sistemik İsotretinoin Tedavisi Alan Akne Vulgaris Hastalarında Nötrofil-Lenfosit Oranı ve C-Reaktif Protein Düzeyleri

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Abstract

Introduction: Inflammatory mediators have importance in acne vulgaris pathogenesis. Which mediators cause lesions or increase with which variants is not clear. Neutrophil-lymphocyte ratio and C-reactive protein are the inflammatory indicators that used for follow up of inflammatory diseases. There are various studies state that neutrophil-lymphocyte ratio and C-reactive protein levels are important for systemic isotretinoin treatment or not. Evaluation of changes in neutrophil-lymphocyte ratio and C-reactive protein levels with systemic isotretinoin treatment is the aim of this study.

Material and Method: Acne vulgaris patients who are treated with systemic isotretinoin and healthy control subjects between January 2006 and December 2016 in Konya Training and Research Hospital Dermatology outpatient clinic are included to study. Neutrophil-lymphocyte ratio and C-reactive protein levels compared in each group at the beginning of treatment and at the 3rd month.

Results: 50 patients (28 of women and 22 of men) who are treated with systemic isotretinoin for acne vulgaris and 50 healthy control patients (21 of women and 29 of men) included to study. Mean age of treatment group was 21 (19-23) and control group was 29.5. Neutrophil-lymphocyte ratio are not found statistically significiant in patients and control group at the begining and middle of the treatment (1.84 [3.36-0.51] – 1.62 [4.07-0.68], p:0.107), C-reactive protein levels show a statistically significiant decrease in patient group with treatment (p<0.028).

Conclusion: Systemic isotretinoin treatment may affect neutrophil-lymphocyte ratio and C-reactive protein levels in patients. Further studies are needed to clarify this relation.

Keywords: Acne vulgaris, C-reactive protein, Neutrophil-Lymphocyte ratio

Öz

Giriş: Akne vulgaris patogenezinde inflamatuar medyatörler önem taşımaktadır. Hangi medyatörlerin hangi değişkenler ile lezyon gelişimine veya artışına sebep olduğu net değildir. Nötrofil lenfosit oranı ve C-reaktif protein kronik hastalıkların takibinde kullanılan inflamatuar belirteçlerdir. Sistemik isotretinoin tedavisi bazı çalışmalarda inflamatuar belirteçler üzerine etkili bulunurken bazı çalışmalarda etkisiz olduğu bildirilmiştir. Bu çalışmanın amacı sistemik isotretinoin tedavisinin C-reaktif protein ve nötrofil/lenfosit oranı üzerine olan etkisinin araştırılmasıdır.

Gereç ve Yöntem: 1 Ocak 2016 ile 31 Aralık 2016 tarihleri arasında Konya Eğitim ve Araştırma Hastanesi Deri ve Zührevi Hastalıklar polikliniğine ayaktan başvuran ve sistemik isotretinoin tedavisi alan 18 yaş üstü akne vulgaris hastalarının kayıtları taranarak tedavi başlangıcı ve tedavinin 3.ayındaki nötrofil lenfosit oranları ve C-reaktif protein düzeyleri karşılaştırılmıştır. Bulunan sonuçlar benzer demografik yapıdaki normal hasta grubuyla karşılaştırılmıştır.

Bulgular: 28 kadın,22 erkek olmak üzere toplam 50 hasta ve 21 kadın, 29 erkek olmak üzere toplam 50 sağlıklı kontrol hastası çalışmaya dahil edildi. Tedavi grubundaki hastaların yaşları 19 ile 23 arasında, kontrol grubu hastalarının yaşları ise 18 ile 35 arasında değişmekteydi. Nötrofil lenfosit oranı başlangıç ve tedavi ortasında hem hasta hemde kontrol grubunda anlamlı bulunmezken (1,84 [3,36-0,51] – 1,62 [4,07-0,68], p:0,107), C-reaktif protein düzeyleri hasta grubunda tedavi ile istatistiksel olarak anlamlı azalma göstermiştir (p<0,028).

Sonuç: Sistemik isotretinoin tedavisi nötrofil-lenfosit oranı ve C-reaktif protein düzeyleri üzerinde etkili olabilir. Bu ilişkiyi açıklamak için daha geniş kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Akne vulgaris, C-reaktif protein, Nötrofil-Lenfosit oranı

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INTRODUCTION

Acne vulgaris is a self-limited, chronic inflammatory disease, which usually affects the pilosebaceous unit in adolescents.[1] It is seen nearly in 80% of the adolescents and the young adults between the ages of 11-30.[2] Oral isotretinoin (13-cis retinoic acid) was approved by US Food and Drug Administration (FDA) in 1982. It is one of the most used drug preferred in dermatology practical from that day to the present. In the past 30 years, there is no more effective treatment for acne vulgaris. It emerges as first choice in treatment for severe and resistant acne vulgaris. Isotretinoin is the only drug that effective for all the factors in acne vulgaris pathogenesis. It's effects are;

1. Decrease in sebum secretion,
2. As a secondary of decrease in sebum secretion, decrease in P.acnes colonisation by disrupting suitable environment for P.acnes colonisation because of shrinkaging of pilosebaceus channels,
3. The prevention of comodegenesis by decreasing hyperkeratinisation,
4. Anti-inflammatory effect by stimulating of monocyte chemotaxis.

Since the introduction of isotretinoin treatment for acne, a variety of laboratory monitoring intervals have been used in clinical practice.[3] Routine monitoring for complete blood count is unwarranted.[4] Reports of severe leukopenia and or thrombocytopenia are likely idiosyncratic.[5,6] Lipid abnormalities are the most common laboratory abnormality seen with isotretinoin therapy.[7]

The patients must be evaluated carefully at the beginning of systemic isotretinoin treatment;

- Detailed personal medical history must be obtained from patient,
- Is there any familial or personal history for hypertriglyceridemia or related lipid disorders?
- Is there any disorder that can effect liver functions?
- Is there any medication currently for any disorder at beginning?, and
- All female patients in childbearing age must be monitored preferably monthly for pregnancy.

Inflammatory mediators have importance in acne vulgaris pathogenesis.[8] Which mediators cause lesions or increase with which variants is not clear. Neutrophil-lymphocyte ratio and C-reactive protein are the inflammatory indicators which are used for follow up of inflammatory diseases. Systemic isotretinoin treatment found as effective on inflammatory indicators in some studies but it is found ineffective some other studies. The aim of this study is evaluate the effect of isotretinoin treatment on c-reactive protein and neutrophil-lymphocyte ratio.

MATHERIAL AND METHOD

Study design

It's a single center, retrospectively designed study. Local ethic commitee approval was obtained. Medical records of dermatology outpatient clinic patients between January 2016 and December 2016, retrospectively scanned with hospital information management system (HBYS). Acne vulgaris patients who are treated with systemic isotretinoin are included to study. Patients with concomitant systemic disease (diabetes mellitus, goiter etc) and under 18 years of age are excluded. Neutrophil-lymphocyte ratio and C-reactive protein levels of patients recorded at the beginning of treatment and at the 3rd month of treatment. Records have been compared with healthy patient group which has similar demographic structure .

Statistical analysis

Categorical variables were expressed as percent (%). Central tendency is expressed by mean and median, and dispersion by standard deviation and range, interquartil range Normal distribution was ruled out by the Kolmogorov-Smirnov and histogram plots. The differences between groups were assessed using Mann-Whitney U test for independent samples and Wilcoxon Signed Rank test for related samples with non-normal distrubiton. Values of $p < 0.05$ were considered statistically significant. The statiscal analysis of study has been done with SPSS Version 15.0 programme. (SPSS Inc., Chicago, Illinois, ABD)

RESULTS

50 patients (28 (56%) of women and 22 (44%) of men) and 50 healthy control patients (21 (42%) of women and 29 (58%) of men) are included in the study. The median age of treatment group patients is 21 [19-23] and the mean age of control group patients is 29.5±7. The isotretinoin doses are between 20mg/day and 50mg/day (**Table 1**). Pretreatment neutrophil-lymphocyte ratio is not significantly different between patient and control groups (1.6 [1.32-2.02] vs 1.84 [1.39-2.46], p:0.134). Neutrophil-lymphocyte ratio difference between the begining and third month of the treatment is not found statistically significant (7.6 [6.6-9.2] vs 1.79 [1.32-2.1], p:0.172) (**Figure 1**). C-reactive protein levels showed a statistically significant decrease in patient group between the first and third month of the treatment (3.27 [3.19-7.7] vs 3.27 [3.02-5.84], p: 0.028) (**Figure 2**).

Table 1. Patient and control group characteristics

	Patient Group n:50	Control Group n:50
Female n(%)	28 (56%)	21 (42%)
Male n(%)	22 (44%)	29 (58%)
Age n(%)	21 [19-23]	29.5±7
Isotretinoin Dosage		
20 mg/day	4(8%)	-
30 mg /day	9(18%)	-
40 mg/day	31(62%)	-
50 mg/day	6(12%)	-

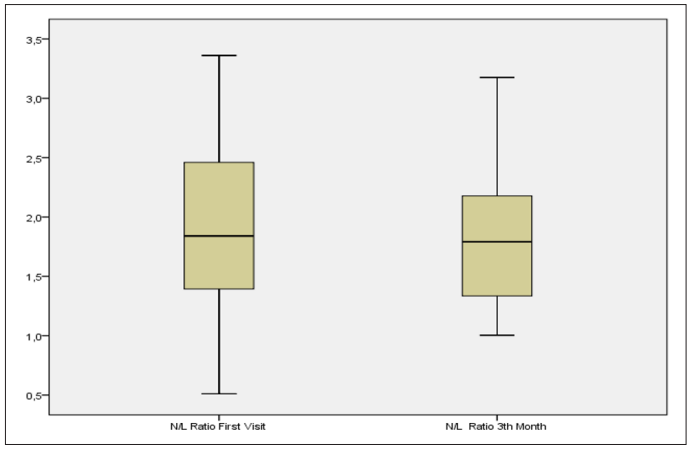

Figure 1. Neutrophil-Lymphocyte ratio, First and 3rd month

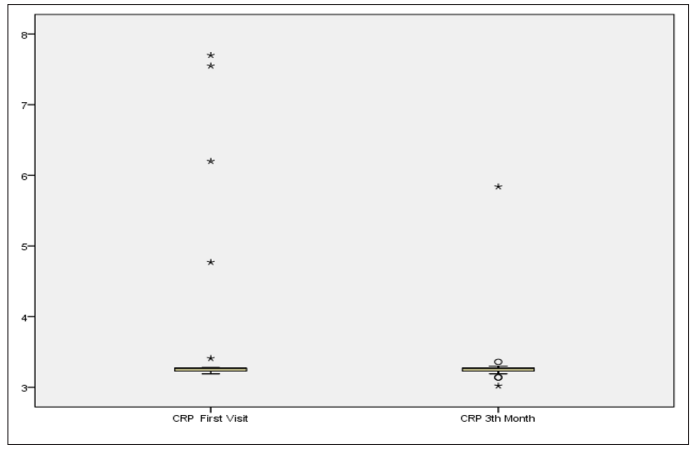

Figure 2. CRP levels, First and 3rd month

DISCUSSION

We try to evaluate neutrophil-lymphocyte ratio and C-reactive protein levels in acne vulgaris patients who are treated with systemic isotretinoin. We found neutrophil-lymphocyte ratio is not affected with treatment compared with healthy control group at first and third month of treatment. But C-reactive protein levels are significantly decreased between first and third month of treatment in patients. It was compatible for observation that C-reactive protein levels decrease with diminished inflammation.

Acne vulgaris is one of the most treated disorder by dermatologists. It often affects adolescents. Acne vulgaris is a public health problem. It's estimated that nearly 80% of people affected with acne vulgaris in lifetime. There are many different treatment modalities for acne vulgaris. Systemic isotretinoin is the most effective one in this group. It is effective for all types of acne but it is preferrable for severe or resistant acne vulgaris because of it's advers affects.

C-reactive protein is an acute phase protein which increase with injury, infection and inflammation and decreases with healing or improvement.[9] CRP concentration may increase more than 1000 times in severe inflammatory states.[10] CRP is a multifunctional component of the human innate host defense system. All humans have CRP but it's unknown that all CRP is functional or not. CRP levels increase in inflammation and injury but it's not same as in all humans.[11] Liver is the main organ for CRP synthesis. Liver synthesizes CRP with the stimulation of cytokine.[12] It's possible to lead elevated CRP levels in acne vulgaris. Disease severity maybe the decisive for CRP levels. Neutrophil-lymphocyte ratio is foreseen that it will be used as inflammatory indicator in recent years.

There are various studies about C-reactive protein levels in acne vulgaris patients and neutrophil-lymphocyte ratio. Ataseven et al. indicate that there is no any important differences in neutrophil count, lymphocyte count and neutrophil-lymphocyte ratio in the patients who get systemic isotretinoin treatment.[13] Namazi et al. indicate that C-reactive protein levels in severe acne vulgaris patients is not different from normal population.[14] For psoriasis, Sen et al. indicate that neutrophil-lymphocyte ratio is significantly high in psoriasis vulgaris patients.[15] It is possible to conclude that different disorders have different pathogenetic mechanisms. Inflammatory markers are not the same changes in all situations.

Systemic isotretinoin therapy has multiple effects on acne vulgaris pathogenesis. Anti-inflammatory effect is one of them. Decrease in CRP levels in patients with treatment may be associated with anti-inflammatory effect of isotretinoin therapy. Isotretinoin makes this effect through suppression of mTORC1 and downregulation of inflammatory driving protein, S100a7a.[16,17]

Limitations: This was a single-center retrospective study and the results may not be generalizable to other populations. The historical laboratory data was extracted from our hospital management system, not a controlled trial.

CONCLUSION

It is stated in our study that there is a significant changes only in C-reactive protein levels. CRP or Neutrophil-lymphocyte ratio alone or both can be use for treatment follow up. It is thought that reduction in inflammation with the regression of acne vulgaris lesions can cause decrease in CRP levels. Follow up of C-reactive protein levels in patients who get systemic isotretinoin treatment can be suitable for usage as lab indicator. The questions should be asked are; is there any relationship between the severity of acne lesions and CRP levels and are there any changes in CRP levels with healing level of acne. Further prospective controlled studies are needed to find answers for these questions.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Faculty of Medicine Ethics Committee of Selçuk University (Date: 24.10.2018, Decision no: 2018/365).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Orjinal Araştırma / Original Article

Investigation of Pediatric Poisoning in Aksaray

Aksaray'da Çocuk Zehirlenmesinin Araştırılması

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Abstract

Introduction: Pediatric poisoning is a common cause of emergency department admissions. The epidemiology of pediatric poisonings can vary in different countries, even different regions of the same country. It is important to determine the regional factors to decrease morbidity and mortality. This study was aimed to evaluate the epidemiological features, clinical signs, and risk factors of pediatric poisonings.

Material and Method: This retrospective descriptive study was carried out in the pediatric emergency department of a tertiary hospital and medical records between January 2016 and December 2020 were retrospectively reviewed. Demographic characteristics, laboratory results, and treatments were recorded.

Results: 835 patients aged 4 months-18 years including 450 females (53.9%) were included in the study. Poisonings were most common in summer (n=280, 33.5%) and in the daytime (n=490, 58.7%). The mean age of suicidal poisoning was significantly higher then accidental poisonings (p<0.001). Pharmaceutical agents were statistically significantly higher in patients poisoned due to suicidal attempts (p<0.001). On the other hand, there was not a statistically significant difference between accidental and suicidal poisoning in terms of clinical presentation, length of stay in the hospital, and, intensive care unit requirement (p>0.05).

Conclusions: Childhood poisoning is one of the important emergencies that need attention. Pediatric emergency physicians should always keep in mind the possibility of poisoning, even with the lack of medical history. It could be estimated the possible ingested agents according to the age group, and this allows physicians to avoid delay in treatment of these patients.

Keywords: Pediatric poisoning, pediatric emergency medicine, suicide, accident

Öz

Giriş: Pediatrik zehirlenme, acil servise başvuruların yaygın bir nedenidir. Pediatrik zehirlenmelerin epidemiyolojisi farklı ülkelerde, hatta aynı ülkenin farklı bölgelerinde bile değişebilir. Morbidite ve mortaliteyi azaltmak için bölgesel faktörlerin belirlenmesi önemlidir. Bu çalışmada çocukluk çağı zehirlenmelerinin epidemiyolojik özellikleri, klinik bulguları ve risk faktörlerinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Bu retrospektif tanımlayıcı çalışma, üçüncü basamak bir hastanenin pediatrik acil servisinde gerçekleştirildi ve Ocak 2016 ile Aralık 2020 arasındaki tıbbi kayıtlar geriye dönük olarak incelendi. Demografik özellikler, laboratuvar sonuçları ve tedaviler kaydedildi.

Bulgular: Çalışmaya 450 kadın (%53.9) olmak üzere 4 ay-18 yaş arası 835 hasta dahil edildi. Zehirlenmeler en sık yazın (n=280, %33,5) ve gündüz (n=490, %58,7) mevsiminde görüldü. Ortalama intihar zehirlenmesi yaşı, kaza sonucu zehirlenmelere göre anlamlı derecede yüksekti (p<0.001). İntihar girişimi nedeniyle zehirlenen hastalarda ilaç ajanları istatistiksel olarak anlamlı derecede yüksekti (p<0,001). Öte yandan kaza ve intihar zehirlenmeleri arasında klinik prezentasyon, hastanede kalış süresi ve yoğun bakım ünitesi gereksinimi açısından istatistiksel olarak anlamlı fark yoktu (p>0,05).

Sonuçlar: Çocukluk çağı zehirlenmesi, dikkat edilmesi gereken önemli acil durumlardan biridir. Pediatrik acil hekimleri, tıbbi öykü olmasa bile zehirlenme olasılığını her zaman akılda tutmalıdır. Yaş grubuna göre alınabilecek olası etkenler tahmin edilebilir ve bu, hekimlerin bu hastaların tedavisinde gecikmelerden kaçınmasını sağlar.

Anahtar kelimeler: Pediatrik zehirlenme, pediatrik acil tıp, intihar, kaza

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INTRODUCTION

Pediatric poisoning is a common cause of emergency department admissions.[1] In 2019, 1,236,227 (57.5% of all ages) individuals under the age of 20 were admitted to the pediatric emergency department (ED) due to poisoning in the United States.[2] While the rate of poisoning was 0.5 per 100,000 population in developed countries, it was 2 per 100,000 population in developing countries.[3]

Pediatric poisonings can occur accidentally or intentionally. While accidental poisoning is more common in children under 5 years and boys, intentional poisoning is more common in adolescents and girls.[4,5] Household cleaning products, gas oil, thinner, toxic gases, prescribed/nonprescribed drugs, insecticides, and pesticides are the most common causes of poisoning in childhood.[6,7]

The epidemiology of pediatric poisonings can vary in different countries, even different regions of the same country. It is important to determine the regional factors to decrease morbidity and mortality. Therefore, the present study was aimed to evaluate the epidemiological features, clinical signs, and risk factors of pediatric poisonings.

MATERIAL AND METHOD

This retrospective descriptive study was carried out in the pediatric emergency department of a tertiary hospital in the Aksaray, Central Anatolian region of Turkey, and approved by the local ethical committee (2021/01-54).

Study population and setting

The medical records of all poisoning-related admissions to the pediatric emergency department between January 2016 and December 2020 were retrospectively reviewed. The study was included the following patients: 1) those aged <18 years; and 2) those diagnosed with acute poisoning at the pediatric emergency department. The following patients were excluded:1) those aged >18 years; 2) those poisoned due to food over-ingestion except for the mushroom and plant poisonings; 3) those poisoned due to foreign body ingestion (coins, plastics, or toys); 4) those poisoned due to vaccination; and 5) those with missing data.

Age (0-5, 6-12, and 13-18 years), gender, admission time (night, 00:00-08:00; daytime, 08:00-16:00; and evening, 16:00-00:00), admission season (winter, spring, summer, and autumn), poisoning agent (pharmaceutical and non-pharmaceutical), cause of poisoning (accidental and suicidal), location of the poison exposure (home and outside home), medical history of the previous poisoning, symptoms at the admission (nausea-vomiting, dizziness, mucosal erythema-edema, abdominal pain, confusion, shortness of breath and cough, tachycardia, mydriasis-miosis, and hypotension-shock), the length of stay in the hospital (hours), the requirement of intensive care unit and mortality were recorded. Patients poisoned with a pharmaceutical agent were divided into six major groups based on the categories of pharmaceutical: (1) neurologic system agents (anxiolytic/hypnotic agents, antidepressant agents, antiepileptic drugs, and narcotics); (2) analgesics (acetaminophen and nonsteroid anti-inflammatory drugs); (3) respiratory system agents (bronchodilators and dextromethorphan); (4) cardiovascular system agents (antihypertensive drugs and anticoagulants); (5) metabolic and nutrient agents (vitamins and iron); and (6) others (7). Non-pharmaceutical agents were categorized as (1) alcohol, drug; (2) carbon monoxide; (3) corrosive substances (cleaning substances, deodorizers, desiccants, personal care products); (4) mushrooms, plants; (5) venoms (bite or sting); and (6) insecticides, herbicides, rodenticides.

Data Analysis

Data were analyzed using Statistical package social sciences (SPSS, version 22.0 Inc., Chicago IL, USA). Descriptive analyzes were expressed as number (%) for categorical variables, and mean±standard deviation (SD) for normally distributed variables (age and length of stay in hospital). In the comparison of accidental and suicidal poisonings, chi-square and Fischer exact test was used for categorical variables, whereas Student's t-test was used for continuous variables. A p-value of <0.05 was considered statistically significant.

RESULTS

In the pediatric emergency department, 1,164 children were diagnosed with poisoning during the study period. Seventy-two patients who had missing data, 210 patients who were poisoned due to food over-ingestion, 45 patients who were poisoned due to foreign body ingestions, and two patients who poisoned due to vaccination were excluded from the study. Finally, 835 patients aged 4 months-18 years (mean 77.67±59.21 months) including 450 females (53.9%) were included in the study.

Poisonings were most common in summer (n=280, 33.5%) and in the daytime (n=490, 58.7%). Three hundred and fifty-nine (43%) patients were poisoned due to pharmaceutical agents, whereas 476 (57%) patients were poisoned due to non-pharmaceutical agents. The reason for poisoning was a suicide attempt in 138 (16.5%) patients and 81 (9.7%) patients had a history of the previous poisoning. Five hundred and thirty-three patients (63.8%) were asymptomatic. Among symptomatic patients (n=302, 36.2%), the most common symptom was nausea-vomiting (n=83, 27.4%), followed by dizziness (n=46, 15.2%), and multiple symptoms (n=40, 13.2%). The mean length of stay in the hospital was 28.35±12.87 (median=27, min-max=4-105) hours. Twenty-two (2.6%) patients required intensive care unit (ICU) admission. The baseline characteristics of the study population according to the age groups were summarized in **Table 1**.

There was only one patient who died due to poisoning during the study period. She was 211 months old, had not a history of previous poisoning, or a psychiatric disorder. She took her grandmothers' verapamil tablets at 03:30 AM, at home. She was hemodynamically unstable at the admission to the pediatric emergency department. She was admitted to the ICU and died at the 4th hour of treatment.

Table 1. Baseline characteristics of the study population according to the age groups

	0-5 years (n=543, 65%)	6-12 years (n =132, 15.8%)	13-18 years (n=160, 19.2%)	Total (n=835, 100%)
Gender				
Male	255 (47)	56 (42.4)	74 (46.3)	385 (46.1)
Female	288 (53)	76 (57.6)	86 (53.7)	450 (53.9)
Admission season				
Winter	67 (12.3)	37 (28)	49 (30.6)	153 (18.3)
Spring	154 (28.4)	36 (27.3)	43 (26.9)	233 (27.9)
Summer	175 (32.2)	42 (31.8)	63 (39.4)	280 (33.5)
Autumn	147 (27.1)	17 (12.9)	5 (3.1)	169 (20.2)
Admission hour				
Night, 00:00-08:00	31 (5.7)	8 (6.1)	74 (46.3)	113 (13.5)
Daytime, 08:00-16:00	383 (70.5)	72 (54.5)	35 (21.9)	490 (58.7)
Evening, 16:00-00:00	129 (23.8)	52 (39.4)	51 (31.9)	232 (27.8)
Poisoning agent				
Pharmaceutical	171 (31.5)	54 (40.9)	134 (83.8)	359 (43)
Non-pharmaceutical	372 (68.5)	78 (59.1)	26 (16.3)	476 (57)
Reason for poison exposure				
Accidental	543 (100)	121 (91.7)	33 (20.6)	697 (83.5)
Suicidal	0 (0)	11 (8.3)	127 (79.4)	138 (16.5)
Location of poison exposure				
Home	467 (86)	111 (84.1)	136 (85)	714 (85.5)
Outside home	76 (14)	21 (15.9)	24 (15)	121 (14.5)
Previous poisoning history				
No	506 (93.2)	122 (92.4)	126 (78.8)	754 (90.3)
Yes	37 (6.8)	10 (7.6)	34 (21.3)	81 (9.7)
Clinical presentation				
Asymptomatic	345 (63.5)	88 (66.7)	100 (62.5)	533 (63.8)
Symptomatic	198 (36.5)	44 (33.3)	60 (37.5)	302 (36.2)
Nausea-vomiting	67 (33.8)	11 (25)	5 (8.3)	83 (27.4)
Dizziness	20 (10.1)	11 (25)	15 (25)	46 (15.2)
Mucosal erythema-edema	18 (9)	3 (6.8)	3 (5)	24 (7.9)
Abdominal pain	22 (11.1)	5 (11.3)	7 (11.6)	34 (11.2)
Confusion	16 (8)	4 (9)	5 (8.3)	25 (8.2)
Shortness of breath, cough	18 (9)	4 (9)	5 (8.3)	27 (8.9)
Tachycardia	10 (5)	3 (6.8)	2 (3.3)	15 (4.9)
Mydriasis-miosis	0 (0)	1 (2.2)	5 (8.3)	6 (2)
Hypotension-shock	0 (0)	0 (0)	2 (3.3)	2 (0.6)
Multiple symptoms	27 (13.6)	2 (4.5)	11 (18.3)	40 (13.2)
The length of stay in hospital, hours, mean±SD	28.24±12.42	26.98±13.75	29.86±13.57	28.35±12.87
Intensive care unit admission				
No	533 (98.2)	127 (96.2)	153 (95.6)	813 (97.4)
Yes	10 (1.8)	5 (3.8)	7 (4.4)	22 (2.6)

Data were presented as n (%) except the length of stay in hospital.

Analgesics were the most common (n=136, 37.9%) pharmaceutical poisons, followed by neurologic system agents (n=82, 22.8%), and cardiovascular system agents (n=43, 12%). Corrosive substances were the most common (n=167, 35.1%) non-pharmaceutical poisons, followed by carbon monoxide (n=153, 32.1%), and mushrooms and plants (n=52, 10.9%). Detailed information on agents causing the studied poisonings is presented in **Table 2**.

The mean age of suicidal poisoning was significantly higher then accidental poisonings (179.28±31.65 months, p<0.001). At night, between 00:00 and 08:00, the poisonings were more likely to be result of suicidal attempts (p<0.001). Pharmaceutical agents were statistically significantly higher in patients poisoned due to suicidal attempts (p<0.001). On the other hand, there was not a statistically significant difference between accidental and suicidal poisoning in terms of clinical presentation, length of stay in the hospital, and, ICU requirement (p>0.05). The comparison of accidental and suicidal poisonings is summarized in **Table 3**.

Table 2. Detailed information on agents causing the studied poisonings

Pharmaceutical poisons	359 (43)
Neurologic system agents	82 (22.8)
Analgesics	136 (37.9)
Respiratory system agents	27 (7.5)
Cardiovascular system agents	43 (12)
Metabolic and nutrient agents	36 (10)
Others	35 (9.7)
Non-pharmaceutical agents	476 (57)
Alcohol, drug	47 (9.9)
Carbon monoxide	153 (32.1)
Corrosive substances	167 (35.1)
Mushrooms, plants	52 (10.9)
Venoms (bite or sting)	34 (7.1)
Insecticides, herbicides, rodenticides	23 (4.8)

Data were presented as n (%) except age and the length of stay in hospital.

Table 3. The comparison of accidental and suicidal poisonings

	Accidental (n=697)	Suicidal (n=138)	P value
Age, months, mean±SD	57.55±39.39	179.28±31.65	<0.001
Gender, n (%)			
Male	317 (45.5)	68 (49.3)	0.414
Female	380 (54.5)	70 (50.7)	
Admission season, n (%)			
Winter	114 (16.4)	39 (28.3)	
Spring	189 (27.1)	44 (31.9)	<0.001*
Summer	230 (33)	50 (36.2)	
Autumn	164 (23.5)	5 (3.6)	
Admission hour, n (%)			
Night, 00:00-08:00	42 (6)	71 (51.4)	<0.001*
Daytime, 08:00-16:00	451 (64.7)	39 (28.3)	
Evening, 16:00-00:00	204 (29.3)	28 (20.3)	
Poisoning agent, n (%)			
Pharmaceutical	241 (34.6)	118 (85.5)	<0.001
Non-pharmaceutical	456 (65.4)	20 (14.5)	
Location of poison exposure, n (%)			
Home	598 (85.8)	116 (84.1)	0.596
Outside home	99 (14.2)	22 (15.9)	
Previous poisoning history, n (%)			
Yes	643 (92.3)	111 (80.4)	<0.001
No	54 (7.7)	27 (19.6)	
Clinical presentation, n (%)			
Asymptomatic	443 (63.6)	90 (65.2)	0.711
Symptomatic	254 (36.4)	48 (34.8)	
The length of stay in hospital, hours, mean±SD	28.32±13.55	28.47±8.71	0.173
Intensive care unit admission, n (%)			
Yes	680 (97.6)	133 (96.4)	0.389
No	17 (2.4)	5 (3.6)	

* Suicidal poisonings are significantly lower (p<0.001) in autumn in post-hoc analysis.

DISCUSSION

Acute poisoning in children is a life-threatening emergency. Epidemiological evaluations and identification of predisposing risk factors in this field can be a research priority, especially in our city where the population triples in summer. In every summer, approximately 1 million expatriate visits our city, and they affect the active lifestyles of local people. In our study, suicidal poisonings were increased in summer, in contrast with the literature,[8,9] and this may be related to the changes in population structure in the summer months.

Regarding age distribution, most of the poisoning patients were under 5 years old, and they were poisoned more commonly in the daytime and summer, as expected.[8] Considering that younger children spend more time outside the home, especially in the summer months, poisonings in this age group are expected to occur more outside the home. However, poisonings at home were more common in this age group in our study. The most common agents of poisonings were corrosive substances and carbon monoxide. This may explain the dominancy of home poisonings. In addition, poisonings that occurred outside of the home may be related to venoms and plants.

In the adolescent group, poisonings were more common at night hours, with pharmaceutical agents, and as suicide attempts, similar to the literature.[9,10] An adolescent who plans to attempt suicide can read the contents of the drugs, understand the effects, reach enough dose, and hide them from parents. Lin et al.[11] reported a high rate of previous suicide attempt history in these patients. Yang et al.[10] reported a 1.4% rate of mortality and suggested that pediatric poisoning is a fairly serious problem. In this study, 34 (21.3%) patients in this age group had a suicide attempt history. Only one patient died due to verapamil intoxication. It was a planned suicide. On the other hand, most of the poisonings in this age group occurred at home. These suicide attempts at home may be aimed at secondary gains from parents or lovers, especially among female patients.[1,10]

Etiological causes of poisonings may vary according to the geographical region, socio-cultural and economic conditions of the societies. Therefore, each country, even each region, should determine its own poisoning agent and take necessary precautions according to the risks and threats it faces. However, in developing countries, it is difficult to predict the severity of childhood poisonings due to the lack of reliable data. In our country, drugs usually were the most common agents in childhood poisonings with a range of 43.6% - 60%, followed by corrosive substances, insecticides, and mushrooms.[12-19] In this study, which is conducted in the Central Anatolian region of Turkey, the most common agents for poisonings were drugs, followed by corrosive substances, and carbon monoxide. The fact that coal stoves are used instead of natural gas in some villages of our region may be the reason why carbon monoxide poisoning is in the third place, in contrast with other studies from Turkey. In addition, similar to the literature from Turkey, the most common agents for pharmaceutical poisonings were analgesics, followed by neurologic system agents, and cardiovascular system agents.[13,14,20,21]

Childhood poisonings are generally asymptomatic due to ineffective agents or low doses, and they are usually been discharged after the pediatric emergency department observation.[12] Symptoms of poisonings usually depend on the ingested agent. While nausea-vomiting, dizziness, and multiple nonspecific complaints are the most frequent symptoms, they can also cause life-threatening conditions such as arrhythmia, hypotension, shock, and as a result serious morbidity.[22,23] The length of stay in the hospital, the requirement of intensive care unit and mortality depend on the agent, ingested dose, and time from ingestion to treatment.[7] In this study, 22 (2.6%) patients required intensive care unit admission, and it did not differ between suicidal or accidental poisonings. This result supports the idea of secondary gain in suicidal attempts.

Our study had several limitations due to its retrospective design. The time from ingestion to admission to the hospital is an important prognostic factor and we could not evaluate this subject because of the lack of data. In addition, the source of the drugs ingested was another lacked data. A comprehensive multicenter prospective study is needed to evaluate all sides of childhood poisoning and improve precautions according to the risk factors.

CONCLUSION

Childhood poisoning is one of the important emergencies that need attention. Patients may admit in various clinical conditions such as asymptomatic or in a coma. Pediatric emergency physicians should always keep in mind the possibility of poisoning, even with the lack of medical history. It could be estimated the possible ingested agents according to the age group, and this allows physicians to avoid delay in treatment of these patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: Aksaray Education and Research Hospital Scientific Research Evaluation Committee with decision no: 2021/01-54.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Orjinal Araştırma / Original Article

Evaluation of the Outcomes of Gastrointestinal Endoscopic Examination in Patients with Iron Deficiency in the Light of Current Guidelines

Demir Eksikliği Olan Hastalarda Gastrointestinal Endoskopik İnceleme Sonuçlarının Güncel Klavuzlar Eşliğinde Değerlendirilmesi

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Abstract

Introduction: Chronic blood loss and intestinal malabsorption of iron are two important causes of iron deficiency (ID) in adult patients. We evaluated the demographic data and endoscopy findings of patients who underwent endoscopic examination due to iron deficiency.

Material and Method: The study was designed retrospectively.The database of patients who underwent endoscopic examination due to ID and/or iron deficiency anemia (IDA) in the endoscopy unit of our hospital between June 2017-April 2020 were found by scanning the hospital database. After exclusion of patients with active bleeding, remaining 326 patients were evaluated.

Findings: Median age of the patients was 58 years. The participants included 182 males and 144 females. Ninety three patients were below 50 years of age whereas 133 patients were over 50 years old. Endoscopy (EGD) was performed in 13.2% of the patients; colonoscopy was performed in 2.5% of them; and endoscopy + colonoscopy (bidirectional procedure) was performed in 84.4%. Endoscopic examinations revealed pathological findings that may cause ID/IDA in 69.3% of the patients; however, no gastrointestinal pathology was detected in 30.7%. Twelve patients were diagnosed with malign diseases. Detection of any pathology that may cause ID/IDA during endoscopic examinations was significantly more in the bidirectional examination group when compared to patients who had only EGD or colonoscopy ($p<0.001$). Furthermore, concomitant pathologies in both lower and upper GIS were detected in 17.5% of the patients in the bidirectional examination group.

Conclusion: Bidirectional endoscopic examinations according to guideline recommendations increase diagnostic efficiency compared to one-sided examinations.

Keywords: Iron deficiency, anemia, endoscopy, colonoscopy

Öz

Giriş: Erişkin hastalarda kronik kan kaybı ve demirin intestinal emilim bozukluğu demir eksikliğinin (DE) iki önemli nedenidir. Bu çalışmamızda demir eksikliği nedeniyle endoskopik inceleme yaptığımız hastaların demografik verilerini ve endoskopi bulgularımızı değerlendirdik.

Gereç ve Yöntem: Çalışma retrospektif olarak dizayn edildi. Haziran 2017-Nisan 2020 tarihleri arasında hastanemiz endoskopi ünitesinde DE ve/veya DEA nedeniyle endoskopik inceleme yapılan hastalar veri tabanı taranarak bulundu. Aktif kanama bulgusu olan hastalar dışlandıktan sonra kalan 326 hasta değerlendirildi.

Bulgular: Hastaların median yaşı 58'di. 182'si erkek (%55,8), 144'ü kadındı (%44,2). Hastaların %28,5'i (n=93) 50 yaş ve altında iken, %71,5'i (n=133) 50 yaşın üzerindeydi. %13,2'sine endoskopi (ÖGD), %2,5'ine kolonoskopi, %84,4'üne endoskopi+kolonoskopi (çift yönlü işlem) birlikte yapılmıştı. Yapılan endoskopik incelemeler sonrasında hastaların %69,3'ünde DE/DEA'ya neden olabilecek patolojik bulgular saptanırken %30,7'sinde DE/DEA'ya neden olabilecek sindirim kanalı patolojisi izlenmedi. Hastaların 12'sinde (%3,8) malignite saptandı. Endoskopik incelemeler esnasında DE/DEA'ya neden olabilecek herhangi bir patoloji saptanması; sadece ÖGD veya kolonoskopi yapılan hastalarla (%43,1) karşılaştırıldığında; çift yönlü inceleme yapılan hasta grubunda (%74,2) istatistiksel olarak daha fazlaydı ($p<0,001$). Ayrıca çift yönlü inceleme yapılan hastaların %17,5'inde hem alt hem de üst GİS'te DE/DEA'ya neden olabilecek eş zamanlı patoloji saptandı.

Sonuç: Klavuzlarda önerildiği şekilde endoskopik incelemelerin çift yönlü yapılması, tek yönlü incelemelere göre tanısal etkinliği artırır.

Anahtar kelimeler: Demir eksikliği, anemi, endoskopi, kolonoskopi

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INTRODUCTION

The World Health Organization defines anemia when hemoglobin (Hb) concentration below 13 g/dl in adult males, less than 12 g/dl in adult non-pregnant females, and less than 11 g/dl in pregnant women.[1] Iron deficiency anemia (IDA) is the most common anemia type all over the world. It is detected in 2% to 5% of men and post-menopausal women in developed countries.[1,2]

Absorption of dietary iron mostly occurs in duodenum and proximal jejunum.[3]

Insufficient dietary iron intake, impaired intestinal absorption of iron or conditions that cause chronic blood loss lead to iron deficiency.[1,3] In addition, common causes for IDA include phlebotomy, gastrectomy and use of non-steroidal anti-inflammatory drugs (NSAIDs).[1]

Serum markers of iron deficiency (ID) are low ferritin, low transferrin saturation, low iron, increased total iron binding capacity, increased alveolar zinc protoporphyrin level and increased serum transferrin receptor (sTfR) levels. Serum ferritin level is the strongest test to indicate IDA. In order to diagnose iron deficiency in patients with anemia, the threshold value for ferritin level has been reported as 15 ng/mL.[1,3]

Chronic blood loss and impaired intestinal absorption of iron are two important causes of ID. Such both conditions are closely related to the gastrointestinal (GI) tract.[4] GI lesions were shown in 40% to 70% of adult males and post-menopausal females with IDA in the etiology. In these studies, increased age, male gender, low ferritin level, the use of NSAID, positive fecal occult blood test, and presence of GI symptoms were stated as predictors of endoscopic lesions.[5]

IDA is accepted as an alarm sign for GI malignancy. Inadequate evaluation of patients with IDA may delay the diagnosis of GI tumors, especially colorectal cancer.[5] The American guideline (AGA) also stated that gastrointestinal malignancy is the most serious potential cause of IDA.[3]

Both AGA and English (BSG) guidelines recommend bidirectional endoscopic evaluation (both esophagogastroduodenoscopy (EGD) and colonoscopy) at the same time in order to evaluate post-menopausal females and males.[1,3] BSG recommends that premenopausal women under the age of fifty undergo colonoscopy if they have colonic symptoms, and if there is persistant IDA despite iron therapy. However, the AGA guideline recommends bidirectional endoscopic evaluation in premenopausal women with IDA.[1,3]

We evaluated the demographic data and endoscopy findings of patients who underwent endoscopic examination of upper and lower GI tract because of ID and/or IDA.

MATERIAL AND METHOD

Totally 326 patients who underwent endoscopic examination due to ID and/or IDA in the endoscopy unit of our hospital between June 2017 and April 2020 were evaluated. Patient age, gender, use of NSAIDs and anticoagulants, hemoglobin, hematocrit, iron, total iron binding capacity, ferritin levels at the time of endoscopy, endoscopic diagnosis, and biopsy results were evaluated. Patients younger than 18 years old and patients with active bleeding findings such as melena were not included in the study.

All endoscopic procedures were performed by a single specialist. Malignancies, erosive esophagitis and gastritis, esophageal varices and portal hypertensive gastropathy (PHG), ulcer detected in any localization, gastrectomy, polyp, angiodysplasia, appearance of celiac disease, inflammatory bowel disease (IBD), diverticules, hemorrhoids, and anal fissure diagnoses during endoscopic examination were recorded. Our study was carried out according to Helsinki declaration. Approval of the ethical committee for the study was obtained with E.11346 numbered on July 15th,2020.

Statistical Analysis

Statistical evaluation was performed by the Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc.,Chicago,IL) program. Normal distribution of the data was evaluated by Kolmogorov-Smirnov test. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used for evaluation of the study data.

Pearson Chi-Square test and Fisher's Exact test were used for comparison of the qualitative data.

Any p level below 0.05 was evaluated at significance level.

RESULTS

The study population included 144 (44.2%) females and 182 (55.8%) males. The ages of the cases were between 18 and 89 years.The average age was 58.85±14.52 years. Ninety three (28.5%) patients were below 50 years of age whereas 133 (71.5%) patients were above 50 years of age. The review of past-medical history of the patients was shown in **Table 1**. Analysis of laboratory parameters was represented in **Table 2**. Ten (10.4%) of 96 patients whose stool occult blood (SOB) tests were examined were detected positive for SOB. Furthermore, parasite eggs were found in 2 (3.1%) of 65 patients who were examined for stool parasites (**Table 2**).

Endoscopic examinations revealed pathological findings that may cause ID/IDA in 69.3% (n=226) of the patients; however, no pathology was detected in 30.7% (n=100). While no pathology was found in 63.5% of the patients by EGD evaluations, erosive gastritis was the most common upper GIS pathology. No pathology was found in 42.7% (n=120) of the patients who had colonoscopy examinations and the polyps were the most common lesions (**Table 3**).

Celiac disease was diagnosed in 7 (10.9%) of 64 (20.1%) patients whose celiac biopsy was collected for screening. All these 7 patients had endoscopic appearance compliant to Celiac disease. Biopsy was collected from 213 (67%) of 318

patients during the EGD examinations for the analysis of *Helicobacter pylori* (HP) and pathological examination. Among these patients, HP was detected in 62.4% (n=133), and atrophy in 27.2% (n=58) of the patients (**Table 3**).

Anamnesis of the patients who had no pathology in the endoscopic examinations revealed that 5 patients were blood donors and 1 patient had medical leech and cupping therapies (**Table 3**).

Forty-three (13.2%) patients had EGD only, 8 (2.5%) patients had colonoscopy only, and 275 (84.4%) patients had EGD and colonoscopy (bidirectional) examinations. Detection of any pathology that may cause ID/IDA endoscopically was significantly more in the bidirectional examination group (43.1%) when compared to patients who had unidirectional procedure (74.2%) (p<0.01) (**Table 4**). Furthermore, 48 (17.5%) patients who underwent EGD and colonoscopy together revealed concomitant pathologies that may cause ID/IDA (**Table 3**).

When the patients were grouped according to the age as below 50 years (n=93) and above 50 years (n=233), no statistically significant difference was found between the groups for gender, NSAID use, malignancy, celiac disease, HP positivity, and atrophy (p>0.05). In the patient group above 50 years of age, findings such as comorbid diseases, use of anticoagulants, bidirectional endoscopic procedures, endoscopic diagnosis, concomitant pathology in the lower and upper GIS were detected more in the group younger than 50 years (p<0.001). The rate for biopsy from the duodenum was higher in the group younger than 50 years than the other group (p<0.001) (**Table 5**).

The analyzes in **Table 5** were made by grouping female patients as younger than 50 years old and 50 years and above (**Table 6**).

Table 1. Demographic characteristics of the patients

		n	%
Age (years)	Min-Max (Medyan)	18-89	
	Mean±Sd	56.85±14.52	
	≤ 50 age	93	28.5
	≥ 50 age	133	71.5
Gender	Female	144	44.2
	Male	182	55.8
Comorbid diseases	No	135	41.4
	Ischemic heart disease	40	12.5
	Diabetes mellitus	55	16.9
	Hypertension	59	18.1
	COPD	2	0.6
	CVA	2	0.6
	Liver cirrhosis	8	2.5
	Arrhythmia	5	1.5
	Other	20	6.1
Antithrombotic drug use	No	245	75.2
	Acetyl salicylic acid	40	12.3
	Clopidogrel	19	5.8
	Warfarin	2	0.6
	Apixaban	3	0.9
	Acetyl salicylic acid + Clopidogrel	4	1.2
	Acetyl salicylic acid + Ticagrelor	7	2.1
	Other	6	1.8
NSAID use	Yes	107	32.8
	No	219	67.2

COPD: chronic obstructive pulmonary disease, CVA: cerebrovascular accident

Table 2. Laboratory parameters of patients with DE / IDA

	Min-Max	Mean±Std. Deviation
Hemoglobin (g/dL)	5.7-15.3	11.61±1.85
Hematocrit (%)	19.8-48.7	36.7±4.8
Platelet (x109)	87000-668000	262760±79.8
MCV (fL)	53.4-98.8	79.1±7.4
Serum Iron (ug / dL)	6-207	44.1±30.7
TIBC (ug / dL)	55-731	370.74±88.5
Serum Ferritin (ug / L)	1.5-169	14.92±17.3
Vitamin B12 (ng / L)	100-2000	360.16±223.3
Folate (ug / L)	1.7-304	11.8±26.4
FOBT	10	
Stool parasite (n: 65)	2	

MCV: Mean corpuscular volüme, TIBC: Total iron binding capacity, FOBT: Fecal occult blood test

Table 3. Endoscopic examination findings in all patients with iron deficiency

		n	%
Endoscopic procedure	Endoscopy	43	13.2
	Colonoscopy	8	2.5
	Endoscopy + Colonoscopy	275	84.4
Endoscopy findings (n: 318)	No pathology	202	63.5
	Gastric ulcer	15	4.7
	Erosive Gastritis	32	10.1
	Duodenal ulcer	9	2.8
	Gastric cancer	5	1.6
	Polyp	17	5.3
	Angiodysplasia	4	1.3
	GIST	2	0.6
	Esophagitis	11	3.5
	PHG / Varicose Veins	5	1.6
	Celiac disease	7	2.2
	Operation history	9	2.8
Colonoscopy findings (n: 281)	No pathology	120	42.7
	Polyp	56	19.9
	Colon cancer	5	1.8
	Hemorrhoids	46	16.4
	Angiodysplasia	11	3.9
	Solitary rectal ulcer	2	0.7
	Colon diverticulum	18	6.4
	Colitis / ileitis / IBD	7	2.5
	Anal fissure	16	5.7
Simultaneous pathology in upper and lower GIS (n: 275)	Yes	48	17.5
	No	227	82.5
Diagnosis by endoscopic examination	Yes	226	69.3
	No	100	30.7
Celiac biopsy (n: 318)	Yes	64	20.1
	No	254	79.9
HP biopsy (n: 213)	There is	133	62.4
	No	80	37.6
Atrophy (n: 213)	There is	58	27.2
	No	155	72.8
Other Causes	Phlebotomy	5	1.5
	Leech therapy / cupping theraphy	1	0.3

GIST: Gastrointestinal stromal tumor, PHG: portal hypertensive gastropathy, IBD: inflammatory bowel disease, HP: *Helicobacter pylori*.

Table 4. Endoscopic diagnosis by unidirectional and bidirectional endoscopic examination

		Endoscopic procedure		p
		Gastroscopy / Colonoscopy (n:51)	Gastroscopy + Colonoscopy (n:275)	
Endoscopic diagnosis	Yes	22 (43.1%)	204 (74.2%)	0.0001[a]
	No	29 (54.9%)	71 (25.8%)	

[a]Pearson Chi-Square

Table 5. Endoscopic examination findings of the patients according to age

		≤50 age (n:93)	> 50 age (n:233)	p
Gender	Female Male	42 (45.2%) 51 (54.8%)	102 (43.8%) 131 (56.2%)	0.82[a]
Comorbid diseases	Yes No	24 (25.8%) 69 (74.2%)	167 (71.7%) 66 (28.3%)	0.0001[a]
Antithrombotic drug use	Yes No	4 (4.3%) 89 (95.7%)	77 (33%) 156 (67	0.0001[a]
NSAID use	Yes No	32 (34.4%) 61 (65.6%)	75 (32.2%) 158 (67.8%)	0.7
Endoscopic procedures	Unidirectional Bidirectional	28 (30.1%) 65 (69.9%)	23 (9.9%) 210 (90.1%)	0.0001[a]
Duodenal biopsy (n:318)	received not received	46 (49.5%) 47 (50.5%)	18 (8%) 207 (92%)	0.0001[a]
Endoscopic diagnosis	Yes No	51 (54.8%) 42 (45.2%)	175 (75.1%) 58 (24.9%)	0.001[a]
Malignancy diagnosis	Yes No	1 (1.1%) 92 (98.9%)	11 (4.7%) 222 (95.3%)	0.19[b]
Celiac diagnosis (n:318)	Yes No	4 (4.3%) 89 (95.7%)	3 (1.3%) 222 (98.7%)	0.2[b]
Simultaneous pathology in upper and lower GIS	Yes No	4 (6.2%) 61 93.8%)	44 (21%) 166 (79%)	0.006[a]
Helicobacter pylori (n:213)	Positive Negative	51 (69.9%) 22 (30.1%)	82 (58.6%) 58 (41.4%)	0.1
Atrophy (n:213)	There is No	19 (26%) 54 (74%)	39 (27.9%) 101 (72.1%)	0.7
Phlebotomy/Leech therapy / cupping therapy	Yes No	6 (6.5%) 87 (93.5%)	0 233 (100%)	0.0001[b]

[a]Pearson Chi-Square, [b]Fisher's Exact Test, NSAID: non-steroidal anti-inflamatuar drug

Table 6. Endoscopic examination findings of patients by age in women

		≤50 age (n:42)	> 50 age (n:102)	P
Comorbid diseases	Yes No	11 (26.2%) 31 (73.8%)	78 (76.5%) 24 (23.5%)	0.0001[a]
Antithrombotic drug use	Yes No	0 42 (100%)	29 (28.4%) 73 (71.6%)	0.0001[a]
NSAİD use	Yes No	17 (40.5%) 25 (59.5%)	40 (39.2%) 62 (60.8%)	0.88
Endoscopic procedures	Unidirectional Bidirectional	20 (47.6%) 22 (52.4%)	10 (9.8%) 92 (90.2%)	0.0001[a]
Duodenumdan biyopsi (n:141)	Yes No	19 (45.2%) 23 (54.8%)	8 (8.1%) 91 (91.9%)	0.0001[a]
Endoscopic diagnosis	There is No	21 (50%) 21 (50%)	71 (69.6%) 31 (30.4%)	0.002[a]
Malignancy diagnosis (144)	Yes No	1 (2.4%) 41 (97.6%)	4 (3.9%) 98 (96.1%)	0.1[b]
Celiac diagnosis (n:141)	Yes No	2 (4.8%) 40 (95.2%)	2 (2%) 97 (98%)	0.58 [b]
Simultaneous pathology in upper and lower GIS (n:114)	Yes No	0 22 (100%)	15 (16.3%) 77 (83.7%)	0.007[b]
Helicobacter pylori (n:93)	Positive Negative	23 (69.7%) 10 (30.3%)	35 (58.3%) 25 (41.7%)	0.27
Atrophy (n:93)	There is No	6 (18.2%) 27 (81.8%)	24 (40%) 36 (60%)	0.003

[a]Pearson Chi-Square. [b]Fisher's Exact Test

DISCUSSION

Iron deficiency anemia is the most common anemia type all over the world.[6] The cause for endoscopic examination is IDA in 4% to 13% of the patients.[7]

Both AGA and BSG guidelines stated that serum ferritin level is the strongest test to indicate iron deficiency. The guidelines determined the threshold level of ferritin for IDA as 15 ng/ml.[1,3] The mean ferritin level was detected 14.9 ng/ml in our study in line with the guidelines. The cause for higher ferritin level in our patients was initiation of iron replacement treatment by primary healthcare centers for the patients referred to our hospital (**Table 1**).

The most common cause of IDA is menstruation in premenopausal women, and blood loss from gastrointestinal system for men and post-menopausal women.[6] Bidirectional endoscopy is recommended by BSG and AGA guidelines for post-menopausal female patients and male patients with IDA.[1,3]

Çetinkaya et al.[7] detected the rate of not finding any pathology that may be cause of IDA in patients who underwent unidirectional procedures as 18.75% in gastroscopy and 46.55% in colonoscopy. However, the rate of not finding any pathology for bidirectional procedures was found 3.48%.

In the study above, gastroscopy was performed in 59% of the patients, colonoscopy was performed in 23.8% of the patients, and both procedures were performed together in a very small portion by 17.2%.[4] In our study, majority of the patients underwent bidirectional procedures in line with the guidelines (84.4%). Bidirectional endoscopic examination was recommended for most of the patients who had only underwent EGD; however, some patients did not accept colonoscopic examination. Detection of any etiological cause for ID/IDA during endoscopic examinations was significantly more in the bidirectional examination group (74.2%) when compared to patients who had EGD or colonoscopy individually (43.1%) ($p<0.001$).

Presence of any significant cause for bleeding in upper and lower GIS (double pathology) was reported in 1% to 10% of the patients.[1] Hovewer, in our study 48 (17.5%) patients who underwent EGD and colonoscopy together revealed concomitant pathologies that may cause ID/IDA.

Many possible causes exist in the etiology of IDA; however, gastrointestinal system malignancies are primary diagnoses that should be noted.[4] In a meta-analysis including 18 studies on the diagnostic efficiency of bidirectional endoscopy in postmenopausal women and men with IDA, the malignancy rate in the lower GIS was 8.9% and in the upper GIS was 2%.[8] Furthermore, a previous study including 695 patients detected malignancy in the GIS in 11.2% of the patients. In that study above, risk factors were age above 50 years, a Hb level at and below 9 gr/dl, and male gender.[9] Unal et al. detected that 0.9% of the patients who underwent EGD, and 4.7% of the patients who underwent colonoscopy were diagnosed with adenocancer. Yaylaci et al. detected that gastric cancer was detected in 10 (7.7%) patients by EGD, and in 6 (9.5%) patients by colonoscopy. In our study, malignancy was detected in 3.8% (n=12) of the patients. These were gastric adenocancer (n=5), GIST (n=2) and colonic adenocancer (n=5). Malignancy rates were found lower than those reported in the literature. We considered the possible cause as our study population including those with both anemia and iron deficiency. In addition, exclusion of patients with active bleeding from the study may be effective in this situation.

Age is the strongest predictor of the pathology in patients with IDA. It was stated that age over 50 years is a significant risk factor for malignancy.[1,10] The BSG guideline recommends colonoscopy in women under the age of 50 years, if there are colonic symptoms, strong family history, or if there is an ongoing IDA despite iron replacement therapy; however, the AGA guideline recommends bidirectional endoscopic examination in asymptomatic premenopausal women with IDA.[1,3] When female patients were grouped according to the age as below 50 years (n=42) and above 50 years (n=102) in our study, no statistically significant difference was found between the groups for gender, NSAID use, malignancy, celiac disease, HP positivity, and atrophy ($p>0.05$). One female patient below 50 years was diagnosed with gastric cancer. Findings such as comorbid diseases, use of anticoagulants, the rate for diagnosis established endoscopically, concomitant pathology in the lower and upper GIS, and the rate of atrophy in biopsy samples collected during EGD were detected more in the patient group at and above 50 years of age. The higher rates of diagnosis established endoscopically in patients older than 50 years of age supported the recommendation of BSG guideline for avoiding unnecessary endoscopic examination and possible complications.

However, due to the lack of difference between the malignancy rates between the groups, the lower complication rate and lower endoscopic procedure costs in our country, it seems reasonable to perform bidirectional endoscopic examination according to the recommendation of the AGA guideline.

Celiac disease is a well-known cause for IDA even in asymptomatic patients and should be noted for differential diagnosis of IDA.[3] The BSG and AGA guidelines recommend serological tests for Celiac disease in patients with IDA, and small intestine biopsy if the serological test is positive (1,3). In the study conducted by Emami et al., the frequency of celiac disease was found 10% in duodenal biopsy samples collected from 130 patients with ID without visible explanatory endoscopic findings. Unal et al. detected the rate for villous atrophy as 4.8% in their study.[4] Karnam et al. detected the prevalence of occult celiac disease as 2.8% in their prospective study including patients referred due to IDA (11).In line with the literature, the rate of Celiac disease was 2.2% in our study.

Helicobacter pylori (HP) infection is associated with atrophic gastritis and hypochlorhydria which may reduce iron absorption.[3] Hudak et al. reported in their meta-analysis including 14 studies that the probability of iron deficiency anemia is higher in individuals infected with HP when compared with those who were not infected by HP.[12] In addition, Lee et al. stated in their meta-analysis that the incidence of gastric cancer is lower in individuals who received eradication treatment for HP infection than those who did not receive any eradication treatment , and this was reported as a significant situation for ID treatment.[13] HP eradication is a consensus decision in unexplained IDA.[14] The AGA guideline recommends performing a non-invasive test for HP in patients with IDA without an identifiable etiology after bilateral endoscopic examination, and then, if positive, treatment without invasive testing. HP infection was detected in 35% of the patients with ID, and 51% of the patients with IDA in the study conducted by Cardenas et al. In that study above, Cardenas et al. stated that a significant part of ID and IDA prevalences (14% and 32%, respectively) may be associated with *H. pylori* infection.[15] Cetinkaya et al. found HP positive in 66% of the patients with pangastritis by gastroscopy.[7] In line with the literature, biopsy was collected from 213 (67%) of 318 patients during the EGD examinations for the analysis of

HP and pathological examination in the present study. Among the patients whom biopsy was taken, HP was detected positive by 62.4% (n=133), and eradication treatment was prescribed for those patients.

The AGA guideline recommends routine gastric biopsies to diagnose atrophic gastritis in patients with IDA.[3] The rate of atrophy was found significantly higher in patients with IDA compared to the control group in the study conducted by Kaye et al. (p <0.001). They suggested that gastric atrophy is strongly associated with IDA and that biopsies should be taken especially from the corpus part of the stomach.[16] Biopsy was collected from 213 (67%) of 318 patients during the EGD examinations in our study. Among the patients whom biopsy was taken, atrophy was detected in 27.2% (n=58) of the patients. No age difference was found between patients with and without atrophy in the anemic group in the study conducted by Kaye et al. When the patients were grouped according to the age as below 50 years and above 50 years in our study, no statistically significant difference was found between the groups (p>0.05). However, atrophy rate was more in female patient group over 50 years of age than those younger than 50 years. We thought that the possible cause might be related due to the higher rate of comorbid diseases in this group and the use of more proton pump inhibitors. However, we could not investigate this factor due to retrospective design of our study.

Gastrectomies and achlorhydria are two other important conditions that impair iron absorption. IDA is a very common condition in patients with partial or total gastrectomy.[17] Beyan et al. found IDA in 94.4% of the patients who underwent gastrectomy.[18] In our study, gastrectomy was found as an etiological cause in 2.8% (n=9) of 318 patients who underwent EGD.

The BSG guideline states that the fecal occult blood test (FOBT) is useless in the investigation of ID and IDA, and it is an insensitive and nonspecific test.[1] In our study, FOBT was performed in 29.4% (n=96) of all patients and only 10 (10.4%) of these patients were FOBT positive. The test being negative in 90% of the patients indicates that it is not useful as in the literature.

It was stated in the BSG guidelines that there was no significant difference in the prevalence of GI cancer in patients who received aspirin or warfarin alone or in combination when compared to patients who have not taken these drugs. Therefore, the guideline indicates that IDA should not be associated with such drugs until GIS researches are completed.[1] In our study, 24.8% of the patients had history of previous single or multiple anticoagulant drug use. Four (33.3%) patients whom malignancy was detected had history of concomitant use of anticoagulant/antiaggregant drugs.

The AGA guideline recommends the evaluation of underlying etiologies such as frequent blood donation, nutritional deficiencies (i.e., vegan or vegetarian diet), non-gastrointestinal blood loss and malabsorption syndromes.[3] It was determined in re-investigation of patients without any pathology endoscopically that 5 patients were blood donors and 1 patient had leech and cupping treatments.

Bidirectional endoscopy is an invasive procedure; however, overall risk of complication is lower in both upper endoscopy and colonoscopy.[3,19] In our study, no complications or mortality secondary to endoscopic procedures were observed in any patient in accordance with the literature.

A limitation of our study was retrospective design. Since we could not access all data, we could not make detailed evaluations. Therefore, further prospective studies under suggestions of the guidelines are required.

CONCLUSION

Upper and lower GIS endoscopy examinations are important and necessary diagnostic methods in the investigation of the ID etiology. Bidirectional endoscopic examinations according to guideline recommendations increase diagnostic efficiency compared to unidirectional examinations. Phlebotomy and traditional alternative medical treatments that cause blood loss in patients with no pathology should be questioned in the etiology.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Local Ethics Committee of Amasya University (approval number: 2020/E.11346).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

First Intervention in Firearm Injuries and Management of Compliations

Ateşli Silah Yaralanmalarında İlk Müdahale ve Komplikasyonların Yönetimi

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Abstract

Aim: Soft tissue, neurovascular injuries and bone fractures are seen in the extremity as a result of firearm injuries. The fact that these injuries are violent and that forensic incidents are more frequent, especially in young people, make treatment more difficult. Our aim in this study is to evaluate the effects of a stepwise approach to neurovascular, soft tissue injuries and bone fractures on the final treatment results in firearm-related musculoskeletal injuries.

Material and Method: This study retrospectively evaluated patients over the age of 18 who had firearm-related extremity injuries and received surgical treatment between 2015 and 2020.Demographic characteristics of the patients, injury sites, accompanying neurovascular injuries, patients who received first aid, final treatment results, developing complications and management of the complications were evaluated.

Results: The mean age of 54 patients (52 males, 2 females) in the study was 28.3 (age range 19-61) years. Twenty-nine (53.7%) lower extremity, 20 (37.1%) upper extremity, and 5 (9.2%) both lower and upper extremity injuries were detected. Vascular injury was detected in 3 (5.5%) patients, amputation in 3 (5.5%) and nerve injury in 6 (11.1%) patients. Five (9.2%) of 6 patients, underwent fasciotomy in the early period because the development of compartment syndrome was highly anticipated. In one of the patients, fasciotomy was performed due to the development of the compartment syndrome during the follow-up. The most common complication we encountered was loss of joint range of motion in 7 (12.9%) patients.

Conclusion: Switching to definitive treatment after antibiotherapy, bone fixation and serial debridements in the early period with a multidisciplinary and damage-controlled approach to firearm injuries positively affects the success of treatment. In addition, necessary consents should be obtained to minimize medico-legal problems.

Keywords: Firearm injuries, neurovascular injury, fasciotomy, complications

Öz

Amaç: Ateşli silah yaralanmaları sonucu ekstremitede yumuşak doku, nörovasküler yaralanmalar ve kemik kırıkları görülmektedir. Bu yaralanmaların şiddete yönelik olması ve adli olayların gençlerde daha sık görülmesi tedaviyi daha da zorlaştırmaktadır. Bu çalışmadaki amacımız, ateşli silahlarla ilişkili ekstremite yaralanmalarında nörovasküler, yumuşak doku yaralanmaları ve kemik kırıklarına aşamalı bir yaklaşımın nihai tedavi sonuçlarına etkisini değerlendirmektir.

Gereç ve Yöntem: Bu çalışmada 2015-2020 yılları arasında ateşli silahla ilişkili ekstremite yaralanması olan ve cerrahi tedavi uygulanan 18 yaş üstü hastalar retrospektif olarak değerlendirildi. Hastaların demografik özellikleri, yaralanma bölgeleri, eşlik eden nörovasküler yaralanmalar, ilk müdalede yapılanlar, son tedavi sonuçları, gelişen komplikasyonlar ve komplikasyonların yönetimi değerlendirildi.

Bulgular: Çalışmaya katılan 54 hastanın (52 erkek, 2 kadın) yaş ortalaması 28,3 (yaş aralığı 19-61) idi. Yirmi dokuz (%53,7)'si alt ekstremite, 20 (%37,1)'si üst ekstremite ve 5 (%9,2)'i hem alt hem üst ekstremite yaralanması tespit edildi. Üç (%5,5) hastada damar yaralanması, 3 (%5,5) hastada amputasyon ve 6 (%11,1) hastada sinir yaralanması tespit edildi. Altı hastanın beşine (%9,2) fasyotomi uygulandı. En sık karşılaşılan komplikasyon olarak 7 (%12,9) hastada eklem hareket açıklığı kaybıydı.

Sonuç: Ateşli silah yaralanmalarında multidisipliner ve hasar kontrollü bir yaklaşımla erken dönemde antibiyoterapi, kemik tespiti ve seri debridmanlar sonrası nihai tedaviye geçilmesi tedavi başarısını olumlu yönde etkilemektedir.

Anahtar Kelimeler: Ateşli silah yaralanmaları, nörovasküler yaralanma, fasiatomi, komplikasyonlar

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INTRODUCTION

Recently, firearm injuries are among the most common causes of admission to emergency departments.[1] The type of firearm, the firing distance, the entry and exit points of the bullet, the characteristics of the injured area and tissues determine the treatment approach.[2,3] Successful results can be obtained with a multidisciplinary approach in the treatment of such complex injuries that affect many systems in the body. In the emergency room, basic life support is provided to the patients with firearm wounds as the first aid and then the intervention by the relevant branch is performed. Extremity wounds are common in firearm injuries.[4] Many complications such as soft tissue injuries, neurovascular injuries and bone fractures are seen in the extremity.Firearm injuries to the extremities more frequently occur in young people and medico-legal problems arise because they are forensic events.[5]

Management of the approach to these patients begins with the first medical and/or surgical intervention and continues until the end of the final treatment. With a multidisciplinary and stepwise treatment approach, first of all, control of the bleeding, and infection and then planning bone and soft tissue reconstruction reduce the morbidity rates.[5] Inter-institutional cooperation is needed to minimize complications and to prevent emerging possible medico-legal problems in such injuries.

Our aim in this study is to evaluate the effects of the approach to neurovascular structures, soft tissue debridements, prophylactic antibiotics and temporary and permanent fixation in bone fractures on the final treatment results as a first line treatment in the firearm-related extremity injuries.

MATERIAL AND METHOD

In this study, patients over the age of 18 who underwent surgical treatment and follow-up due to firearm -related extremity injuries between 2015 and 2020 were evaluated. This study, which was planned as a retrospective cohort study, included patients registered in the archives of our hospital due to a firearm injury, emergency physicians requested a consultation from the Orthopedics and Traumatology department and surgery was planned. Demographic characteristics of the patients, injured extremity, accompanying neurovascular injuries, orthopedic interventions from the first admission to the end of treatment and complications were evaluated.

After the first intervention in extremity injuries, radiographs, computed tomography (CT) and angiography are performed according to the general condition of the patient and the type of trauma (**Figure 1,2**).

All patients with extremity fractures as a result of gunshot wounds were evaluated according to the Gustilo and Anderson classification and the same protocols were applied.[6] The patients were priorly assessed with damage control approach specific to the type of trauma that occurred. Superficial tissue wounds were cleansed and debrided in the emergency room after bleeding control was achieved with a stepwise treatment approach.

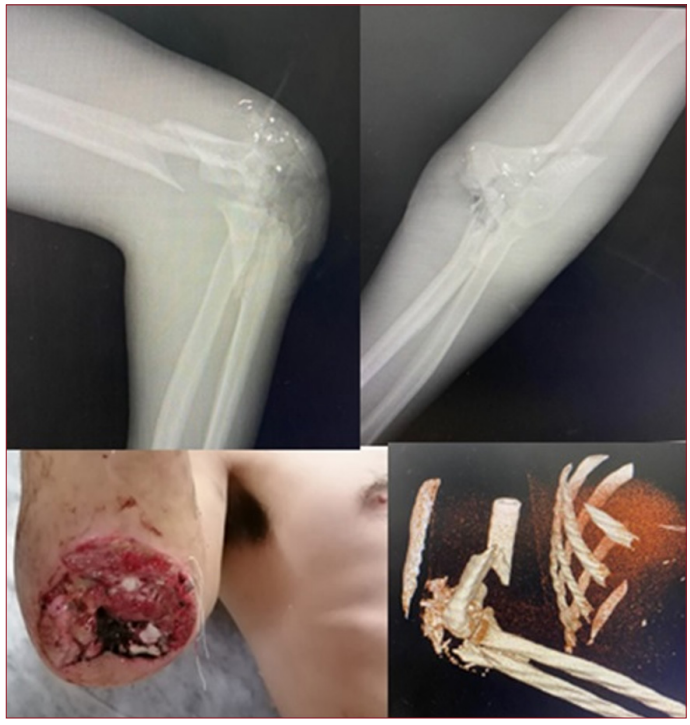

Figure 1. Radiography and CT of a patient with upper extremity injury

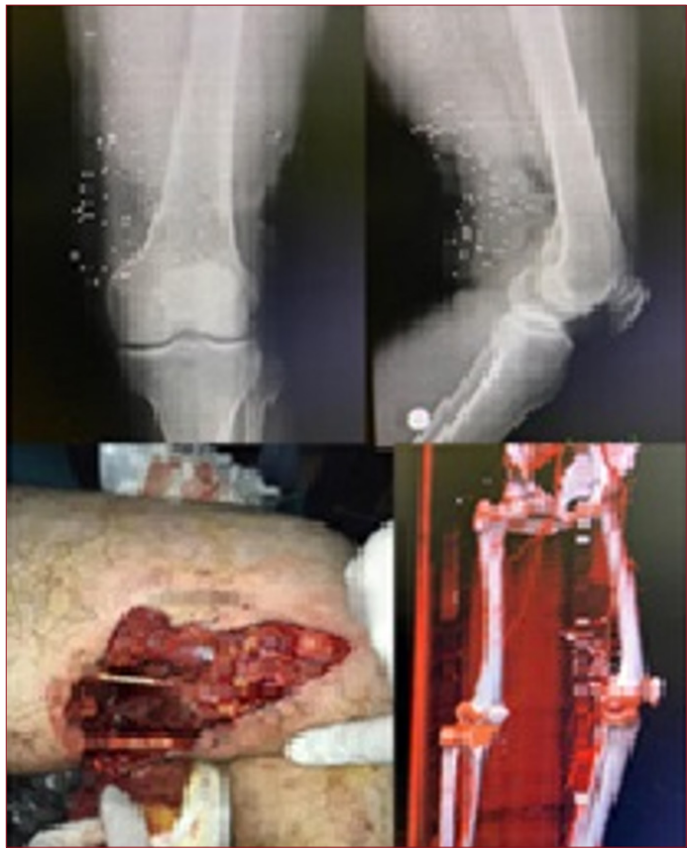

Figure 2. Radiography and Angiography of a patient with lower extremity injury

The entry and exit points of the bullet were closed with sterile dressing, then antibiotherapy and tetanus prophylaxis were administered. After hemodynamic stabilization was achieved in all patients at the first admission, antibiotics were started and continued for the first 48-72 hours. Depending on the condition of the wound, first-generation cephalosporin and aminoglycoside as a dual antibiotic, or metronidazole as a third antibiotic were added to the antibiotherapy of the patients with contaminated wounds. Patients with deep muscle and bone injuries were operated on and more detailed irrigation and debridement were performed.

Neurovascular and soft tissue injuries requiring reconstruction were evaluated in more detail in the operating room. While vascular injuries and total or near-total nerve cuts were primarily repaired, patients with neurological findings but nerve integrity, and contuinity were not intervened. Before and after all these procedures, the relevant forensic minutes and consent forms were obtained from the patient, if the patient was conscious, if not fromthe patient's relatives.

Statistics

Descriptive statistics for emphasized continuous variables were expressed as mean, and standard deviation, while for categorical variables it is expressed as numbers and percentages. SPSS (ver: 21) statistical package program was used for the calculations.

RESULTS

The mean age of 54 patients (52 males, 2 females) included in the study was 28.3 (age range 19-61) years. Twenty-nine (53.7%) lower extremity, 20 (37.1%) upper extremity, and 5 (9.2%) both lower and upper extremity injuries were detected. Demographic data of our patients are given in **Table 1**.

Table 1. Demographic data of the patients

	Male	Female	Total
Number of patients	52	2	54
Mean age	28.1	33.5	28.3
Lower extremity	29	0	29
Upper extremity	18	2	20
Lower and upper extremities	5	0	5

Vascular injury was present in 3 (5.5%) patients (Popliteal artery in two, and radial artery in one patient) and vascular reconstruction was performed by a vascular surgeon, and no complications developed. Temporary fixation was performed with external fixator in 11 of 17 patients with bone fractures, while osteosynthesis was performed with intramedullary nailing as definitive treatment in 4 patients and with plate-screw in 2 patients. Three of these patients underwent amputation. Forearm -elbow amputation was performed in one, and below-knee amputation was performed in two patients. MESS (Mangled Extremity Severity Score) criteria were used when making the decision of amputation.[7,8] Neurological findings due to nerve injury were detected in 6 (11.1%) patients.

Primary nerve repair was performed when a total transection of the nerves was detected in two patients (one median and one ulnar nerve) during the operation. Four of our patients had preoperative signs of neurologic injury (wrist drop due to radial nerve damage in three patients and foot dropdue to peroneal nerve damage in one patient) and nerve exploration was not performed for these patients and they were followed up. Nerve regeneration was achieved in two of three patients with radial nerve damage within six months, and tendon transfer was performed in one patient one year later, when symptoms of wrist drop persisted. In the patient with peroneal nerve injury, tendon transfer was carried out for the ankle when there was no recovery within one year.Serial soft tissue debridements were performed three times in three patients with large tissue defects at the injury site and twice in two patients before soft tissue reconstruction. Complications seen in the patients are given in **Table 2**.

Table 2. Complications due to firearm injuries

	Lower extremity	Upper extremity
Compartment syndrome	4	2
Vascular injury	Popliteal artery (2)	Radial artery
Nerve injuries	1 (Peroneal)	5 (3 Radial, 1 Ulnar, 1 Median)
Amputation	2 (Below-knee amputation)	1 (At the level of wrist)
Non-union	2	1
Loss of range of joint movement	3	4

Since the likelihood of the compartment syndrome was high in five patients, fasciotomy was performed in the early period. In one of our patients, fasciotomy was performed due to the development of compartment syndrome during the follow-up. The surgical wounds of two of the patients who underwent fasciotomy were closed primarily, while the other two required skin grafts. Non-union developed in 3 (5.5%) of the patients. In our patient with non-union humerus fracture, osteosynthesis was performed with iliac wing graft and plate-screw, while intramedullary fixation was performed on two tibial non-unions using thicker nails.

One of the complications most frequently encountered by us was loss of range of motion. Limitation of joint movement was detected in 7 (12.9%) patients. Patients showing resistance to manipulations were manipulated under anesthesia and functional range of motion was achieved after physical therapy applications. However, severe limitation of motion at the elbow persisted in one patient.

DISCUSSION

Incidence rates of firearm injuries are increasing worldwide.[4,9] They occur especially in men under the age of 40 and extremity injuries are common.[4,10,11] Similar to the literature, it was mostly seen in young men in our study. In our center, most of the patients with gunshot wounds were treated with stepwise

treatment protocols. As a stepwise treatment approach, after damage control, the wound is closed after superficial debridement and washing as the first intervention in the emergency room, and antibiotics and tetanus prophylaxis are given.

More detailed debridement and permanent or temporary bone fixation are performed in the operating room. In patients followed up in the service after the first intervention, treatment is planned depending on the severity of the trauma and the response of the patient. The use and duration of antibiotics in gunshot wounds is widely discussed in the literature.[9,11,12] It is mostly accepted as type 3 according to the Gustilo-Anderson classification and antibiotics are recommended.[6] However, there is no consensus in the literature regarding the duration of antibiotic use, and there are studies recommending it to be used between 48-120 hours.[13] Antibiotics were used in all patients for the first three days. Depending on the condition of the wound, first-generation cephalosporin and aminoglycoside as a dual antibiotic, or metronidazole as a third antibiotic were added to the antibiotherapy of the patients with contaminated wounds.

Debridement and temporary external fixation or permanent internal fixation are recommended for these injuries.[3,4,8,14,15] However, discussions on fixation type continue in the literature. In some studies, external fixation has been recommended in high-energy traumas and internal fixation in low-energy traumas.[9,12] In another study, internal fixation was recommended after stabilization of general condition and hemodynamic parameters of the patients was achieved.[11]

In the studies performed, it was determined that the living tissues in the wound area became devitalized in the follow-ups after the first debridements. It was found that removing the dead tissues by performing serial debridements on devitalized tissues significantly reduced the infection.[11,13,14,19] In our patients, both internal and external fixation were applied according to the general condition, hemodynamics, type of injury in the extremity and the general condition of the patient. Permanent fixation was performed after adequate debridement in patients with adequate soft tissue coverage. Temporary external fixation was applied to our patients without adequate coverage of soft tissue or who needed more than one debridement. Plate-screw osteosynthesis was performed as internal fixation in two patients with intra-articular fractures with suitable soft tissue components. In the literature, slow healing of fractures due to firearm injuries is seen at rates between 5% and 8%.[15] Non-union developed at a similar rate in our cases. Successful results were obtained after the second surgical intervention was performed in our patients who developed non-union.

The most common complication in patients was joint stiffness and related limitation of joint range of motion. In the formation of this situation, the main reason was the injury near the joint or the formation of intra-articular comminuted fractures. In addition, it was observed that the physical therapy and rehabilitation program of the patients was not followed very well in the postoperative follow-ups in our region. All patients with joint stiffness were manipulated under anesthesia, but open surgery was not performed. It is thought that this may play a role in the limitation ofjoint range of movement.

A rate of 3-10% is given regarding the development of compartment syndrome after a firearm injury.[20] In most of our cases, fasciotomy was performed previously in patients with anticipated compartment syndrome. In this type of injuries, fasciotomy is recommended in patients with suspected compartment syndrome due to impaired circulation in the extremities and late effects of gunshot injury.[20] In our study, no serious complication was encountered after this treatment approach to compartment syndrome.

Since neurovascular and bone structures are close to each other, injury to any component increases the risk of injury to the other component.[12] In order to accelerate the treatment in such critical injuries, when vascular injury is suspected,angiography and/or surgical exploration is recommended in the absence of palpable pulse, but in the presence of signs of ischemia, excessive bleeding or an enlarging hematoma.[21,22] Vascular injuries are repaired in the early period, but surgical approach is not recommended for nerve injuries. Since most of the nerve injuries are detected as neuropraxia and axonotmesis, in the literature their spontaneous recovery is reported to be high within 3-9 months.[22,23]

Vascular reconstruction was performed in two popliteal and one radial artery injury in our patients. Spontaneous relapses occurred in most of our cases with neurological injuries. However, in two of our patients, the neurologic injuries did not heal, and the related tendon transfers were performed at the end of the first year. Our most serious complication was amputations in three of our patients. The decision of these amputations was made on the basis of the Mess score scoring criteria.[7,8] The patients were consulted to the psychiatry, physical therapy and rehabilitation and orthotics-prosthesis departments with a multidisciplinary approach for the problems they would experience due to loss of an extremity before amputation.

CONCLUSION

In summary, although there is no consensus in the literature on debridement in gunshot wounds, bone fixation technique, antibiotic prophylaxis, and approach to neurovascular injuries in firearm injuries, the most common opinion dictates bleeding control with a multidisciplinary approach after damage detection, serial debridements, antibiotherapy, bone stabilization, appropriate approach to neurovascular injury, intensive rehabilitation and appropriate follow-up.

Individualized treatment planning with a multidisciplinary, damage-controlled and stepwise treatment approach will increase success in traumas due to gunshot wounds. In addition, we believe that in this period, the medico-legal problems that may occur will be minimized by informing the patients in detail and taking the records regularly.

Limitation

There are several limitations in our study. It is retrospective, the number of patients is small, and the type and distance of the firearm is not known.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Van Yüzüncü Yıl University Non-interventional Clinical Research Ethics Committee, Decision no:2021/06-05.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

Is Laparoscopic Surgery Safe During the Pandemic Period?

Pandemi Döneminde Laparoskopik Cerrahi Güvenli Mi?

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Abstract

Aim: The COVID-19 pandemic has significantly affected healthcare service systems worldwide. Important decisions have been made such as cancelling elective surgery, and shifting surgeons to other medical activities. However, following the collection of new data firstly elective cases and then laparoscopic operations were started again. While it was reported that the Covid-19 virus was detected in the abdominal cavity, there is no clear information about the virulence of this detected virus yet. We aimed in this study to show minimally invasive surgery is safe with all the precautions made preoperatively for both patients and surgical crew.

Material and Method: We retrospectively examined the laparoscopic cases included between August 2020 and December 2020 at the General Surgery Clinic of the Hitit University Erol Olçok Research and Training Hospital. We collected the demographic data, their preoperative Covid diagnostic tests, and their Covid Outpatient Clinic data in their postoperative follow-up. We also examined whether or not the surgical team involved in the surgeries of these patients was diagnosed with Covis-19 within 2 weeks following these surgeries.

Results: A total of 124 laparoscopic cases were performed between August 2020 and December 2020. The patients were followed up for a minimum of 1 month in the postoperative period. Nine patients applied to the Covid Outpatient Clinic with mild complaints in the postoperative period and the PCR test of 3 patients was positive. These 3 patients received Favipiravir treatment on an outpatient basis, the other patients were followed up on an outpatient basis with symptomatic treatment. No patient was hospitalized. Based on verbal questioning, it was determined that no personnel from the surgical team involved in these surgeries was infected with Covid-19.

Conclusion: We think that laparoscopic surgery can be performed safely with taking the necessary precautions during the Covid-19 pandemic period.

Keywords: Laparoscopy, COVID-19, pandemic, minimally invasive surgery

Öz

Amaç: Covid-19 pandemisi bütün dünyada sağlık sistemini önemli bir şekilde etkilemiştir. Pandemi başında küresel olarak önemli kararlar verilmiştir. Bu kararlar içinde elektif ameliyatların durdurulması ve cerrahların başka birimlerde görevlendirilmesi de vardır. Yeni bilgiler ışığında pandeminin birkaç yıl sürebileceği ve pandemi kısmen de olsa kontrol altına alındıkça önce elektif ameliyatlara sonra da laparoskopik vakalara tekrar başlanma kararı alınmıştır. Covid-19 virüsü abdominal kavitede tespit edilmiş olup bu tespit edilen virüsün virulansı ile ilgili bir bilgi henüz doğrulanmamıştır. Cerrahi birliklerin yayınladıkları kılavuzlar doğrultusunda gerekli önlemlerin alınması ile minimal invaziv cerrahilerin yapılabileceği ancak pozitif vakalarda açık/konvansiyonel cerrahinin tercih edilmesi gerektiği vurgulanmıştır. Biz de bu bilgiler ışığında gerekli önlemlerle birlikte laparoskopik ameliyatların hem hasta hem de cerrahi ekip açısından ek bir risk oluşturup oluşturmadığını bulmayı hedefledik

Gereç ve Yöntem: Ağustos 2020 ile Aralık 2020 tarihlerinde Hitit Üniversitesi Erol Olçok Eğitim ve Araştırma Hastanesi Genel Cerrahi Kliniği'nde gerçekleştirilen laparoskopik vakaları geriye yönük olarak taradık. Hastaların demografik verileri, preoperatif Covid test sonuçları ve postoperatif 1 aylık dönemde Covid tanısı konulup konulmadıklarını inceledik. Aynı zamanda bu tarihler arasında laparoskopik cerrahiye katılmış cerrahi ekipleri de bu vakalar sonrasındaki 2 haftalık süreçte Covid tanısı açısından sorguladık.

Bulgular: Belirtilen tarihler arasında toplamda 124 laparoskopik vaka yapıldığı ve bu vakaların büyük çoğunluğunu (%68,5) kolesistektomilerin oluşturduğunu tespit ettik. Hastalar postoperative dönemde minimum 1 ay takip edilmiştir. Dokuz hasta postoperative dönemde hafif şikayetlerle Covid Polikliniğine başvurmuş ve 3 hastanın PCR testi pozitif gelmiştir. Bu 3 hasta ayaktan Favipiravir tedavisi almıştır, diğer hastalar semptomatik tedavi ile ayaktan takip edilmişlerdir. Hiçbir hastanın hastane yatışı olmamıştır. Ayrıca, ameliyat ekibi için yapılan sorgulamada bu ameliyatlara dahil olan ekipten hiç kimsede Covid-19 enfeksiyonu olmadığı saptanmıştır.

Sonuç: Covid 19 virüsünün laparoskopik cerrahi ile sağlık personeline kontamitasyonu gösterilmemiş olmakla beraber bu konuda yeterli çalışma yapılmamıştır. Çalışmamız sonucunda Covid 19 pandemisi döneminde gerekli önemler alınması durumunda laparoskopik cerrahinin güvenle yapılabileceğini düşünmekteyiz.

Anahtar Kelimeler: Laparoskopi, Covid-19, pandemik, minimal invaziv cerrahi

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INTRODUCTION

After its definition in December 2019, the coronavirus disease 2019 (COVID-19) rapidly became a global emergency. The novel human coronavirus causing COVID-19 has since been named the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] The COVID-19 pandemic has significantly affected healthcare service systems and personnel worldwide. Important decisions have been made, such as surgical activity changes, recommendations to cancel elective surgery, and shifting surgeons to other medical activities.[2] Besides this, indications were going on for the surgical treatment of emergency cases and oncology patients. The laparoscopic procedure that had been previously applied in these surgeries led to prejudiced concerns in some people due to the respiratory spread of the COVID-19 virus. While there is no official evidence that the aerosols of the coronavirus that occur during laparoscopic procedures may be dangerous, it is recommended protective preventions must be applied for patients and surgical teams.[3]

The first case in Turkey was seen in March 2020, and cases continue to be prevalently observed. The effect of the SARS-CoV-2 pandemic on surgical branches started between the end of March and June where elective surgical operations were reduced in numbers, and only emergency and malignancy operations were carried out due to the lack of sufficient data and existing uncertainties. However, following the collection of new data and acceptance that this pandemic would last for at least a few years, firstly elective cases and then laparoscopic operations were started again. While it was reported that the COVID-19 virus was detected in the abdominal cavity in studies published in the form of series of a few cases, there is no clear information about the virulence of this detected virus yet. Therefore, the place of laparoscopy in this disease, where aerosolization is especially highly effective in infection, has not gained clarity yet. The benefit of this method that may put especially the surgical team at risk for the postoperative period of the patient is an undeniable fact. Additionally, as it provides immune suppression during the recovery period of the surgical process, it was speculated that SARS-CoV-2 infection would progress more severely in the postoperative period. In guidelines published as recommendations by surgical associations, it is stated that it could be performed by taking the necessary precautions, but open surgery needs to be preferred in positive cases. At the General Surgery Clinic of the Hitit University Erol Olçok Research and Training Hospital, all cases are questioned regarding contact, and preoperative COVID PCR tests are conducted on all elective cases. This test is taken from emergency cases postoperatively, and it is taken before the surgery if semi-emergency cases such as appendicitis visited the hospital in the daytime. Elective patients whose tests come out positive are taken in for treatment by the COVID unit and then discharged, while emergency cases are taken into surgery in a particular operating room allocated for COVID-positive patients by using the required personal protective equipment. Positive cases do not receive laparoscopic procedures. We also started laparoscopic cases again in August, where the pandemic numbers been relatively lower, and aimed to share our experience of 4 months. Additionally, the COVID infection statuses of these patients in the postoperative period were assessed. Moreover, by evaluating the COVID-19 virus infection rates of the surgical personnel in a 2-week process following these laparoscopic cases and examining their status of catching the COVID-19 virus during laparoscopy, we aimed to assess the safety of laparoscopic surgeries.

MATERIAL AND METHOD

This study has obtained approval from the Hitit University Ethics Committee (Application number: 2021-76, Decision No: 2021-66, Date: April 2021). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

We retrospectively examined the laparoscopic cases included between August 2020 and December 2020 at the General Surgery Clinic of the Hitit University Erol Olçok Research and Training Hospital from the hospital's information system. We collected the ages of the found cases, their preoperative COVID diagnostic tests, and their COVID outpatient hospital visit data in their postoperative follow-up. All surgical team (surgeons, anesthesiologists, nurses, and other operating room personnel) had received an educational briefing about recommended precautions about COVID-19 according to the up-to-date guidelines. We also examined whether or not the surgical team involved in these patients' surgeries was diagnosed with COVID-19 within two weeks following these surgeries. Precautions applied according to the guidelines; Each patient received surgery under pneumoperitoneum at a pressure of 12 mmHg. Electrocauterization usage kept at a minimum level. At the end of the operation, the gas was evacuated from the abdomen with the help of a closed exhaust system, and it was aimed to minimize its spread inside the operating room. The entire surgical team involved in the surgery wore FFP2 N95 facemasks over a surgical mask and wore one additional surgical mask over these. Using surgical protective goggles and protective face shields varied from person to person, and their usage was decreased in time. Routinely, all patients who planned to undergo surgery were tested with COVID-19 PCR (polymerase chain reaction) test, and if its result is positive, the operation was canceled and postponed to another date.

RESULTS

A total of 124 laparoscopic cases were included at our clinic between August 2020 and December 2020. Most of these cases (68.5%) were laparoscopic cholecystectomy cases. Other cases are presented in detail in **Table 1**. The ages of the patients varied between 18 and 87, and their median age was 49. A total of 124 laparoscopic cases were included at our clinic between August 2020 and December 2020. Most of these cases (68.5%) were laparoscopic cholecystectomy cases.

Table 1. List of laparoscopic operations

Operation	Frequency	Percent (%)
Appendectomy	4	3.2
Bridectomy	1	0.8
Anterior resection	1	0.8
Right hemicolectomy	1	0.8
Inguinal hernia repairs (TEP*/TAPP**)	28	22.6
Cholecystectomy	85	68.5
Diagnostic	2	1.6
Low anterior resection	2	1.6

*: Totally extraperitoneal, **: Transabdominal pre-peritoneal)

The surgical team comprised the surgical nurse and operating room personnel under the leadership of the surgeon. Based on verbal questioning, it was determined that no person from the team involved in these surgeries was infected with SARS-CoV-2.

DISCUSSION

In December 2019, in the city of Wuhan in the Hubei province of China, a viral pneumonia epidemic connected to a new coronavirus (2019-nCoV / SARS-CoV-2) occurred.[4] The virus quickly took the entire world under its effect especially as it is transmitted through respiratory airways. Because of this reason, the virus poses a high risk for healthcare workers who work in environments where aerosols are produced. Environments that are at risk of aerosol contamination involve intubation, extubation, chest tube placement, bronchoscopy, gastrointestinal endoscopy, laparoscopy, and the use of energy devices like electrocautery. Pneumoperitoneum is an indispensable component of laparoscopic surgery; however, it brings about the risk of the surgical team being exposed to aerosols.[5] Aerosol exposure mostly occurs during entry and removal of trocars, tool entries and removals, and evacuation of the gas during and after the operation. Due to the leaking of pneumoperitoneum gas that may contain high concentrations of suspended viruses, the contamination risk of the operating room personnel may be increased by laparoscopy.[6] On the other hand, a closed surgical site (abdomen, thorax, etc.) reduces the risk of contamination, and there is no certain evidence yet in the literature on the viral infection of COVID-19 during laparoscopy.[5] Although there is evidence on the detection of SARS-CoV-2 in peritoneal fluid, the information on the virulence and infection capacity of this virus is not yet clear.[7]

During laparoscopic surgery, especially for hemostasis and dissection, electrocautery, ultrasonic dissectors, and laser ablation devices are used. Ultrasonic dissector use produces bio-aerosol-containing surgical smoke besides living and inanimate cellular material. This surgical smoke poses a risk of viral infection and leads to lung irritation, causing acute and chronic inflammatory changes.[8] While the aerosolization of viruses with electrocautery devices is a danger for human health, whether or not the COVID-19 virus is aerosolized in the abdomen is not known so far. Additionally, as these electrocautery devices used in laparoscopy are also used in open operations, it is more difficult to control aerosol distribution in open operations. Therefore, in terms of virus infection, we think open operations are riskier compared to laparoscopic and robotic surgeries.

In both conventional and laparoscopic surgery, minimizing the use of electrocautery and avoiding certain devices like ultrasonic dissectors may reduce the aerosolization of particles and this way reduce the potential viral emission risk.[9] In our operations, we also tried to use devices like electrocautery devices to a minimum extent by performing dissections with laparoscopic surgical scissors as much as possible.

Aerosolization of viruses that are transmitted through blood like the Hepatitis B virus, HIV (Human Immunodeficiency Virus), and HPV (Human Papilloma Virus) was previously detected in surgical smoke during laparoscopy.[10] However, infection with surgical smoke was shown only with HPV. Until now, the COVID-19 virus has not been detected in surgical smoke, and infection with laparoscopy has not been shown. As a result of our study, too, no contamination of the surgical team was observed in any of the 124 laparoscopic surgical interventions.

Contamination of healthcare workers with SARS-CoV-2 during laparoscopy has not been reported yet, but researchers recommend careful precautions for healthcare workers to avoid the risk of contamination during the pandemic process.[9] At our hospital, we had also stopped elective surgeries and laparoscopic operations at the first stage when the pandemic started. However, with the extension of the process and continuation of the pandemic, we started to provide services again for patients who had regular healthcare needs. As soon as we started surgeries again, the entire surgical team used the recommended personal protective equipment to protect themselves during surgeries. Upon the fact that there was no case of infection related to laparoscopy in the literature concerning this particular virus, laparoscopic operations were also started by using protective equipment, and considering all 124 laparoscopic cases, COVID-19 infection was not observed in any healthcare personnel within the 2 weeks following the surgeries. When the hospitalization, preoperative and postoperative periods of the 124 patients were examined, no patients displayed COVID-19 symptoms within the 2 weeks following the surgeries. Only 9 patients showed symptoms after 6 weeks after surgery, visited the hospital for COVID-19 PCR tests, and only 3 of these patients turned out positive. These 3 patients experienced the disease mildly by receiving outpatient treatment.

The benefits of laparoscopy compared to open operations have been known for a certain time. Some publications argued that, during the COVID-19 pandemic, open surgeries last shorter.[11] However, studies have also revealed that there is no significant duration difference between the two techniques of the operations are performed by laparoscopic surgical experts.[12] In our study, too, all surgeries were performed by surgeons with laparoscopy experience, and there was no duration difference.

While the debate on laparoscopic surgery in the COVID-19 pandemic period is going on, the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) recommends laparoscopic and robotic surgery to be performed with CO_2 filtration devices.[13] Moreover, the Association of Laparoscopic Surgeons of Great Britain and Ireland (ALSGBI) supports the use of laparoscopy, while the American College of Surgeons (ACS) argues that there are not enough data to recommend one of open or laparoscopic surgery over the other, and surgeons need to apply the approach that minimizes the duration of the operation and maximizes safety.[14,15]

CONCLUSION

While contamination of healthcare personnel with the COVID-19 virus through laparoscopic surgery has not been shown, there have not been enough studies on this topic. However, studies in the literature argue that laparoscopic surgery may be performed safely with recommendations such as using protective equipment, using electrocautery less, and working at lower pressures. In our study, as a result of our application of all these recommendations in the literature, we did not encounter any contamination in the 124 laparoscopic surgery cases we examined. In conclusion, we think that laparoscopic surgery may be performed safely by taking the necessary precautions during the COVID-19 pandemic period.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study has obtained approval from the Hitit University Ethics Committee (Application number: 2021-76, Decision No: 2021-66, Date: April 2021).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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The Efficacy of Greater Occipital Nerve Block in Patients with Chronic Migraine

Kronik Migrenli Hastalarda Büyük Oksipital Sinir Bloğunun Etkinliği

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Abstract

Background: In chronic migraines(CM), the rate of benefiting from medical treatment is relatively low, and it is known that patients use analgesics extensively. Greater occipital nerve (GON) block, have been started to be used in chronic migraine patients who were refractory to treatment. In this study, we aimed to evaluate the headache attack frequency, analgesic use, VAS (Visual Analog Scale) and MIDAS (Migraine Disability Assessment Scale) scores in the 3-month follow-up of patients we had performed a GON block in our clinic for chronic migraine refractory to medical treatment.

Material and Method: A total of 120 CM patients were included in the study. The number of analgesics used, the number of days with pain, and the VAS and MIDAS scores were recorded before the GON block and at one and three months of treatment.

Results: There was a statistically significant (p<0.001*) reduction in the number of days with pain, analgesic use, and the VAS and MIDAS scores in the first and third months compared to the pre-treatment baseline values in patients who had undergone a GON block. No significant differences between the first and third months.

Conclusions: After the GON block, we noted a significant reduction of headaches and improved quality of life in patients who had been experiencing severe headaches despite medical treatment. The GON block has an exceptionally high benefit rate, might be considered as a treatment option before migraines gain chronicity, patients are not exposed to an excessive medical burden and increased treatment costs.

Keywords: Headache, migraine, chronic migraine, greater occipital nerve block, pain, VAS , MIDAS, quality of life

Öz

Amaç: Kronik migrende medikal tedaviden faydalanma oldukça düşük olup, hastalarda sıklıkla yoğun analjezik kullanımı olduğu bilinmektedir. Bu nedenle periferal sinir blokajı özellikle GON blokajı tedaviye dirençli kronik migren hastalarında kullanılmaya başlanmıştır. Bu çalışmada kliniğimizde medikal tedaviye dirençli kronik migren tanısı nedeniyle GON (Greater Occipital Nerve) blokajı uyguladığımız hastalarımızın 3 aylık takiplerinde başağrısı atak sıklığını, analjezik kullanımını, VAS (Vizuel Analog Skala) değerleri ve MİDAS (Migren Özürlülük Değerlendirilmesi Ölçeği) skorlarını değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışmaya 120 kronik migren hastası dahil edildi. Hastaların GON blokajı öncesi ve sonrası 1. ve 3. ayda analjezik kullanımı, ağrılı gün sayısı, VAS ve MİDAS skorları değerlendirildi.

Bulgular: GON blokajı uygulanan hastalarda ağrılı gün sayısı, analjezik kullanımı, VAS ve MİDAS skorlarında tedavi öncesi değerlerine göre 1.ve 3. ayda istatiksel olarak anlamlı (p<0,001*) azalma gözlenirken, 1. ve 3. ay bulguları arasında istatiksel olarak anlamlı fark gözlenmedi.

Sonuç: Çalışmamızda medikal tedaviye rağmen günlük yaşam aktivitelerini engelleyen şiddetli baş ağrıları olan hastalarda blokaj uygulanması sonrası baş ağrısında belirgin azalma ve hayat kalitesinde iyileşme dikkati çekmiştir. Tüm çalışmalarda etkin olduğu gösterilmiş, oldukça yüksek faydalanımı olan GON blokajının, migren hastalığı kronikleşmeden ,hastalar fazla medikal yüke maruz kalmadan ve tedavi maliyetleri artmadan tedavi seçeneği haline gelmesi düşünülebilir.

Anahtar Kelimeler: Baş ağrısı, kronik migren, büyük oksipital sinir blokajı

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INTRODUCTION

Migraine is one of the primary headaches, manifested as headache attacks lasting for 4-72 hours, mostly localized to one half of the head, increasing in severity with physical activity, and affecting the individual's daily living activities. Chronic migraine (CM) has been included as a subheading in the migraine classification due to its characteristics. According to the diagnostic criteria of the 2018 International Classification of Headache Disorders (ICHD-3 beta)[1], a migraine headache, present for more than three months, eight days or more in a month, and with intervals of less than 15 days, was defined as CM.[2] In a prevalence study conducted in Turkey, the prevalence of CM was reported as 0.066% without medication overuse and 0.56% in newly diagnosed patients.[3]

It is known that the rate of benefiting from medical treatment is relatively low in chronic migraines, analgesics are extensively used besides frequent use of prophylactic drugs, and patients encounter disabilities because of pain. Recently, peripheral nerve blocks have been reported to be effective in particularly chronic migraine, and the greater occipital nerve (GON) block has started to be used in chronic migraine patients. It is known that in the GON block, low-concentration local anesthetics manifest their effects by selectively blocking sensory nerve fibers to provide improvement in painful conditions.

In the study conducted by Caputi et al., reductions in headache duration, frequency, and severity for six months were reported in patients in whom the supraorbital and GON blocks were performed.[4] Peripheral nerve blocks technically involve the blockage of trigeminal nerve branches such as supraorbital, supratrochlear, auriculotemporal nerves in addition to the greater and smaller occipital nerve blocks. In migraine patients, the GON block is the most preferred method, with studies most frequently conducted on its effectiveness.[5] The GON block's effect is known to be via the trigeminovascular system. Conducted studies have emphasized a functional connection between the caudal trigeminal nucleus and the upper cervical segments.[6,7] When the GON block is performed, the injected anesthetic substance creates modulation by blocking afferent stimuli at the field innervated by the nerve and preventing sensitization at the C2 and C3 dorsal horn convergence neurons.[5]

This study aimed to evaluate the headache attack frequency, analgesic use, VAS (Visual Analog Scale) and MIDAS (Migraine Disability Assessment Scale) scores in the 3-month follow-up in patients in whom we had performed a GON block for chronic migraine refractory to medical treatment.

MATERIAL AND METHOD

A total of 120 chronic migraine patients, aged between 18-65 years, admitted to the Neurology Outpatient Clinic between January 2017 and June 2019 were included in the study. The patients diagnosed with chronic migraine following the international classification for headaches were reviewed, and previous data were recorded. The patients who had undergone GON block were informed about the procedure in detail, and then, their consent was obtained and archived. The study's inclusion criterion was to be a chronic migraine patient who was refractory to treatment (refractory to treatment should be defined) and had not benefited from medical treatment options. Due to the frequency of pain in patients with chronic migraine, treatment-resistant headaches ocur as a results of excessive use of drugs such as triptan, ergotamine, and opioids more than 8 days a month, and analgesics more than 15 days a month.[1] Patients were using analgesic, ergot, triptan derivatives for attack treatment, beta-blockers, calcium channel blockers, antidepressant derivatives, topiramate group-antiepileptic treatments, and their combinations for prophylaxis.

Patients with an acute pathology or space-occupying lesion identified by cranial imaging, pregnant or breastfeeding patients, those with a history of malignancy, major psychiatric disorders, bleeding diathesis, those receiving anticoagulant treatment with coumadin and its derivatives, those allergic to local anesthetics, patients who had undergone cervical or cranial surgery, patients with neuromuscular dysfunctions, and those with infection at the procedure site were excluded from the study.

Patients' sterilization and emergency response conditions were provided. After cleaning the intervention area with an antiseptic solution, the occipital artery located at 1/3 medial to the imaginary line between the occipital protuberance and mastoid process was palpated. The needle was inserted and withdrawn when the bone was reached, aspirated to check whether it was in the artery, and then 1.5 ml of 2% lidocaine was administered. A 13 mm, 26-gauge (G) was used for the procedure. Compression was applied after the injection. The patient was followed-up for approximately 30 minutes. The blockade procedure was bilaterally performed for six sessions, once a week in the first month and once a month in the second and third months. The VAS scores, attack frequency, attack duration, analgesic requirements before the procedure were recorded together with the 1-month and 3-month data.

Ethical approval

Approval was obtained from the Local Ethics Committee (Protocol No: 2021- 032) and the Ministry of Health for this retrospective study.

Statistical Analysis

The Shapiro Wilk test tested the normality of the distribution of continuous variables. The Freidman test and Dunn multiple comparison tests were used to compare non-normal data across the three time points. Statistical analysis was performed with SPSS for Windows version 24.0, and a p-value < 0.05 was considered statistically significant.

RESULTS

One hundred twenty chronic migraine patients who had undergone GON block were included in the study. The mean age of these patients was 42.68±7.14 years. Of the patients, 102/120 (85%) were female, and 18/120 (15%) were male. The patients' mean pain duration was 11.63±5.66 hours. 17/120 (14.2%) patients described pre-headache aura. The demographic and clinical characteristics of the patients were presented in **Table 1**.

The number of days with pain, the number of analgesics used per month, the VAS and MIDAS scores before and one and three months after the treatment were recorded. With the GON block, the number of days with pain regressed from its pre-treatment value of 8.5 [8-12] to 4 [3-4] at the 1st month and 3 [2-4] at the 3rd month. The number of analgesics used monthly by the patients was 14 [10-16] before treatment, 5.5 [4-6.5] at the 1st month, and 6 [5-7] at the 3rd month. The VAS score regressed from its pre-treatment value of 8 [7-9] to 4 [3-4] at the 1st and 3rd months. The MIDAS score also regressed from its pre-treatment value of 4 [3-4] to 2 [1.5-2] at the 1st and 3rd months. Significant reductions were observed regarding the number of days with pain, analgesic use, and the VAS and MIDAS scores when the 1st-month and 3rd-month values were compared to the pre-treatment baseline values ($p<0.001$*). There were no statistically significant differences between the 1st-month and 3rd-month values (**Table 2**) (**Figures 1**, **2**, and **3**).

Table 1. Demographic and clinical characteristics of the patients

Variables		Descriptive Statistics (n=120)	
		Mean±SD	Median (Min-Max)
Age (years)		42.68±7.14	43 (25 -64)
Duration (hours)		11.63±5.66	10.5 (3 -24)
		n	%
Gender	Male	18	15.0
	Female	102	85.0
Aura	Present	17	14.2
	Absent	103	85.8

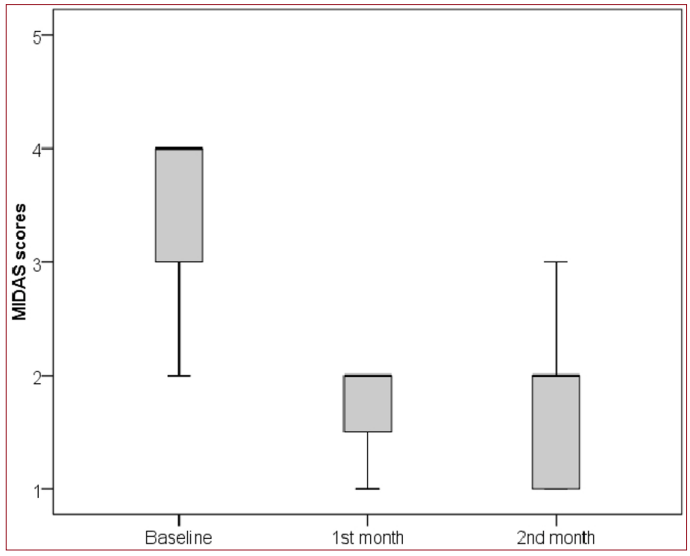

Figure 2. Comparison of MIDAS scores among three different time points

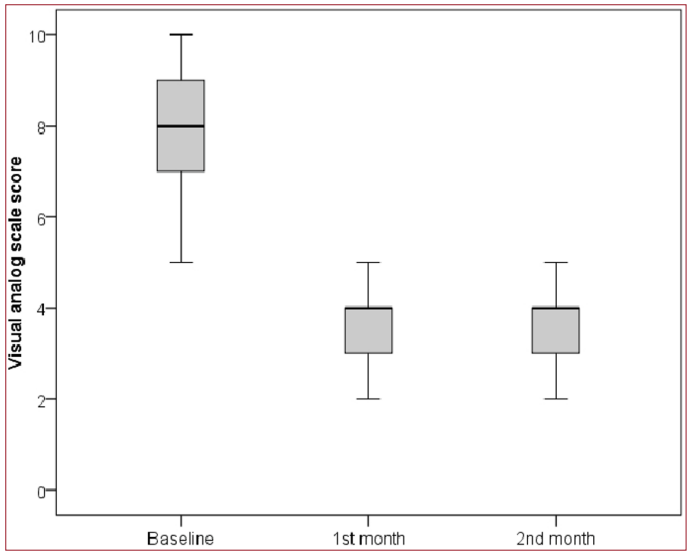

Figure 1. Comparison of VAS scores among three different time points

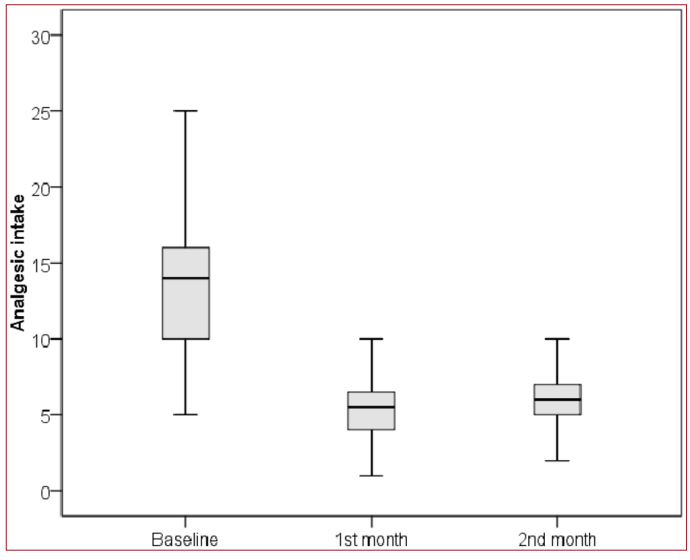

Figure 3. Comparison of analgesic use among three different time points

Table 2. Clinical findings related to migraine during follow-up

Variable	Baseline Median [25%-75%]	1st-month Median [25%-75%]	3rd-month Median [25%-75%]	P-value		
				1st-month vs. Baseline	3rd-month vs. Baseline	1st-month vs. 3rd-month
Number of days with pain	8.5 [8 -12]	4 [3 -4]	3 [2 -4]	0.001*	0.001*	0.439
Analgesic use	14 [10 -16]	5.5 [4 -6.5]	6 [5 -7]	0.001*	0.001*	0.220
VAS score	8 [7 -9]	4 [3 -4]	4 [3 -4]	0.001*	0.001*	0.949
MIDAS score	4 [3 -4]	2 [1 -2]	2 [1 -2]	0.001*	0.001*	0.897

*Significant at 0.05 level; Freidman test, Dunn multiple comparisons.

DISCUSSION

Peripheral nerve blocks have recently become a preferable treatment option for primary headaches' acute and preventive treatments. Numerous randomized, controlled studies have shown that the GON block was effective.[4,8,9] Its contributions to patient satisfaction, daily activities, and treatment costs are too significant to be ignored, mainly due to improvements in migraine treatments. There were statistically significant reductions in our study when the first and third-month values were compared to the pre-treatment values regarding the days with pain, analgesic use, VAS, and MIDAS scores in 120 patients in whom we had performed a GON block (**Figures 1** and **2**).

In many studies, it has been shown that significant improvements occurred with a GON block, injecting a local anesthetic substance, and steroids in migraines of resistant patients who were unresponsive to prophylactic treatment.[4-8] Caputi et al. performed GON and supraorbital blocks using bupivacaine and determined decreasing headache severity in 85% of their patients. This study determined significant pain severity reductions when we compared the periods before and after the treatment.

The American Headache Society made practical recommendations regarding peripheral nerve and GON blocks in 2013; however, they stated that a consensus had not been reached on the amount to be administered and the repetition frequency since there were not enough randomized, controlled studies.[10] Numerous studies have been conducted on the effectiveness and use of the GON block in primary headaches to clarify such issues and determine the boundaries; however, standardization has not been yet achieved, and in most studies, different options were preferred regarding the administration technique, drug preference, and dosage.[9,11,12]

Lidocaine and bupivacaine are commonly preferred in peripheral nerve blocks. We preferred lidocaine in our patients because of its shorter half-life when compared to bupivacaine. Local anesthetics create a reversible blockade in sodium channels of nerve fibers and provide efficient control by causing depolarization in demyelinated C-fibers and myelinated A-fibers, which play roles in pain signal transmission. Since pain control's duration is longer than the administered local anesthetic agent's half-life, pain control has been considered to be associated with central modulation. Corticosteroids may be preferred for treatment from time to time to prolong the block duration. Even though less common in chronic migraine patients, corticosteroids have been preferred particularly for the treatment of cluster headaches, and they were determined to be more efficacious.[13] The corticosteroids' long-term effects are unknown. Corticosteroids are known to inhibit pro-inflammatory cytokines' synthesis and release and suppress inflammation. Moreover, they provide efficient pain control through membrane stabilization, reversible inhibition of nociceptive C-fibers, and modulation of nociceptive input to the substantia gelatinosa.[5,14]

Numerous studies have been conducted on local anesthetics' effectiveness, superiorities to each other, and combination treatments with steroids. Gül et al. compared bupivacaine and saline and determined that the 2-month and 3-month VAS scores were significantly superior to those of the placebo group.[15] When 0.25 ml of lidocaine 0.5% was compared to 2.5 ml of bupivacaine 0.5% and methylprednisolone, it was determined that their efficacies were not superior to each other. Studies on steroids' addition to treatment have shown that steroids did not contribute.[12,16,17]

There is no standardization regarding unilateral or bilateral GON block applications, and the block is performed on an optional basis. The study comparing unilateral and bilateral GON blocks' efficacies reported no difference between them.[18] We preferred to perform bilateral GON blocks in our method.

Single block or repeated nerve blocks? Numerous studies have reported that repeated nerve blocks were more effective than single blocks.[16,18-21] In our clinic, we preferred to perform six sessions of blocks in total, once a week in the first month and once a month in the second and third months. The treatment responses of patients in whom a GON block was performed together with prophylaxis were compared to those in whom only a GON block was performed, and no significant differences were determined between the two groups regarding the headache duration and attacks. Most of our patients had been receiving prophylactic treatment, and some of them stated that their requirement for prophylactic treatment had decreased in later treatment stages, and they had quit their medications. We determined significant reductions in patients' analgesic requirements in the course of treatment (**Figure 3**). The GON block is reliable for patients; however, vasovagal syncope, temporary numbness at the injection site, and particularly when combined with steroids, alopecia, and cutaneous atrophy were reported.[9] No significant side effects were observed during and after the GON block in our study.

Our study had various limitations. Our study's shortcomings were its small sample size, absence of a control group, and our inability to follow up the patients for a longer duration. Prospective, randomized, and placebo-controlled future studies with longer duration and larger sample sizes are required.

CONCLUSION

Chronic migraine headache is a disorder restricting daily living activities despite medical treatments, adversely affecting patients' quality of living. The recently used GON block has brought a new perspective to both acute and chronic migraine treatments. The GON block has become an easily applicable, preferred method with proven efficacy

and few side effects in chronic migraine patients. Besides increasing the chronic migraine patients' quality of life, it also reduces chronic drug consumption, related side effects, and treatment costs. The GON block, the efficacy of which has been shown in numerous studies and which has an exceptionally high benefit rate, might be considered as a treatment option before migraines gain chronicity, patients are not exposed to an excessive medical burden, and increased treatment costs.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval was obtained from the Local Ethics Committee (Protocol No: 2021- 032) and the Ministry of Health for this study.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

Remitting Seronegative Symmetrical Synovitis with Pitting Edema (RS3PE) Syndrome: A Single-Center Experience

Tekrarlayıcı Seronegatif Pitting Ödemli Simetrik Sinovit (R3SPE) Sendromu: Tek Merkez Deneyim

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Abstract

Objective: Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) is a rare disorder characterized by pitting edema, the onset of acute polyarthritis, and negative rheumatoid factor. The absence of joint erosion and good long-term response to low-dose steroids are its other characteristics. The present study aimed to evaluate the characteristics and accompanying conditions of RS3PE for contributing to the literature on the issue.

Material and Method: This is descriptive casebased retrospective study was carried out in a rheumatology clinic between January 2019- October 2020. Fifteen patients over 18 diagnosed with RS3PE were included in the study.

Results: Of 15 patients diagnosed with RS3PE, seven were female, and eight male. The following comorbid disorders were present: relapsing polychondritis, scleroderma, seropositive rheumatoid arthritis, gout, monoclonal gammopathy of unknown significance, and primary myelofibrosis. Most patients other than the ones who have hematological malignities and those diagnosed with relapsing polychondritis responded rapidly to steroids, and no recurrence occurred.

Conclusion: RS3PE may be associated with neoplasia, drugs, and various rheumatismal conditions, suggesting that it may be heterogeneous and considered a paraneoplastic rheumatic disease. The rare occurrence of this syndrome leads clinicians to miss it commonly. It is essential to increase awareness of this entity among clinicians.

Keywords: Comorbidities, paraneoplastic; arthritis; pitting edema, remitting seronegative symmetrical synovitis with pitting edema syndrome

Öz

Amaç: Tekrarlayıcı seronegatif pitting ödemli simetrik sinovit sendromu (R3SPE), akut poliartrit başlangıcı olan, negatif romatoid faktör ve pitting ödem ile karakterize nadir bir hastalıktır. Eklem erozyonu yapmaması ve düşük doz steroide iyi yanıt vermesi diğer özellikleridir. Bu çalışma, RSPE sendromu özelliklerini ve eşlik eden durumları değerlendirmeyi ve literature katkıda bulunmayı amaçlamaktadır.

Gereç ve Yöntem: Bu tanımlayıcı vaka bazlı retrospektif çalışma Romatoloji kliniğinde Ocak 2019- Ekim 2020 tarihleri arasında yapıldı. 18 yaş üstü on beş RS3PE hastası çalışmaya dahil edildi.

Bulgular: RS3PE tanısı konulan 15 hastanın yedisi kadın ve sekizi erkekti. Tekrarlayan polikondrit, skleroderma, seropozitif romatoid artrit, gut, önemi bilinmeyen monoklonal gamopati ve primer miyelofibroz komorbid bozuklukları mevcuttu. Hematolojik malignitesi olanlar ve tekrarlayan polikondrit tanısı konanlar dışındaki hastaların çoğu steroid tedavisine hızla yanıt verdi ve nüks gözlenmedi.

Sonuç: RS3PE sendromu, heterojen bir hastalıktır. Neoplazi, ilaçlar ve çeşitli romatizmal hastalıklar ile ilişkili olabilmekte ayrıca paraneoplastik romatizmal hastalik olabileceği düşünülmektedir. Bu sendrom nadir görülmesi nedeniyle klinisyenlerin gözünden kaçabilir ve bu yüzden klinisyenler arasında hastalık açısından farkındalığını arttırmak esastır.

Anahtar Kelimeler: Artrit; komorbiditeler; paraneoplastik; pitting ödem; tekrarlayıcı seronegatif pitting ödemli simetrik sinovit

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INTRODUCTION

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) was initially described by Mc Carty et al. in 1985 as one of the subgroups of seronegative rheumatoid arthritis (RA).[1] Subsequently, it has been suggested that it is a distinct clinical entity from RA.[2] Although the prevalence of RS3PE is not entirely known, it is considered quite rare. Clinically, it frequently presents with acute, symmetrical, and polyarticular involvement. The most typical disease feature is marked pitting edema on dorsal aspects of hands and feet developing due to tenosynovitis. In all ten original cases described by McCarty the disease was bilaterally symmetrical. Since McCarty's original description over 150 cases of RS3PE has been reported. In almost all the cases it is described as a symmetrical disease involving both hands and rarely the feet .Thus symmetrical presentation is considered as one of the hallmark of disease. However exceptions are always there. RS3PE too presents in an asymmetrical and unilateral pattern, though it is extremely rare. Thus diagnosing it always poses a clinical challenge, and correct diagnosis is delayed often.[3] The absence of specific diagnostic criteria and asymmetrical unilateral patterns makes the diagnosis of RS3PE more difficult. RS3PE may be associated with neoplasia and various rheumatismal conditions, suggesting that it may be heterogenous natüre. The present study aimed to evaluate the clinical, laboratory, and radiological characteristics of 15 cases given the literature.

MATERIAL AND METHOD

This is a descriptive casebased and retrospective study on RS3PE syndrome, which is a rare rheumatological disorder. This single-center study was carried out between January 2019 and October 2020 in Rheumatology Department. Retrospectively, 15 patients over the age of 18 who were clinically diagnosed with RS3PE syndrome were registered in this study.[4] We excluded renal, liver, cardiovascular disease, elderly-onset rheumatoid arthritis, and polymyalgia rheumatica (PMR) based on clinical characteristics, imaging (radiological and ultrasound findings). Data on patients with RS3PE were reached by reviewing patient files and medical records. Age, sex, history, involvement type and site, the symptoms and comorbidities, probable etiological factors, laboratory findings, and treatment options were recorded. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) hemogram parameters were recorded to evaluate activation in patients. For screening probable accompanying malignity, mammography, abdominal and neck USG examination, and gynecological examination were carried out in women and men; in addition to neck and abdominal USG, prostate malignity was attempted to be ruled out. In patients suspected to have hematological malignities, hematology consultation was made. For differential diagnosis, extremity graphics, uric acid, rheumatological antibodies, antinuclear antibodies (ANA), Anti-cyclic citrullinated peptide antibody (anti-CCP), and RF analysis were ordered. To eliminate the probable infection in suspected patients, procalcitonin, brucella test, urinalysis, and lung radiography were ordered. An echocardiography examination was ordered to exclude heart failure. Total protein and albumin evaluation, thyroid, kidney, and liver function tests, and proteinuria investigation in urine were carried out.

The present study was performed by following the principles of the Helsinki Declaration, and written informed consent was obtained from all participants. Patients gave their informed consent to be subjected to the protocol. Approval for the study was obtained from the ethics committee with the decision dated 22.04.2020 and numbered. 2020/181.

Statistical Analysis

All statistical analyses were performed with IBM SPSS 22.0 software. Demographic characteristics and laboratory findings of the patients were summarized using descriptive statistics. Numerical variables were expressed as mean±standard deviation (range: min-max) or median, and also categorical variables were described as counts (n) and percentages (%).

RESULTS

Of 15 patients diagnosed with RS3PE, seven were female, and eight male. The mean age of the patients was 65.53±14 years (47-86); physical examination findings were as follows: arthritis in bilateral ankle three patients, in bilateral wrists in 5 patients, in the unilateral wrist and metacarpophalangeal joints in 2 patients, the unilateral ankle and metatarsophalangeal joints in 3 patients and asymmetrical wrist and ankle joints in 2 patients and pitting edema in the dorsum of hand or foot in all patients (shown in **Figure 1, 2** and **Table 1**). In the radiological examination, no erosive changes were observed in joints. Mean value of CRP was found to be 68.5±61.6 mg/dl and ESR 58±20 mm /s. RF, anti-CCP tests were negative except for one patient with the diagnosis of RA and, the ANA test was negative except for cases with relapsing polychondritis and scleroderma, respectively. No pathological findings were established in procalcitonin, brucella tests, total protein, albumin, thyroid, kidney, liver function tests, and urinalysis and proteinuria tests in the urine. Laboratory results are summarized in **Table 2**. Abdominal and pelvis ultrasonography demonstrated normal size and structure in the liver, spleen, and kidneys. No lymphadenopathy or malignity was found. There was no finding suggesting heart failure, and in lung radiography in the echocardiographic examination, no pathological findings such as infection and mass were observed. Two patients had no known systemic disease. In the Doppler USG examination carried out in patients with unilateral foot involvement, deep vein thrombosis was not found. As to accompanying rheumatological diseases, one had relapsing polychondritis, one scleroderma, one gout, and one seropositive rheumatoid arthritis. After screening for

malignity, MGUS was detected in one patient and primary myelofibrosis in another, and the hematology department followed them. Five patients had hypertension, and three patients' diabetes mellitus. Of diabetes patients, one was on empagliflozin treatment as oral antidiabetic, and 2 received insulin treatment. Patients responded rapidly to steroids.

Recurrence occurred in two patients with hematological malignity and one with relapsing polychondritis. RP responded to methotrexate treatment, while MGUS and myelofibrosis cases went into remission with high dose steroid treatment. The rheumatology department is still following them up.

Table 2. RS3PE syndrome laboratory characteristics

Variables	RS3PE syndrome (n = 15) Median (minimum-maximum)
CRP(mg/L) [0–8]	62 (8.5-266)
ESR (mm/hour) [0–20]	52 (30-93)
Leukocyte(10^9/L) [3.5–10.5]	10.4 (6.8-25.5)
Hemoglobin(g/dL) [12–15.5]	12 (10-15)
Platelet (10^9/L) [150–450]	130 (185-601)
Neutrophil (10^9/L) [1.7–7]	7 (4.5-12.7)
Lymphocyte (10^9/L) [0.9–2.9]	0.7 (0.1-3.1)
Monocytes (10^9/L) [0.2–0.8]	1.6 (0.1-4.5)

* Data were presented as mean±standard deviation (range: min–max) or median, and described as counts(n); RS3PE syndrome- Remitting seronegative symmetrical synovitis with pitting edema; ESR–erythrocyte sedimentation rate; CRP–C-reactive protein

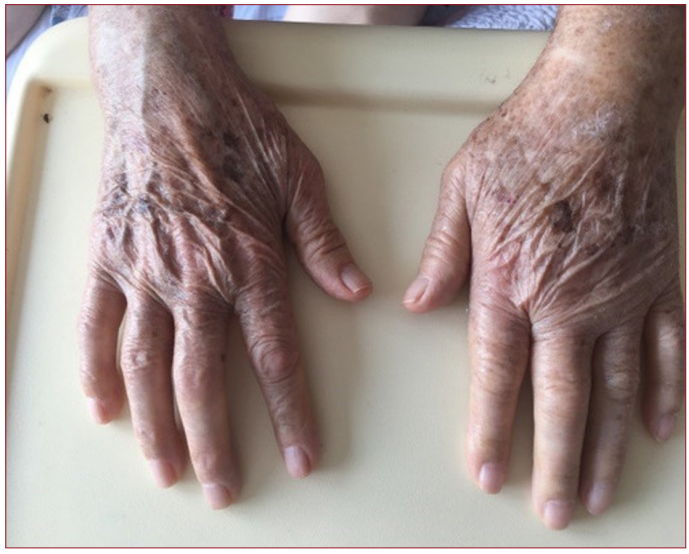

Figure 1. Clinical photograph of the patients showing pitting edema of the hands

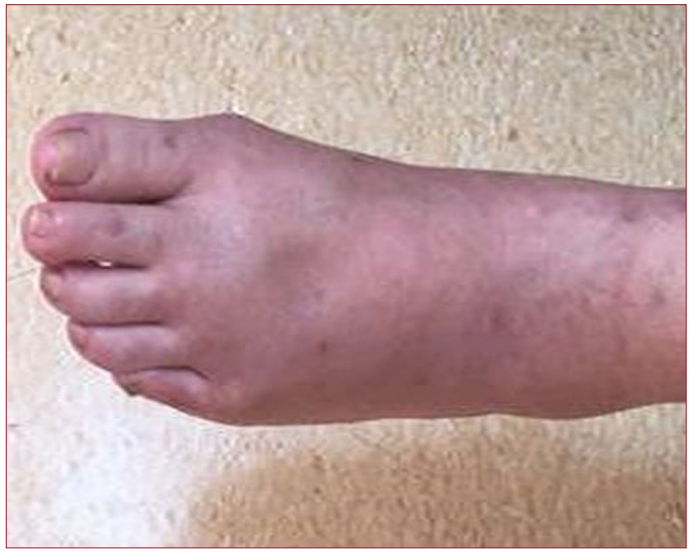

Figure 2. Clinical photograph of the patient showing pitting edema over the dorsum of the foot

Table 1. Demographic and clinical characteristics of RS3PE disease patients

	Age	Gender	Comorbidity (Disease Duration, years)	Treatment	Articular İnvolvement	Pitting Edema
Patient 1	78	F	HT (10)	Ramipril+ hydrochlorothiazide	Bilateral wrist	Bilateral hand
Patient 2	76	F	DM (6)	Insulin+vildaglibtin	Left MCP and wrist	Bilateral hand
Patient 3	86	M	MGUS (1)	None	Bilateral ankle	Bilateral foot
Patient 4	47	F	RP (1)	Methotrexate	Left wrist, right MTF and ankle	Bilateral hand and foot
Patient 5	61	F	PMF (1)	None	Left MTF and ankle	Bilateral foot
Patient 6	76	F	Gout (3)	Allopurinol	Left MCP and wrist	Bilateral hand
Patient 7	73	F	HT (8)	Candesartan	Left MTF and ankle	Bilateral foot
Patient 8	48	F	SSc (8)	Azathioprine+hydroxychloroquine	Right MTF and ankle	Bilateral foot
Patient 9	54	M	DM (3)	Insulin	Bilateral wrist	Bilateral hand
Patient 10	58	M	HT (7)	Valsartan+hydrochlorothiazide	Bilateral ankle	Bilateral foot
Patient 11	82	M	DM (10)	Empagliflozin	Bilateral wrist	Bilateral hand
Patient 12	72	M	HT (9)	None	Left wrist and ankle	Bilateral hand and foot
Patient 13	76	M	HT (2)	Metoprolole	Bilateral wrist	Bilateral hand
Patient 14	48	M	None	None	Bilateral wrist	Bilateral hand
Patient 15	48	M	RA (6)	Methotrexate+hydroxychloroquine	Bilateral ankle	Bilateral foot

F; Female, M; Male, PMF:Primary myelofibrosis, DM; diabetes mellitus, HT; essential hypertension, SSc; Systemic sclerosis, RA; rheumatoid arthritis, RP; relapsing polycondritis, MGUS; monoclonal gammopathy of undetermined significance, MCP: metacarpophalangeal, MTP; metatarsophalangeal

DISCUSSION

RS3PE cases are mostly idiopathic. Albeit etiopathogenesis remains to be completely elucidated, it has been stated that genetic susceptibility, infections, drugs, rheumatological and autoimmune diseases play a role.[5] The role of vascular endothelium growth factor (VEGF), which contributes to subcutaneous edema in extremities and polysynovitis by increasing vascular permeability, has been demonstrated recently. It is assumed that neoplasia, other drugs, and medical conditions may trigger VEGF production and other molecules, stimulating vascular permeability in RS3PE syndrome, resulting in pitting edema and polyarthritis/ polysynovitis in extremities. Studies on the pathogenesis of RS3PE are restricted to Japanese reports, and sample magnitudes are small. Considering that RS3PE is a heterogeneous syndrome and is associated with malignities in a substantial number of cases, further investigation of different potential mechanisms is needed in RS3PE patients, particularly in the ones with neoplasia. Studies including few patients demonstrated that high interleukin 6 (IL-6) levels in serum and synovial fluid reveal the disease's inflammatory characteristics.[6] Even though it is known as a disease of the elderly population, it may occur in younger age groups.[7] In the present study, 5 out of 15 patients were under the age of 60.

Pitting edema is the most specific property. Edema of both hand and foot have been reported. The most commonly affected joints are the wrist, ankle, metacarpophalangeal, and proximal interphalangeal joints. It is thought that it does not lead to permanent damage in joints, but mild residual joint limitations may occur. Until Pariser and Canosa reported two unilateral RS3PE cases, it was regarded as a symmetrical entity.[8] Then, in the case series of Finnell and Cuesta, asymmetrical involvement in lower extremities was reported.[9] In our series, the involved joints were similar to those reported in the literature, but cases with unilateral asymmetrical involvement made up the majority. Laboratory parameters include high levels of acute-phase reactants (ESR, CRP), indicating an underlying inflammatory process. RF and anti-CCP are typically negative, and the ANA test has rarely been reported to be positive. Radiologically, there are no erosions.[10] Tenosynovitis has been demonstrated with the imaging of extremities using ultrasonography and /magnetic resonance imaging. In our cases, laboratory and radiological findings were consistent with those reported in the literature.[11] Although diagnostic criteria of RS3PE are clear, due to accompanying systemic complaints in geriatric age groups and probable concurrence with other diseases, the differential diagnosis may become challenging. In the differential diagnosis of RS3PE, polymyalgia rheumatica (PMR) and late-onset RA are essential as they affect similar age groups and have some common characteristics.[12] Although it was originally defined as a subgroup of RA, it is distinct from RA in that RA leads to erosive changes and marked morning stiffness, rheumatic nodules are present, is associated with HLA-DRB1 alleles, is RF positive, and requires long terms, disease modifying agents. In PMR, shoulder hip girdle pain is predominant in the clinical picture, complaints are associated with systemic symptoms that emerge in the longer term, and high dose steroids are required, which are differentiating characteristics. The occurrence at advanced ages, being seronegative, high sedimentation levels, and dramatic response to steroids cause the syndrome to be confused with PMR. However, the preponderance of male patients and pitting edema are not expected in PMR. Other rheumatological diseases, hypothyroidism, congestive heart failure, nephrotic syndrome, venous failure, lymphedema, cellulitis, osteomyelitis, and tenosynovitis should be considered in the differential diagnosis. Particularly in long-standing dialysis patients, extracellular fluid accumulation in hands and feet and development of amyloid arthropathy may produce a clinical picture resembling RS3PE syndrome. The diagnosis was made following differential diagnosis established with the clinical, physical examination, laboratory, and radiological findings in the present study. However, it should be kept in mind that differential diagnosis may be quite challenging.

A study[13] evaluated 331 RS3PE cases reported by 121 studies, concurrent rheumatological conditions were reported in 22 cases (6.65%), and malignity in 54 cases. (16.31%). The aforementioned data support the idea that RS3PE is a syndrome, which potentially has heterogeneous etiology. Various rheumatismal diseases have been reported to be concurrent with RS3PE'. They include systemic lupus erythematosus, gout, Sjögren syndrome, polyarteritis nodosa, ankylosing spondylitis, sarcoidosis, amyloidosis, recurrent polychondritis, and bronchiolitis obliterans organizing pneumonia. RS3PE may also be associated with infections such as bacillus Calmette-Guerin (BCG), parvovirus, and Streptobacillus moniliformis.[14,15] Özşahin et al. reported the occurrence of unilateral RS3PE in a patient with rheumatoid arthritis who received DMARD treatment but later discontinued it as symptoms could not be controlled.[7] RS3PE developed three years after the discontinuation of drugs. Another case was controlled well with DMARDs, and similar to our case, RS3PE developed during treatment. This case indicates that RS3PE may be considered a different clinical entity since it occurred regularly in a patient receiving DMARD.

Pittau et al.[16] described a case of SLE with pitting edema in distal lower limbs. In 1999, Günaydın et al.[17] reported two cases of SLE with unproven pathogenesis and lower extremity pitting edema who responded to steroids rapidly. In 2008, Alpigiani et al. reported a case of pediatric SLE whose symmetrical pitting edema in hands and feet improved.[18] In a literature review, 7 RS3PE cases associated with SLE were reported.[17] Young Mi Choi et al. and Fietta P et al. reported the coexistence of Sjögren disease and RS3PE in their cases, respectively.[20] In Scleroderma, as dermatological findings, usually bilateral sclerodactyly and nonpitting edema are observed. Edema is the earliest finding of scleroderma. In our

scleroderma cases, whose disease duration was eight years, bilateral foot pitting edema and asymmetrical ankle arthritis were observed. This coexistence was not described before in the literature. It is a rare concurrence and may easily be confused with other diagnoses, which renders it significant.

In one of our cases, dyspnea, hoarseness, arthritis in metatarsophalangeal joints, left wrist and right ankle, and pitting edema on hand and foot dorsum were present. Nasal, auricular chondritis and bronchial involvement were detected, and the patient was diagnosed with relapsing polychondritis (RP) and RS3PE. In the literature, a 72-year-old male case with concurrent RS3PE and MDS, which were diagnosed simultaneously, has been reported.[21] A few months later patient displayed a clinical and pathological picture consistent with RP. Although the relation between RP and RS3PE and MDS is well known, RS3PE cases developing after RP have not been reported.[22] In our case, only RP and RS3PE concurrence were present without any hematological malignity. Also, unlike the other case, RS3PE developed after RP findings in a young female patient

RS3PE syndrome, caused by crystal arthritis, in particular gout, is quite rare. In reported cases, patients were previously diagnosed with gout. However, they did not continue treatment and had recurrent gout attacks. In our case, RS3PE developed under treatment. Even though RS3PE caused by gout is very seldom, clinicians should take gout-associated RS3PE syndrome into account when diagnosing symmetrical inflammatory diseases since gout/hyperuricemia is a widespread disease irrespective of race. Palazzi et al. reported that gout RS3PE syndrome was successfully treated with ten days of meloxicam cure.[23] Sugisaki and Hirose reported another gout-associated RS3PE syndrome case in which NSAID treatment exerted no therapeutic effect and was finally successfully treated with low-dose oral prednisolone.[24]

Recent studies have demonstrated the association of RS3PE with antidiabetic drugs such as insulin and dipeptidyl peptidase-4 (DPP-4) inhibitör Yamauchi et al. reported two Japanese cases of RS3PE syndrome, which arose after the onset of DPP4 treatment.[25,26] Yokota and Igaki reported a case of polyarthritis developing after the initiation of sitagliptin, diagnosed with RA, and whose arthritis improved after the withdrawal of sitagliptin.[27] Insulin directly increases VEGF-A mRNA and protein expression in various tissues, including cardiac myocytes and renal podocytes. Cases associated with insulin treatment have been reported.[28] However, recently K. Oyama et al. Have reported four cases of RS3PE, who have type 2 diabetes mellitus or impaired glucose tolerance without DPP-4 inhibitor drug.[29] In our case series, three patients had DM. Two were on insulin, while one received empagliflozin, which was instituted six months before the appearance of arthritis. No relation between syndrome and empagliflozin has been reported in previous literature. Further studies are required in order to corroborate the relation between DM and its treatment and RS3PE.

Both cancer and benign masses have been reported since 1985 in association with RS3PE.[30] Malignities reported in this syndrome involve both hematological malignities and solid tumors. The relation between RS3PE and neoplasms may suggest that it may be a paraneoplastic syndrome. Among solid tumors, a more common relation was reported with prostate, colon, and stomach adenocarcinomas. There are other cases of RS3PE associated with the ovary, endometrial carcinoma, bladder, lung, breast, and cryptogenic hepatocellular carcinoma. It has also been reported that some hematological malignities such as chronic lymphocytic leukemia, T cell lymphoma, angioimmunoblastic T cell leukemia, B cell non-Hodgkin lymphoma, and myelodysplastic syndrome are associated with RS3PE syndrome. It is thought that inflammatory cytokines released from tumor cells play a role in its pathogenesis. The best management of paraneoplastic RS3PE syndrome is the treatment of malignant processes.[31] Malignity may develop before, during, or after the appearance of the syndrome. Therefore, in patients diagnosed with RS3PE syndrome, the paraneoplastic syndrome should be ruled out, and patients should be monitored for a long time if necessary for life long due to the probability of malignity. Yao et al. reviewed the literature on RS3PE and proposed that the rate of malignity associated with RS3PE may be as high as 54%.

Nevertheless, there is no large case series or population survey on RS3PE, and the actual prevalence of neoplasms in this syndrome is unknown. More severe disease with systemic symptoms and weak response to treatment increases the probability that this clinical picture may represent a neoplastic process. Therefore, cancer screening appropriate to the age of the patient is recommended. No solid malignity was found in our case series, but two hematological malignities were identified. i.e., one case of primary myelofibrosis and one case of MGUS, diagnosed after screening made following the diagnosis of RS3PE. Recurrence occurred in two patients after the dose of steroid was decreased. The Hematology department followed them. A case associated with multiple myeloma has been reported in the literature, but no association with myelofibrosis has been reported.

To treat RS3PE patients with no underlying disease, steroids at low doses should be used for 18 months. Most patients respond well to steroids, and symptomatic improvement is observed within 24-72 hours of glucocorticoid onset. Disease-Modifying Anti Rheumatismal Drugs play a minimal role. Generally, RS3PE cases without any accompanying neoplasm have a favorable prognosis. This remission is usually permanent.

Conversely, in the presence of an underlying malignity, RS3PE has an inadequate response to treatment, and primary treatment of underlying malignity is necessary. In patients with RS3PE, resistance to low-dose corticosteroid treatment and the presence of concurrent systemic symptoms should warn the clinicians about the presence of probable malignity.[32] Therefore, increasing awareness of associated clinical characteristics and possible comorbid conditions is of significance.

Limitations of the study: The study's main limitation is that it was carried out at a single center with few cases.

CONCLUSION

The rare occurrence of this syndrome leads clinicians to miss it commonly, which gives rise to the administration of unnecessary long-term treatments. Another essential point that clinicians should be borne in mind is that RS3PE may be encountered as paraneoplastic syndrome in various hematological and solid malignities and may also be associated with various autoimmune and rheumatological diseases and drugs. The relation between RS3PE and four new conditions, i.e., scleroderma and relapsing polychondritis, monoclonal gammopathy of unknown significance, and primary myelofibrosis The present study aimed to discuss cases diagnosed with RS3PE, review the literature on this issue, and increase awareness of this entity among clinicians by describing its characteristics.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for the study was obtained from the ethics committee with the decision dated 22.04.2020 and numbered. 2020/181.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Orjinal Araştırma / Original Article

Morphometric Analysis of Cervical Spinal Cord and Spinal Canal with Magnetic Resonance Imaging in Turkish Adults

Türk Yetişkinlerde Manyetik Rezonans Görüntüleme ile Servikal Spinal Kord ve Spinal Kanalın Morfometrik Analizi

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Abstract

Aim: We aimed to evaluate the normal values of cervical spinal canal diameter and spinal cord diameter-area by magnetic resonance imaging (MRI) in adult Turkish population, in this study. It was investigated whether the values changed according to age, gender and spinal cord levels.

Material and Method: We retrospectively examined cervical MRI of 300 adult patients (150 female / 150 male). The patients were divided into 3 groups (18-39, 40-59 and over 60 years old) according to their age. Spinal canal and spinal cord diameter were measured in the sagittal plane and the spinal cord area in the axial plane from the C3 and C6 levels.

Results: Gender affects the normal values of the cervical spinal canal and spinal cord diameter. Both spinal cord and spinal canal measurements were found to be higher in men than in women. Spinal cord diameter and area were found to be lower at the C6 level than at the C3 level, regardless of gender. Both spinal canal diameter and spinal cord area decreased from cranial to caudal (C3-C6). Significant differences were detected in our data in the evaluation of age-related groups, and age was found to be effective in determining the normal parameter.

Conclusion: In conclusion, cervical spinal canal and spinal cord measurements in healthy individuals vary depending on age, gender and cord level.

Keywords: Magnetic resonance imaging, cervical spine, spinal cord, spinal canal, morphometry

Öz

Giriş: Yetişkin Türk popülasyonunda servikal spinal kanal çapı ve spinal kord çap-alanı normal değerlerinin manyetik rezonans görüntüleme (MRG) ile değerlendirilmesi amaçlandı. Değerlerin yaşa, cinsiyete ve spinal kord düzeylerine göre değişip değişmediği araştırıldı.

Gereç ve Yöntem: 300 erişkin hastanın (150 kadın / 150 erkek) servikal MRG'sini geriye dönük olarak inceledik. Hastalar yaşlarına göre 3 gruba (18-39, 40-59 ve 60 yaş üstü) ayrıldı. Spinal kanal ve spinal kord çapı sagital planda, spinal kord alanı aksiyal planda, C3 ve C6 seviyelerinden ölçüldü.

Bulgular: Cinsiyet, servikal spinal kanal ve spinal kord çapı normal değerlerini etkiler. Erkeklerde hem spinal kanal hem de spinal kord ölçümleri kadınlara göre daha yüksek bulundu. Spinal kord çapı ve alanı, cinsiyete bakılmaksızın C6 düzeyinde C3 düzeyindekinden daha düşük bulundu. Hem spinal kanal çapı hem de omurilik alanı kranialden kaudale azaldı (C3-C6). Yaşa bağlı grupların değerlendirilmesinde verilerimizde önemli farklılıklar tespit edilmiş ve yaşın normal parametrenin belirlenmesinde etkili olduğu görülmüştür.

Sonuç: Sonuç olarak, sağlıklı bireylerde servikal spinal kanal ve spinal kord ölçümleri yaş, cinsiyet ve kord düzeyine göre değişmektedir.

Anahtar Kelimeler: Manyetik rezonans görüntüleme, servikal vertebra, spinal kord, spinal kanal, morfometri

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INTRODUCTION

It is important to know the normal parameters of the cervical spinal cord and spinal canal in the evaluation of degenerative, traumatic and inflammatory conditions.[1] Age, gender, body mass index and spinal cord level are the parameters that should be taken into account in spinal cord and spinal canal measurements.[2] Normal cervical spinal cord and spinal canal measurements determined using the these parameters are required for the detection and differential diagnosis of possible pathologies.

There are many studies about evaluating canal diameter, canal-corpus ratio, and interpeduncular distance measurements via conventional radiographs and computed tomography.[3-8] However, these imaging techniques are insufficient for soft tissue evaluation. Today, magnetic resonance imaging (MRI) is the most effective and widely used in the evaluation of the cervical spinal canal. With MRI, both soft tissue and bone structures are evaluated, spinal canal and spinal cord dimensions are measured accurately.[9] There are relatively few studies in the literature evaluating cervical spinal canal and cord diameters with MRI. In this study, it was aimed to evaluate the normal values of cervical spinal canal diameter and spinal cord diameter-area by MRI in an adult Turkish population.

MATERIAL AND METHOD

A local ethics committee approved this single-center retrospective study (2021/98). Patients over the age of 18 who underwent cervical MRI (indication: neck-shoulder pain, disc herniation, etc.) in our center between June 2016 and December 2020 were randomly selected and included in the study. The patients were divided into 3 groups according to their age (18-39, 40-59 and over 60 years old). A total of 300 patients were selected, with 50 male and 50 female patients in all age groups. Exclusion criteria; spinal stenosis (spinal canal diameter <10 mm), compressive myelopathy (change in spinal cord signal and diameter), spinal cord tumor, spinal cord ischemia, spinal cord injury, history of head and neck surgery, trauma and pregnancy.

All examinations were performed with a 1.5 Tesla MR system (Sonata; Siemens Medical Solutions, Erlangen, Germany). Imaging was obtained with patients in a neutral supine position. T2-weighted sagittal turbo spin echo sequence (time-to-echo 108 ms; time-to-repetition 3000 ms; slice thickness:3.4 mm; field of view 568x640) and T2-weighted axial (time-to-echo 105 ms; time-to-repetition 4280 ms; slice thickness:3.0 mm; field of view 608x608) images were used for measurements. Anterior-posterior (AP) spinal canal and spinal cord diameter were measured at the mid-vertebral level C3 and C6 in the sagittal plane (**Figure 1**). Spinal cord area was measured at the disc levels in the axial plane using a manual measurement (**Figure 2**). All measurements were made by the same radiologist.

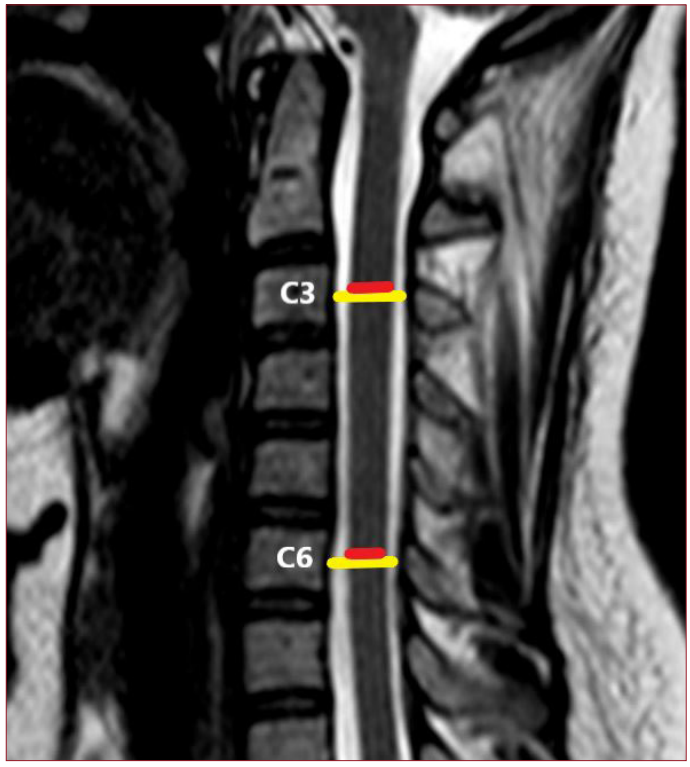

Figure 1. Antherio-posterior (AP) spinal canal (red line) and spinal cord (yellow line) diameter at the mid-vertebral level C3 and C6 in the sagittal plane.

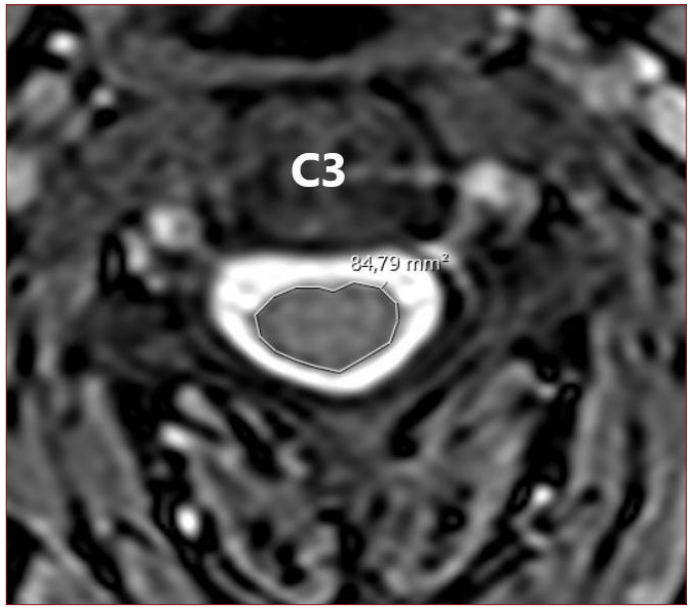

Figure 2. Spinal cord area at the C3 level in the axial plane.

Statistical Analysis

All statistical analysis was performed by using SPSS 23.0 (IBM, Armonk, NY, USA), and p values less than 0.05 was considered statistically significant. Average values of AP spinal canal and cord diameter in sagittal plane and cord area in axial plane were calculated at C3 and C6 levels. The measured values for each level were calculated separately according to age groups and gender. Student's t-test was

used to compare two independent groups, and the Anova test was used to compare three or more groups while comparing them according to gender and age groups. It was observed that age groups were distributed homogeneously and Bonferroni test was used for Post Hoc evaluation. While evaluating among age groups, p value was accepted as 0.017, since there are 3 independent variables.

RESULTS

A total of 300 patients, 150 men and 150 women, participated in the study. The mean age of the patient group over the age of 60 was 68.7±5.7 years, the mean age of the 40-59 age group was 46.18±5.1 years, and the mean age of the 18-39 age group was 28.19±6.3 years. The mean age of the female population was 48.26±17.5 years (range, 18.7-85.6 years), the mean age of the male population was 46.99±17.5 years (range, 18.2-83.4 years).

The spinal canal diameter was calculated as 12.04±1.16 mm at the C3 level and 12.21±1.33 mm at the C6 level. It was observed that there was no significant difference in cord diameter between these levels (p>0.05). Cord diameter mean values at the C3 level are 6.78±0.65 mm, at C6 level 6.20±0.60 mm; cord area mean values 69.87±8.77 mm² at C3 level, 63.73±8.15 mm² at C6 level. It was observed that the difference between cord diameter and area at C3 and C6 levels was significant (p<0.05). As a result, it was found that the cord diameter and area were lower at the C6 level than at the C3 level (**Table 1**).

In **Table 2**, mean values for each level by gender are given and the difference between them is evaluated. In all three parameters, the difference between the male and female groups was found to be significant; the canal, cord diameter and cord area were found to be larger in the male population (p<0.05). **Table 3** shows the mean values and Anova analysis results by age groups. A significant difference was found between the parameters except the C6 cord area by age groups (p<0.05).

Analysis of the difference between age groups was done with the Bonferroni test (**Table 4**). The results between the ages of 18-40 and over 60 were found to be significant. It was observed that the spinal canal diameter and cord diameter decreased over the age of 60 compared to other age groups (p<0.017).

DISCUSSION

The studies on spinal canal and cord measurements in the cervical region date back to the early 1900s. In the early periods, studies were conducted with a limited number of samples using cadavers. With the development of imaging techniques, studies that can reach large populations and use different variables can be performed. Vertebral and spinal canal measurements are more prominent in studies performed with conventional radiographs and computed tomography.[3,7,10,11]

Table 1. The mean values according to C3 and C6 levels.

Variables	Level	N	Mean	SD	p
Spinal canal diameter	C3	300	12.29	1.21	0.4
	C6	300	12.21	1.33	
Spinal cord diameter	C3	300	6.78	0.65	<0.05
	C6	300	6.20	0.60	
Spinal cord area	C3	300	69.87	8.77	<0.05
	C6	300	63.73	8.15	

Table 2. Differences according to gender

Variables	Gender	N	Mean	SD	p
Spinal canal diameter at C3	Female	150	12.04	1.16	<0.001
	Male	150	12.54	1.22	
Spinal cord diameter at C3	Female	150	6.67	0.66	<0.05
	Male	150	6.87	0.62	
Spinal cord area at C3	Female	150	66.96	8.33	<0.001
	Male	150	72.94	8.34	
Spinal canal diameter at C6	Female	150	11.97	1.35	<0.05
	Male	150	12.49	1.28	
Spinal cord diameter at C6	Female	150	6.06	0.58	<0.001
	Male	150	6.34	0.58	
Spinal cord area at C6	Female	150	60.69	7.73	<0.001
	Male	150	66.97	7.51	

Table 3. Analysis of the difference by age groups

Variables	Age	N	Mean	SD	95% Confidence Interval for Mean		p
					Lower Bound	Upper Bound	
Spinal canal diameter at C3	18-40	100	12.63	1.13	12.40	12.85	<0.05
	40-60	100	13.33	1.17	12.10	12.56	
	> 60	100	11.91	1.22	11.67	12.16	
	Total	300	12.29	1.21	12.15	12.43	
Spinal cord diameter at C3	18-40	100	6.84	0.67	6.71	6.98	<0.05
	40-60	100	6.97	0.57	6.86	7.09	
	> 60	100	6.20	0.62	6.38	6.63	
	Total	300	6.78	0.65	6.70	6.85	
Spinal cord area at C3	18-40	100	70.95	9.45	69.08	72.83	<0.05
	40-60	100	71.44	8.18	69.82	73.06	
	> 60	100	67.21	8.08	65.61	68.82	
	Total	300	69.87	8.77	68.87	70.87	
Spinal canal diameter at C6	18-40	100	12.57	1.17	12.34	12.80	<0.05
	40-60	100	12.37	1.39	12.09	12.64	
	> 60	100	11.70	1.28	11.45	11.96	
	Total	300	12.21	1.33	12.06	12.36	
Spinal cord diameter at C6	18-40	100	6.18	0.62	6.05	6.30	<0.05
	40-60	100	6.43	0.48	6.34	6.53	
	> 60	100	5.99	0.61	5.87	6.11	
	Total	300	6.20	0.60	6.13	6.27	
Spinal cord area at C6	18-40	100	64.03	8.91	62.26	65.80	0.77
	40-60	100	64.86	7.31	63.41	66.31	
	> 60	100	62.30	8.02	60.71	63.89	
	Total	300	63.73	8.15	62.80	64.66	

Table 4. Bonferroni test results

Variables			p	98.3% CI	
				Lower Bound	Upper Bound
Spinal canal diameter at C3	18-40 years	40-60 years	0.229	-0.1686	0.7634
		> 60 years	0.000	0.2490	1.1810
	40-60 years	18-40 years	0.229	-0.7634	0.1686
		> 60 years	0.039	-0.0484	0.8836
	> 60 years	18-40 years	0.000	-1.1810	-0.2490
		40-60 years	0.039	-0.8836	0.0484
Spinal cord diameter at C3	18-40 years	40-60 years	0.431	-0.3770	0.1170
		> 60 years	0.001	0.0900	0.5840
	40-60 years	18-40 years	0.431	-0.1170	0.3770
		> 60 years	0.000	0.2200	0.7140
	> 60 years	18-40 years	0.001	-0.5840	-0.0900
		40-60 years	0.000	-0.7140	-0.2200
Spinal cord area at C3	18-40 years	40-60 years	1.000	-3.8757	2.9029
		> 60 years	0.007	0.3509	7.1295
	40-60 years	18-40 years	1.000	-2.9029	3.8757
		> 60 years	0.002	0.8373	7.6159
	> 60 years	18-40 years	0.007	-7.1295	-0.3509
		40-60 years	0.002	-7.6159	-0.8373
Spinal canal diameter at C6	18-40 years	40-60 years	0.785	-0.3029	0.7129
		> 60 years	0.000	0.3591	1.3749
	40-60 years	18-40 years	0.785	-0.7129	0.3029
		> 60 years	0.001	0.1541	1.1699
	> 60 years	18-40 years	0.000	-1.3749	-0.3591
		40-60 years	0.001	-1.1699	-0.1541
Spinal cord diameter at C6	18-40 years	40-60 years	0.006	-0.4848	-0.0272
		> 60 years	0.066	-0.0398	0.4178
	40-60 years	18-40 years	0.006	0.0272	0.4848
		> 60 years	0.000	0.2162	0.6738
	> 60 years	18-40 years	0.066	-0.4178	0.0398
		40-60 years	0.000	-0.6738	-0.2162

* The mean difference is significant at the 0.017 level.

In our study, spinal cord and spinal canal measurements at C3 and C6 levels in the adult Turkish population were compared according to age and gender by using MRI. Studies show that gender affects the normal values of the cervical spinal canal and cord diameter. In our study, these values were found to be higher at men than women. Spinal cord measurements were found to be lower at C6 level than at C3 level, regardless of gender. There is a statistically insignificant reduction at C6 level in the diameter of the spinal canal. Significant differences were detected in the evaluation of age-related groups, and age was found to be effective in determining the normal parameter. There is a statistically significant decrease in all variables, especially in the population above 60 years old. Our results showed age and gender-related differences should be taken into account when evaluating the cervical spinal canal and spinal cord with MRI. In our study, contrary to similar studies in the literature, the spinal canal diameter decreased at the C6 level, while the cord area also decreased.[9,11,12] This situation creates a different perspective in the relative risk assessment for compressive myelopathy at the lower cervical levels.

The studies have shown that the diameter of the spinal canal decreases from the cranial to the caudal in the cervical region, and the spinal cord area increases.[9,12-13] This condition has been evaluated as an increasing risk factor in terms of compressive myelopathy and posttraumatic injury at the lower cervical levels. In our study, there was a non-significant decrease in the spinal canal diameter at the C6 level compared to C3. However, cervical spinal cord area and cord diameter also showed a significant decrease. Okada et al.[14] and Sherman et al.[15] found that the area and diameter of the cervical spinal canal decreased in C6 compared to C3, similar to our results. Considering the spinal canal diameter alone, the risk of compressive myelopathy can be mentioned. Since the space around the spinal cord decreases relatively at the lower cervical levels, the risk is dominant at these levels.[16,17] However, different results in spinal cord area and diameter measurements raise questions about this issue. Another point that should not be forgotten is that morphometric studies may differ according to age, gender, height, weight and ethnic origin.[9] Our study was done only at two levels. In order to make a general inference, new studies are needed in which all levels are evaluated and variables that may cause morphometric differences are taken into account.

In studies in which gender and age-related cervical spinal canal and cord were evaluated; In general, it has been found that canal and cord measurements are higher in men than women, and the measurements progressively decrease in older ages.[9,12,13] Our results are similar to these studies. Both spinal canal and spinal cord measurements were higher in men in all age groups. There was a significant decrease in the measurements, especially over the age of 60.

There were some limitations in our study. First of all, anthropometric measurements could not be used as variables due to the retrospective character of the study. For example, studies have reported that height may affect spinal morphometric measurements.[9,18] Future studies using anthropometric measurement information can provide useful information on this subject. Second, intra- and inter-observer variability could not be evaluated. Third, our sample size is relatively small for morphometric study.

CONCLUSION

In conclusion, cervical spinal canal and spinal cord dimensions in healthy individuals vary according to age, gender and cord level. These results can be used as reference values in future studies on pathologies affecting cervical spinal cord dimensions.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Selcuk University Medical Faculty Ethical Committee. (2021/98).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

Testicular Tumors: A 15-Year Archive Review and Histopathological Evaluation

Testis Tümörleri: 15 Yıllık Arşiv Taraması ve Histopatolojik Değerlendirilmesi

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Abstract

Aim: Testicular tumors are one of the most common malignancies in men in the age group of 15-40 years, although they are rarely observed. In our study, it was aimed to evaluate their histopathological features by retrospectively examining of the cases diagnosed as testicular tumor in our department.

Material and Method: Age, tumor localization, tumor size, pathological stage, tumor type and frozen information of 65 cases diagnosed as testicular tumor in the Department of Medical Pathology at Tokat Gaziosmanpasa University Faculty of Medicine between 2006-2020 were examined.

Results: The mean age of 65 cases diagnosed as tumor was 37.9±17.73 years. Their ages ranged from 1 to 78 years. Macroscopic tumor diameter was an average of 4.6±2.36 cm, 36 (55.4%) of them were located in the right and 29 (44.6%) of them were located in the left testis. Histopathological diagnosis was germ cell tumor in 53 (81.7%) cases and non-germ cell tumor in 12 (18.3%) cases. The most common tumor was seminoma with 22 (33.9%) cases and the second was mixed germ cell tumor with 19 (29.3%) cases. In components forming mixed germ cell tumors, embryonal carcinoma was the most commonly seen. Intraoperative frozen section examination was performed in 17 cases, it was determined that 10 cases were malignant and 7 cases were benign.

Conclusion: The histopathological and general features of our series of testicular tumor was determined to be compatible with the literature to a great extent. Intraoperative frozen section examination is an important auxiliary diagnostic method in terms of organ preserving surgery.

Keywords: Testis, tumor, germ cell, frozen section examination, testis preserving surgery

Öz

Amaç: Testis tümörleri nadir görülmekle birlikte, 15-40 yaş grubundaki erkeklerde en sık görülen malignitelerden biridir. Çalışmamızda bölümümüzde testis tümörü tanısı almış olguların retrospektif olarak incelenip, histopatolojik özelliklerinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: 2006-2020 yılları arasında Tokat Gaziosmanpaşa Üniversitesi Tıp Fakültesi Tıbbi Patoloji Anabilim Dalı'nda testis tümörü tanısı alan 65 olgunun yaş, tümör lokalizasyonu, tümör boyutu, patolojik evre, tümör tipi ve frozen bilgisi incelendi.

Bulgular: Tümör tanısı alan 65 olgunun yaş ortalaması 37,9±17,73 yıl idi. Yaşları 1-78 yıl arasında değişmekteydi. Makroskopik tümör çapı ortalama 4,6±2,36 cm olup, 36'sı (%55,4) sağ, 29'u (%44,6) sol testis lokalizasyonluydu. Histopatolojik tanı 53 olguda (%81,7) germ hücreli tümör ve 12 olguda (%18,3) germ hücreli dışı tümördü. En sık görülen tümör 22 olgu (%33,9) ile seminom ve ikinci sıklıkta 19 olgu (%29,3) ile mikst germ hücreli tümördü. Mikst germ hücreli tümörleri oluşturan komponentlerde en sık embriyonel karsinom görüldü. İntraoperatif frozen kesit inceleme 17 olguda yapılmış olup, 10 olgunun malign, 7 olgunun benign olduğu saptandı.

Sonuç: Testis tümörü serimizin histopatolojik ve genel özelliklerinin büyük oranda literatür ile uyumlu olduğu saptanmıştır. İntraoperatif frozen inceleme organ koruyucu cerrahi açısından önemli bir yardımcı tanı yöntemidir.

Anahtar Kelimeler: Testis, tümör, germ hücre, frozen kesit inceleme, testis koruyucu cerrahi

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INTRODUCTION

Testicular tumors are one of the most common seen malignancies in men in the age group of 15-40 years, although they are rarely observed. It constitutes 1-2% of all malignancies in men. The age standardized incidence rate of testicular cancer was 1,5 per 100000 people in the world. It is more commonly seen in developed countries and its incidence is increasing day by day. As the highest incidence rate is 7.2-8.7 in Europe, the lowest incidence rate is 0.3-0.6 in Africa and 0.4-1.7 in Asia.[1,2] Etiopathogenesis has not been fully elucidated. However, environmental and genetic factors are blamed in the etiology. Family history, undescended testis, testicular microlithiasis, inguinal hernia, low birth weight, maternal smoking during pregnancy, high-fat diet, obesity, occupational exposures are supposed among the risk factors.[3,4] Patients with testicular tumors usually present with a unilateral painless mass. The tumors are more commonly observed in the right testis than the left one. The incidence of bilaterality is reported to be at rate of 1-4%.[5,6] Germ cell tumors (GCTs) constitute 95% of testicular tumors. GCTs are divided into two main groups as seminomatous and nonseminomatous GCTs. Seminomas make up 50% of all GCTs. Nonseminomatous GCTs include embryonal carcinoma (EC), yolk sac tumor (YST), choriocarcinoma (CC) and teratoma (T). Non-germ cell tumors (NGCTs) of the testis are classified as sex cord-stromal tumors paratesticular tumors, mesenchymal tumors of the spermatic cord and testicular adnexa, hematolymphoid tumors and metastatic tumors.[3,4] In The World Health Organization (WHO) 2016 classification of testicular tumors, different from the WHO 2004 classification, germ cell tumors are defined as the tumors derived from germ cell neoplasia in situ and the tumors unrelated to germ cell neoplasia in situ.[3,7]

In our study, we aimed to examine the age, tumor location, tumor size, pathological stage, tumor type and frozen information of cases diagnosed as testicular tumor in our department between 2006-2020, and to evaluate them in the light of literature information.

MATERIAL AND METHOD

A total of 65 cases who were diagnosed as testicular tumor by performing histopathological examination in the Department of Medical Pathology between 2006-2020, were analyzed after obtaining the approval of the Clinical Research Ethics Committee (20-KAEK-320) at Tokat Gaziosmanpaşa University Faculty of Medicine for our study. Pathology reports of the cases were analyzed retrospectively by scanning the pathology archive. Hematoxylin-eosin stained preparations of the cases were reviewed and classified according to the WHO 2016 classification. Age, tumor localization, tumor size, tumor type, pathological stage and frozen information of the cases were registered from the pathology reports and the records in the automation system. The obtained data were evaluated in the light of literature information.

Statistically, categorical measurements were specified as numbers and percentages, and continuous measurements were expressed as mean and standard deviation (median and minimum-maximum where necessary). SPSS 22 package software was used for the analysis.

RESULTS

Testicular tumors were detected in 65 (42.8%) of 152 orchiectomy materials from 2006-2020, which were retrospectively detected from our department archive. The ages of 65 patients diagnosed as tumor ranged from 1 to 78 years and the mean age was found to be 37.9±17.73 years. The age range distribution of the patients was given in **Figure 1**. Macroscopic tumor diameters ranged from 0.8 to 10 cm, with an average of 4.6±2.36 cm. 36 (55.4%) of the tumors were located in the right, 29 (44.6%) of them were located in the left testis. Bilateral testicular involvement was not present in any of the patients. Fify three (81.7%) of our cases were diagnosed as GCT and 12 (18.3%) of them as NGCT. The histopathological distribution of our cases diagnosed as testicular tumor was given in **Table 1**. The most common tumor among our cases was seminoma with 22 (33.9%) cases (**Figure 2**) and the second most common tumor was mixed GCT with 19 (29.3%) cases. In the components forming mixed GCTs, EC (**Figure 3**) was the most common seen. The distribution of mixed GCTs and constituent components was shown in **Table 2.** In our series, there were 17 cases who underwent intraoperative frozen section examination. The characteristics of these cases were given in **Table 3.** Intraoperative frozen section examination was performed in 17 cases, it was determined that 10 cases were malignant and 7 cases were benign. All cases diagnosed as epidermoid cyst were the cases which underwent intraoperative frozen section examination. Of the cases with pathological tumor staging, 31 were found to be pT1, 18 were pT2, and 4 were pT3. Six of our patients became exitus. Two of them had a diagnosis of GCT and the others consisted of one patient each who had a diagnosis of lymphoma, leiomyosarcoma, adenomatoid tumor and malignant melanoma metastasis.

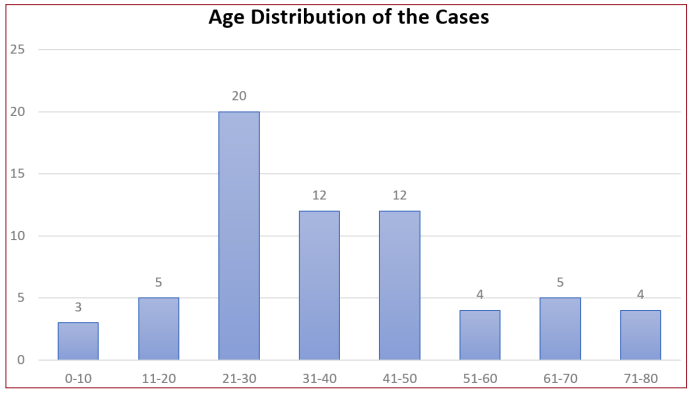

Figure 1. The age distribution of the patients with testicular tumors

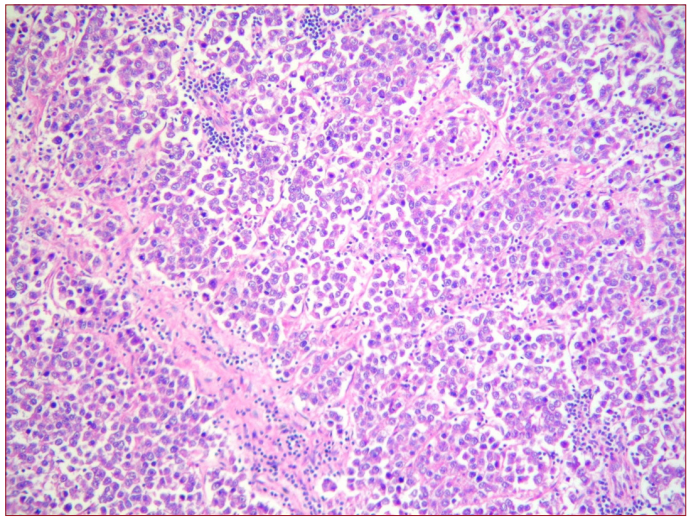

Figure 2. Seminoma. Lymphocytic infiltration between polygonal shaped tumor cells with prominent nucleoli and eosinophilic cytoplasm. (HE x 100)

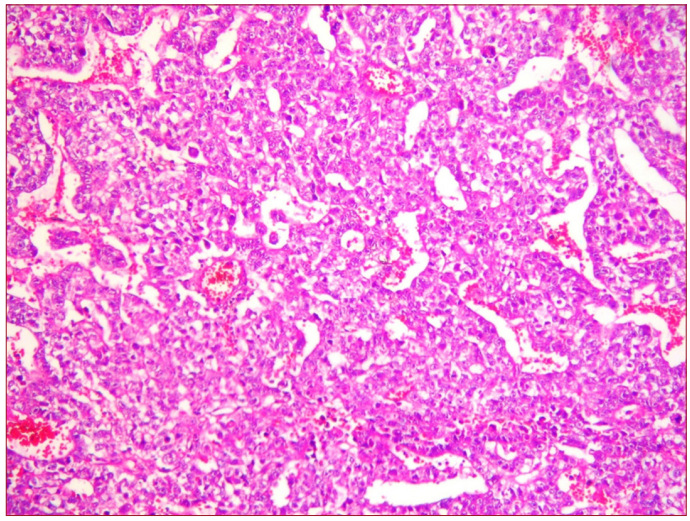

Figure 3. Embryonal carcinoma. Glandular pattern of columnar-shaped tumor cells. (HE x 100)

Table 1. Histopathological distribution of testicular tumors

Diagnosis	n	%
Germ cell tumors		
Seminoma	22	33.9
Embryonal carcinoma	1	1.5
Yolk sac tumor	3	4.7
Choriocarcinoma	1	1.5
Teratoma	1	1.5
Mixed GCT	19	29.3
Spermatocytic tumor	1	1.5
Epidermoid cyst	5	7.8
Sex cord-stromal tumor		
Leydig cell tumor	2	3.1
Hematolymphoid tumors		
Diffuse large B-cell lymphoma	4	6.2
Paratesticular tumors		
Adenomatoid tumor	1	1.5
Mesenchymal tumors of the spermatic cord and testicular adnexa		
Leiomyoma	1	1.5
Leiomyosarcoma	1	1.5
Hemangioma	1	1.5
Metastatic tumors		
Malignant melanoma metastasis	1	1.5
Renal cell carcinoma metastasis	1	1.5
Total	**65**	**100**

Table 2. Distribution of mixed GCTs

Tanı	n	%
EC+YST+T	6	31.5
S+EC	4	21
S+EC+YST	3	15.7
EC+YST	1	5.3
EC+T	1	5.3
S+YST	1	5.3
S+YST+T	1	5.3
S+EC+YST+T	1	5.3
S+EC+T+CC	1	5.3
Total	19	100

EC: Embryonal carcinoma, YST: Yolk sac tumor, T: Teratoma, S: Seminoma, CC: Choriocarcinoma

Table 3. Testicular tumors which intraoperative frozen section examination were performed in

Age	Localization	Tumor size (cm)	Frozen section diagnosis	Final diagnosis
78	Left	3	Malignant	Seminoma
38	Right	2.5	Malignant	Mixed GCT (EC+S)
21	Left	3	Malignant	Mixed GCT (EC+YST)
19	Right	2	Malignant	Embryonal carcinoma
49	Right	10	Malignant	DLBCL
1	Left	5	Malignant	Yolk sac tumor
9	Right	0.8	Benign	Epidermoid cyst
25	Right	4	Malignant	Seminoma
41	Left	1	Malignant	Teratoma
21	Left	1	Benign	Epidermoid cyst
64	Right	1.5	Benign	Hemangioma
6	Right	1.5	Benign	Epidermoid cyst
62	Right	3	Benign	Leiomyoma
16	Right	1.5	Benign	Epidermoid cyst
25	Right	7.5	Malignant	Seminoma
22	Left	3	Mailgnant	Yolk sac tumor
68	Right	3	Benign	Epidermoid cyst

GCT: Germ cell tumor, EC: Embryonal carcinoma, S: Seminoma, YST: Yolk sac tumor, DLBCL: Diffuse large B-cell lymphoma

DISCUSSION

Testicular cancer is the most common cancer of the genital system in men. Approximately 50000 new cases and 10000 deaths are detected every year in the world.[2] In the last few decades, an increase has been observed in the incidence of testicular cancer all over the world, mainly in European countries. However, with early diagnosis, standardization of tumor management and advances in treatment, a significant decrease in mortality rates has been detected. It is seen that the five-year survival rates have increased from 63% to over 90%.[1] The etiology of testicular tumors is not clear, and environmental and genetic factors play a role. Cryptorchidism is one of the most important risk factors and the rate of development of testicular cancer is 2.9-6.3%.[8] Age, family history of testicular tumor, the white race,

high socioeconomic level, testicular microlithiasis, trauma, infection, exposure to in utero diethylstilbestrol, mother's smoking during pregnancy, occupational exposures, chemicals, diet rich in fat and dairy products are among the risk factors.[2,3,8] Testicular tumors are most common in the 15-40 years age range. The mean age of the patients in our series was 37.9 years, and it was consistent with the literature.[1,2] Right side testicular tumor involvement is more common than the left side. The frequency of bilateral testicular tumor involvement is 1-4%. Bilateral tumors can be observed simultaneously (synchronous) or at different times (metachronous).[6] Right side involvement was more common in our cases, and bilateral testicular involvement was not observed.

Approximately 90-95% of testicular tumors consist of GCTs. In our series, 53 (81.7%) of 65 cases were GCT. Seminomas are the most common observed among testicular tumors. Seminomas constituted 22 (33.9%) of our cases (**Figure 2**), in addition they were found at a rate of 58% of the components that made up mixed GCTs (**Table 2**). Radiotherapy is used for the treatment of seminomas and has no place for the treatment of other GCTs, so in the presence of testicular tumor, correct diagnosis of seminomas is important in terms of treatment and prognosis. It has been reported that the biological behaviors of anaplastic seminomas with high mitotic activity do not change the prognosis and treatment of the patient and therefore do not need to be specified in pathology reports.[9,10] Although the rate of embryonal carcinoma in mixed GCTs is over 80%, its pure form is rarely seen (2-10%).[5,9] Pure embryonal carcinoma was detected in one of our cases (1.5%) and embryonal carcinoma was available in 89.7% of mixed GCTs in our cases. Although yolk sac tumor is rarely seen (1%), it is the most common observed testicular tumor of the prepubertal period. In children, its pure form is seen. Its pure form is rare in adults and it is found as a component of mixed GCTs, with a rate of 40%.[11] One of our three cases diagnosed as yolk sac tumor was in the prepubertal period and he was 1 year old, the others were 22 and 38 years old. In 68.4% of our mixed GCT cases, yolk sac tumor component was available. Pure form of choriocarcinoma is rare and accounts for less than 1% of testicular tumors. Finding the vital tumor area becomes difficult due to the widespread presence of bleeding and necrosis. Vascular invasion is an important feature of choriocarcinoma.[11,12] In one of our cases, pure choriocarcinoma was seen and choriocarcinoma was available as a component of mixed GCT in our another case. The age of our pure choriocarcinoma case was 21 years. He was diagnosed as lung metastasis before, and then it was detected that the primary was testis. Microscopic examination revealed that the entire testis was hemorrhagic and necrotic in appearance, there were tumor cells with pleomorphic bizarre nuclei in limited areas, frequent mitosis and widespread vascular invasion (**Figure 4**). Teratomas are rarely seen as pure and constitute 2-3% of GCTs. They accompany mixed GCTs at a rate of approximately 50%. In our series, pure teratoma was observed in a 41-year-old patient. The rate of teratoma accompanying mixed GCTs was 52.7% in our cases. While prepubertal teratomas show benign behavior, it is considered that postpubertal teratomas show malignant behavior.[10,11] Mixed GCTs, which are composed of different combinations of GCT subtypes, constitute approximately half of the testicular GCTs. In our series, the rate of mixed GCTs to all testicular tumors was low, with the rate being 29.3% (**Table 1**). Among the most common combinations there are embryonal carcinoma+teratoma, embryonal carcinoma+seminoma, embryonal carcinoma+yolk sac tumor+teratoma, embryonal carcinoma+teratoma+choriocarcinoma. Embryonal carcinoma is the most common accompanying component to combinations (**Figure 3**).[3,11] In our series, combination of embryonal carcinoma+yolk sac tumor+teratoma was the most frequently observed (**Table 2**). Spermatocytic tumor constitutes 1-2% of GCTs. Average age of occurrence is 52-59 years.[3] In our series, one case (1.5%) with a diagnosis of spermatocytic tumor was available and the age was 47 years. Epidermoid cyst accounts for 1-2% of all testicular tumors and is the most common benign tumor of the testicle. It is frequently seen between the second and fourth decades. It has an average diameter of 2 cm and is mostly observed in the right testicle. It is difficult to distinguish from malignant tumors clinically, and the definitive diagnosis is made by histopathological examination. Intraoperative frozen section examination is useful in determining radical orchiectomy or testicular preserving surgery option for treatment of epidermoid cyst.[13] Four of our five cases diagnosed as epidermoid cyst were localized in the right testicle, and the mean tumor diameter was 1.6 cm. Intraoperative frozen section examination was performed in all of our cases, and testicular preserving surgery was performed because their frozen section diagnoses were benign.

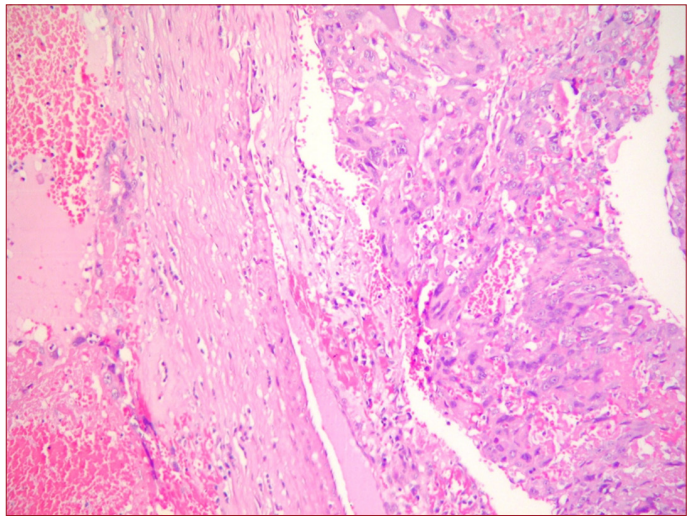

Figure 4. Choriocarcinoma. Hemorrhage, areas of necrosis and vascular invasion of pleomorphic tumor cells. (HE x 100)

Sex cord-stromal tumors account for 8% of all testicular tumors. Leydig cell tumor, which is the most common seen in this group, constitutes 1-3% of all testicular tumors.[11,14] Leydig cell tumor was detected in 2 (3.1%) of our cases, but other tumor types were not observed. Lymphomas are the most common testicular neoplasms of patients over the age of 60 years. It is seen in 1-9% of all testicular tumors. The most common type is diffuse large B-cell lymphoma with a rate of 80-90%.[15] Diffuse large B cell lymphoma was observed in 4 (6.2%) of our cases. Three of these cases were over 60 years old. In our series, an adenomatoid tumor located in the paratesticular area was observed in one case who was sent for consultation. Adenomatoid tumor is the most common paratesticular neoplasm. It accounts for approximately 30% of all paratesticular masses.[3,16] Mesenchymal tumors may develop from interstitial mesenchymal cells and endothelial cells of the spermatic cord and testicular adnexa. In our series, one case each with a diagnosis of hemangioma, leiomyoma and leiomyosarcoma was observed. Secondary tumors of the testis are extremely rare, they are seen at a rate of 0.06-3.6%. The most common metastasis to the testicle originate from the prostate, gastrointestinal tract, kidney, lung, malignant melanoma and urinary tract. In children, neuroblastoma, Willms tumor and rhabdomyosarcoma metastases are seen.[3] In our cases, malignant melanoma metastasis was observed in a 76-year-old patient and renal cell carcinoma metastasis in a 56-year-old patient.

Most of the testicular tumors are GCTs diagnosed with clinical and radiological findings before surgery. With the increasing use of scrotal USG, the diagnosis of small-sized and nonpalpable testicular lesions has increased. It has been shown that 80% of these lesions are benign. Scrotal ultrasonography does not have sonographic features to precisely distinguish intratesticular tumors as benign and malignant. The correct and definite distinction between benign and malignant lesions is only possible with histopathological examination. Frozen section examination is a very sensitive and specific intraoperative procedure to distinguish testicular and paratesticular tumors as benign and malignant. There are few studies suggesting that frozen examination can be accurate and effective to avoid radical orchiectomy. Silverio et al. retrospectively analyzed frozen section examination results and the biopsy permanent sections of 170 patients diagnosed as testicular lesions during fourteen years. As a result, they determined that frozen section examination helped to prevent unnecessary radical orchiectomy in 46 (88.5%) of cases with non-malignant lesions.[17,18] Frozen section examination is an important diagnostic method in determining the preference of organ-preserving surgery or radical orchiectomy surgical methods for childhood testicular tumors.[19] In our series, frozen section examination was performed in 17 cases, and organ preserving surgery was performed in 7 cases whose frozen diagnosis was benign (**Table 3**).

CONCLUSION

As a result, the majority of our series of 65 cases with testicular tumors in our 15-year archive consisted of GCTs by being in accordance with the literature, and most of these were seminomas and mixed GCTs. We think that further studies should be done to emphasize that intraoperative frozen section examination is an important diagnostic method in terms of organ preserving surgery.

ETHICAL DECLARATIONS

Ethics Committee Approval: For this research; Tokat Gaziosmanpaşa University Faculty of Medicine Clinical Research Ethics Committee approval was obtained (Date: 28.01.2021, number 20-KAEK-320)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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Orjinal Araştırma / Original Article

Assessment of Blood Inflammatory Parameters in Elderly Patients with Peripheral Vertigo

Periferik Vertigolu Yaşlı Hastalarda Kan Enflamatuar Parametrelerinin Değerlendirilmesi

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Abstract

Aim: The aim of this study is to evaluate the relationship between infection-induced Peripheral Vertigo and inflammatory parameters levels, white blood cell , neutrophil to lymphocyte ratio , platelet to lymphocyte ratio and C-reactive protein in elderly patients.

Material and Method: In our study, 122 patients with peripheral vertigo complaints were retrospectively evaluated. Their gender, age, the type of admission, emergency room discharge and hospitalization, hospital admission time, complaints, and physical examination findings rates were examined.

Results: The mean age was 73.4 years.. 115 patients (94.3%) were discharged after follow-up in the emergency department, while 7 patients (5.7%) were hospitalized. Complaints were 75.4% dizziness, 18% nausea-vomiting and 6.4% headache, respectively. There was no statistically significant difference in neutrophils, lymphocytes, platelets, neutrophil to lymphocyte ratio and platelet to lymphocyte ratio values.

Conclusion: In our study, white blood cell and C-reactive protein values were found to be higher than the reference values in patients.. The results of our study showed that it can be used actively in the diagnosis of inflammatory causes in the pathogenesis of elderly patients with peripheral vertigo.

Keywords: Peripheral vertigo, inflammatory markers, emergency room, elderly

Öz

Amaç: Bu çalışmanın amacı, yaşlı hastalarda enfeksiyona bağlı periferik vertigo ile inflamatuar parametreler, beyaz kan hücresi, nötrofil lenfosit oranı, platelet lenfosit oranı ve C-reactive protein arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntem: Çalışmamızda periferik vertigo şikayeti olan 122 hasta geriye dönük olarak değerlendirildi. Cinsiyetleri, yaşları, başvuru şekilleri, acil servisten taburculuk ve yatışları, hastaneye başvuru süreleri, şikayetleri ve fizik muayene bulgu oranları incelendi.

Bulgular: Ortalama yaş 73,4 yıldı. 115 hasta (%94,3) acil serviste izlem sonrası taburcu edilirken, 7 hasta (%5,7) hastaneye yatırıldı. Şikayetler sırasıyla %75,4 baş dönmesi, %18 bulantı-kusma ve %6,4 baş ağrısı idi. platelet, nötrofil, lenfosit, nötrofil lenfosit oranı ve platelet lenfosit oranı değerlerinde istatistiksel olarak anlamlı fark yoktu.

Sonuç: Çalışmamızda hastalarda beyaz kan hücresi ve C-reactive protein değerleri referans değerlerine göre daha yüksek bulundu. Çalışmamızın sonuçları, periferik vertigolu yaşlı hastaların patogenezinde inflamatuar nedenlerin, tanıda aktif olarak kullanılabileceğini göstermiştir.

Anahtar Kelimeler: Periferik vertigo, inflamatuar belirteçler, acil servis, yaşlı

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INTRODUCTION

Vertigo is defined as the perception of a rotational or translational movement of the patient himself or surrounding objects. It is one of the most common clinical symptoms and reasons for admission to the emergency department and outpatient clinics.[1,2] It affects approximately 20-30% of the world population and also decreases the quality of life of patients.[3] Peripheral vertigo (PV) is a type of vertigo that usually occurs due to infections of the inner ear such as otitis and labyrinthitis. The most common causes of PV are benign paroxysmal positional vertigo (BPPV), ménière's disease, labyrinthitis, vestibular neuritis, and perilymph fistula.[4,5] Infection, inflammatory and immunological factors are thought to play a significant role in the etiology of PV. But the exact cause of the condition is unknown yet.[6]

Complete blood count (CBC) parameters such as neutrophil, lymphocyte, and platelet provide useful information about infection and general inflammatory conditions. In recent years, the neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have been proposed as novel parameters that demonstrate the systemic inflammatory response. NLR and PLR can be easily calculated from the CBC. Some studies have shown that NLR and PLR ratios are associated with the diagnosis and prognosis of several diseases such as vestibular neuritis, sudden sensorineural hearing loss (SSHL), and peripheral facial palsy C-reactive protein (CRP), an acute-phase protein, is a useful marker of pathological processes including infection, tissue damage, and chronic inflammatory disease.[7,9] The level of CRP in the blood increase when there is a condition causing inflammation.

According to the literature survey, the association between NLR, PLR, CRP, and PV has not been previously studied. These inflammatory markers have been evaluated separately in many studies. However, this is the first study in which they are evaluated together. The aim of this study is to evaluate the relationship between infection-induced PV and inflammatory parameters levels, white blood cell (WBC), NLR, PLR and CRP in elderly patients.

MATERIAL AND METHOD

Study Design

This retrospective study was conducted on 122 patients over the age of 65 who presented to the emergency department, Kafkas University Health Research and Application Center with complaints of peripheral dizziness and infection between 01.10.2018-01.10.2019. The study was carried out with the permission of Kafkas University Faculty of Medicine Ethics Committee (Date: 30.10.2019, Decision No: 11) and was conducted according to the principles of Declaration of Helsinki. Informed consent statements were obtained from all patients. The medical files were reviewed retrospectively and the following data were recorded; demographic properties (age, gender), the type of admission, emergency room discharge and hospitalization, hospital admission time, complaints, and physical examination findings.

Inclusion criteria were complaints of peripheral vertigo due to infection, no history of trauma, no chronic inflammation and infectious diseases, no hematological diseases, no chronic liver disease, no chronic renal failure, no cardiovascular disease, no malignancy, and patients aged 65 years or older. . Patients with a history of trauma, chronic inflammation and infection, hematological diseases, chronic liver disease, chronic renal failure, cardiovascular diseases, malignancy and those under 65 years of age were excluded from the study.

WBC, neutrophils (NEU), lymphocytes (LYM), platelets(PLT), and CRP values at the time of admission to the emergency department were analyzed using hospital registries. An automated blood cell counter was used for CBC measurements using ABX Pentra DX 120 (Horiba, HORIBA ABX SAS, Japan). The NLR values were calculated by dividing the neutrophil count by the lymphocyte count and PLR values were calculated by dividing the platelet count by the lymphocyte count. CRP measurements were done using an automated analyzer (cobas 6000 Series system, c501 module, Roche, Germany) using nephelometric measurement. Results were considered based on laboratory's reference ranges.

Statistical Analysis

Statistical analysis was performed with the SPSS 22 software package. Pearson's chi-square test was used for categorical data analysis. The data were expressed as numbers and percentages. Mean, standard deviation, minimum-maximum values, frequency were included in the descriptive statistics of the data. A p value of $p<0.05$. Was accepted as statistically significant.

RESULTS

A total of 122 patients were enrolled in the current study. 61 (50%) of them, were males, 61 (50%) were females. The mean age was 73.4 years with a minimum age of 65 years and a maximum age of 88 years. The demographic characteristics and laboratory test results of patients are presented in **Table 1**.

Table 1. The demographic characteristics and laboratory data of patients

Variable	Mean	Standard deviation	max	min	Ref
Age (years)	73.4	7.62	88	65	
WBC(10^9/L)	10.91	14.80	167.8	3.4	3.7-10.4
PLT (10^3/μL)	243.60	68.70	416.0	52	149-371
NEU (10^3/mm)	5.24	2.41	13.4	2.2	1.8-7.8
LYM (10^3/mm)	2.18	0.96	5.1	0.7	0.9-3.7
CRP (mg/L)	0.85	3.08	27.8	0.009	0-0.5
NEU/LYM	2.88	2.03	12.97	0.70	
PLT/LYM	133.27	67.16	394.12	41.22	

As shown in **Table 1**, the mean value of WBC, PLT, NEU, LYM, NEU/LMY, PLT/LYM and CRP were 10.91 (3.4-167.8), 243.60 (52- 416.0), 5.24 (2.2-13.4), 2.18 (0.7-5.1), and 0.85 (0.009-27.8), respectively. No statistically significant differences were observed in values of PLT, NEU, LYM, NEU/LYM and PLT/LYM. On the other hand, the mean values of WBC and CRP of the patients were significantly higher than the reference range.

The hospitalization rates of the patients are summarized in **Table 2**. The distribution of genders was similar between females and males. When we evaluated the hospital admission time of all patients, we determined that the most common admission time was between 12:00 a.m and 5:59 p.m. (**Table 2**).

Table 2. Gender and application hours of patients

	Frequency (%)
Gender	
Female	61(50%)
Male	61(50%)
Hospital admission time (h)	
00:00-05:59	7 (5.7%)
06:00-11:59	36 (29.5%)
12:00-17:59	44 (36.1%)
18:00-23: 59	35 (28.7%)

The data are given as numbers and percentages

On the other hand 115 patients (94.3%) were discharged after follow-up in the emergency department, while 7 patients (5.7%) were admitted hospital. When compared the hospitalization rates of patients with peripheral vertigo according to gender by Pearson's chi-square test, 4 were male and 3 were female, there was no significant difference between males and females p<0.696 (**Table 3**).

Table 3. Gender ratio of hospitalized patients

Hospitalization		P value
No	115 (94.3%)	
Male	57	0.688
Female	58	
Yes	7 (5.7%)	
Male	4	0.696
Female	3	

The most common complaints were 75.4% dizziness, 18% were nausea and vomiting and 6.4% were headache. There were both dizziness and abdominal pain in two patients. There were both headache and syncope in one patient. In the physical examination, horizontal nystagmus was observed 95% (116) of the patients.

DISCUSSION

Vertigo is a common symptom worldwide that adversely affects the quality of life and imposes a serious social and economic impact on the health care.[10] In the etiopathogenesis of vertigo, several etiologic factors such as infection, immunologic and inflammatory play a causal role, but the exact causes remain unknown. In recent years, an increasing number of studies have been conducted to demonstrate the relationship between inflammation and vertigo and has been reported that inflammatory diseases could lead to vertigo.[9,11] Inflammation can be measured using a number of biochemical and hematological parameters. Research results indicate that assessment of WBC and its subtypes might have prognostic significance for some diseases related to inflammation.[12] Some changes have been observed in inflammatory markers depend on the underlying pathological conditions. In addition to physical, and neurological examination in the diagnosis and treatment of the disease, various studies have been also conducted on the use of these inflammatory markers.[13,14] Therefore, in the current study, we investigated the relationship between peripheral vertigo and inflammatory parameters. To the best of our knowledge, this is the first study to evaluate together WBC, NLR, PLR, and CRP values in elderly patients with peripheral vertigo.

Higher neutrophil counts were associated with inflammatory conditions and a low lymphocyte count was associated with higher physiologic stress. Under physiological stress conditions, the number of neutrophil count increases, while the lymphocyte count decreases. For this reason, the NLR ratio is considered as a parameter in inflammatory conditions. PLR also provide important information about the inflammatory condition such as NLO.[7,15] Several studies have been shown that the NLR and PLR use as an inflammatory biomarker to determine inflammation in several diseases including tinnitus, acute hearing loss, Bell's palsy and vertigo.[9,11,15]

As seen in the literature, research results about parameters of inflammatory in peripheral vertigo remain controversial. Chung et al.[7] investigated the relationship between NLR and PLR values and vestibular neuritis (VN) and found a significantly higher NLR and PLR value in patients with VN. In this regard, they proposed that these rates are simple and reliable parameters for predicting the cause and the severity of VN. Another study revealed that NLR values were significantly higher in patients with VN, while no significant differences were detected in PLR values. They reported that the results show the presence of a correlation between NLR and VN, suggest the presence of an inflammatory process related to VN, and may help the differential diagnosis of patients presenting with vertigo to the emergency department.[16] According to a study conducted by Tekesin and Tunç[11] for evaluating inflammatory biomarker levels in BPPV patients, NLR and PLR values were found higher in BPPV patients. Thus, results demonstrated that inflammation may be connected with the pathogenesis of BPPV. The study of Sahın et al.[15] evaluated that the NLR differences between the differential diagnoses and follow-up of patients with peripheral, BPPV and VN.

They found that NLR levels were significantly higher in patients with BPPV than in those with VN and demonstrated that the NLR could be used in evaluating the differential diagnosis of peripheral vertigo. Similar results were also obtained in

the study of Ozbay et al.[17] NLR values were significantly higher in patients with peripheral vertigo and a significant relationship between inflammation and peripheral vertigo. In our study, unlike previous studies, we found that PLR and NLR levels were not significantly different for peripheral vertigo caused by infection in elderly patients with peripheral vertigo. Consistent with most previous studies, the study of Temirbekov and Sakalli[18] showed no statistically significant difference in NLR and PLR in patients with peripheral vertigo. In this respect, we think that NLR and PLR ratios can be used in certain vertigo types.

CRP is another one of the markers of inflammation which was widely used for the assessment of inflammation in clinical practice and has been recognized as associated with several inflammatory diseases. In some types of vertigo have been shown an increased value of CRP.[14] Milionis et al.[19] found that CRP increase in patients with vestibular neuritis. However, other studies have not found an increased risk. Akıncı et al.[14] reported that no significant change concerning CRP levels in peripheral vertigo.

The most common symptom in vertigo patients is dizziness. These symptoms are followed by nausea, vomiting and headache.[5,20] The symptom rates of our patients are compatible with the literature, and in our study, dizziness was the most common cause of emergency admissions.

In general, patients with peripheral vertigo can be discharged in emergency departments as soon as symptoms are controlled. Patients with resistant symptoms and signs or with additional chronic diseases can be hospitalized.[21] In our study, we are consistent with the literature, and we think that our hospitalizations were caused by cases of vertigo originating from infection that did not respond to medical treatment applied in the emergency department.

In our study, we found a significantly higher CRP value in patients. However, when we examined the literature, it showed inconsistent infection parameter results. It can be thought that most of the causes of vertigo cannot be attributed to infection. However, we think that CRP is a guide in the diagnosis of patients with peripheral vertigo due to infection.

Limitation

The most important limitation of this study was that it was planned retrospectively and also there are few sample group in the systemic diseases group categories. There is a need for more comprehensive studies investigating the etiology of peripheral vertigo in the elderly.

CONCLUSION

In our study, WBC and C-reactive protein values were found to be higher than the reference values in patients. The results of our study showed that it can be used actively in the diagnosis of inflammatory causes in the pathogenesis of elderly patients with peripheral vertigo.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kafkas University Faculty of Medicine Ethics Committee (Date: 30.10.2019, Decision No: 11).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

Can Home Exercise Programs Be a Low-Cost Alternative to Multiple Sclerosis Treatment?

Evde Egzersiz Programları Multipl Skleroz Tedavisinde Düşük Maliyetli Bir Alternatif Olabilir mi?

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Abstract

Aim: In this study, we aimed to compare the effect of aerobic exercise programs on patients with Multiple Sclerosis (MS) and healthy controls, and to show that home exercise programs can be as effective as supervised exercise programs.

Material and Method: Eighty participants were included in this study and were divided into groups as the home-exercise group (outpatient), supervised exercise group (inpatient), and healthy controls. A 6-weeks aerobic exercise program was given to all participants. Before and after the exercise program, 6-Minute Walking Test (6MWT), Fatigue Severity Scale (FSS), Modified Ashworth Scale (MAS), Berg Balance Scale (BBS), Extended Disability Scale (EDSS), Cardiopulmonary Exercise Test (CPET), and MS Quality of Life (MSQoL-54) were applied to participants.

Results: When 6MWT and CPET data were evaluated, it was observed that the patient and control groups benefited from the exercise program. There was a significant improvement after treatment in the 6MWT, BBS, FSS, MSQoL-54, and CPET data of both the outpatient and inpatient groups, and there was no difference between the groups when the rates of change were compared.

Conclusion: We have observed that the home-based exercise program is as effective as the supervised exercise program. We think that the home program should be recommended first when planning the exercise program in PwMS in terms of cost, effectiveness, and accessibility.

Keywords: aerobic exercise, fatigue, multiple sclerosis, quality of life, rehabilitation

Öz

Amaç: Bu çalışmada, aerobik egzersiz programlarının Multipl Skleroz (MS) hastaları ve sağlıklı kontroller üzerindeki etkisini karşılaştırmayı ve ev egzersiz programlarının denetimli egzersiz programları kadar etkili olabileceğini göstermeyi amaçladık.

Gereç ve Yöntem: Seksen katılımcı bu çalışmaya dahil edildi ve evde egzersiz grubu (ayaktan tedavi), denetimli egzersiz grubu (yatarak tedavi) ve sağlıklı kontroller olarak gruplara ayrıldı. Tüm katılımcılara 6 haftalık aerobik egzersiz programı verildi. Egzersiz programı öncesi ve sonrası, 6 Dakika Yürüme Testi (6DYT), Yorgunluk Şiddet Ölçeği (YŞÖ), Modifiye Ashworth Ölçeği (MAÖ), Berg Denge Ölçeği (BDÖ), Genişletilmiş Yetersizlik Düzeyi Ölçeği (EDSS), Kardiyopulmoner Egzersiz Testi (KPET), ve MS Yaşam Kalitesi Ölçeği (MSYKÖ-54) katılımcılara uygulandı.

Bulgular: 6DYT ve KPET verileri değerlendirildiğinde hasta ve kontrol gruplarının egzersiz programından yararlandığı görüldü. Hem ayaktan hem de yatan hasta gruplarının 6DYT, BDÖ, YŞÖ, MSYKÖ-54 ve KPET verilerinde tedavi sonrası anlamlı düzelme oldu ve değişim oranları karşılaştırıldığında gruplar arasında fark yoktu.

Sonuç: Ev temelli egzersiz programının denetimli egzersiz programı kadar etkili olduğunu gözlemledik. Maliyet, etkinlik ve erişilebilirlik açısından MS hastalarda egzersiz programı planlanırken öncelikle ev programının önerilmesi gerektiğini düşünüyoruz.

Anahtar Kelimeler: aerobik egzersiz, multipl skleroz, rehabilitasyon, yorgunluk, yaşam kalitesi

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INTRODUCTİON

Multiple sclerosis (MS); is a chronic, demyelinating and neurodegenerative disease that often affects young adults.[1] According to the review of 30 studies examining the incidence and prevalence, the male/female ratio is 1.00/1.77.[2] Multiple sclerosis can develop at any stage of life. However, most studies reported a mean age of onset between 29 and 32.[3]

The symptoms of patients with MS (PwMS) vary according to the localization and size of the demyelinated areas; that may come up with complaints such as functional disorders, spasticity, muscle weakness, fatigue, pain, sensory symptoms, bladder problems, intestinal problems, blurred vision, optic neuritis, sexual dysfunctions, tremor, emotional lability, walking and balance disorder.[4]

Rehabilitation in MS is a dynamic process that changes according to the changing symptoms of the disease and must be constantly updated.[5] MS is a lifelong disease; so rehabilitation of the disease should not only be a periodical treatment program, but should be made a lifestyle with the active participation of the patient as much as possible.[5]

Aerobic exercises are low-intensity, rhythmic, dynamic, and long-term activities performed using large muscle groups. They also increase endurance, which is the ability to do work for a long time. Examples of these exercises are activities such as walking, cycling, running, dancing, swimming.[6-8]

Experimental evidence reports that aerobic exercise and rehabilitation increase the satisfaction of the PwMS on their physical, mental and social functionality and they can be included as a routine treatment in MS.[9,10] Since aerobic exercise performed on a treadmill also provides a high volume of task-specific practice, aerobic treadmill training has the potential to improve walking ability, fitness, and quality of life (QoL).[11]

The positive effects of aerobic exercise on walking performance, cardiorespiratory fitness, balance, quality of life, cognitive status, fatigue, and depressive symptoms in PwMS have been demonstrated in various studies.[12-15] In addition, studies have shown that maximum oxygen consumption volume (VO_2max) in PwMS is lower than healthy controls and can be increased with aerobic exercise training.[16,17]

Numerous researchers have examined the impact of intervention involving aerobic exercise training on quality of life in PwMS. However, there are conflicting results among past research on the effect of exercise on quality of life in MS. Such researches emphasizes the importance of conducting a quantitative synthesis documenting the magnitude of the overall impact of exercise education on quality of life in PwMS.[9,18]

Our aims in this study; 1) Evaluating the effects of aerobic exercise programs on fatigue, disability, spasticity, balance, aerobic capacity, and quality of life in PwMS, 2) Comparing home aerobic exercise programs with supervised aerobic exercise programs in PwMS; 3) To compare the effects of aerobic exercise programs on PwMS and healthy controls.

MATERIAL AND METHOD

Ethical Statement

This study was approved by the local Institutional Ethics Committee and was conducted in accordance with the Declaration of Helsinki guidelines. Signed informed consent was obtained from each participant before starting data collection.

Study Design and Participants

This prospective, randomized controlled clinical study evaluated PwMS, who presented to the physical medicine and rehabilitation (PMR) clinic between January and June 2019.

Patients aged 18-70 years, with EDSS score of <5,5, clinically stable, and not exercising regularly were included study. Patients who were regularly exercising for the past six months, with neurological disease other than MS, with severe cardiorespiratory system disease, with severe orthopedic impairment or gait problems, cognitive or mental disability were not included in the study.

Participants were tried to be randomized by using the opaque envelope method. Randomization was conducted by a clinical secretary who was not involved in the study. Patients were divided into groups as "outpatient group" (home exercise program) and "inpatient group" (supervised exercise program). The control group was created sex- and age-matched healthy volunteers including patient relatives or caregivers or health workers.

The sample size was made using the G * power (V3.1.7) program, and to create a minimum change of 10 units in visual analog scale; at least 20 patients were found for each group with α=0.05, 80% power and d=0.631 effect size. The sample size was also compatible with similar previous studies.

The study included 27 outpatients, 27 inpatients, and 27 healthy controls. Since one from the outpatient group did not want to continue the exercise program, so he was excluded. The study was completed with 53 patients and 27 healthy controls (**Figure 1**).

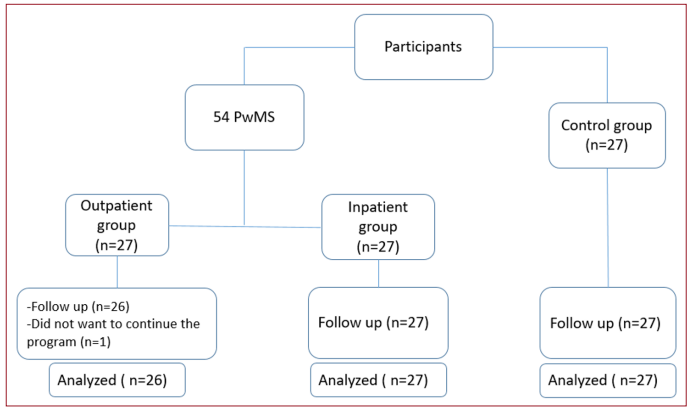

Figure 1. Flow chart of the study
PwMS: Patients with Multiple Sclerosis

Disease and Demographic Characteristics

Sociodemographic and clinical data of the participants were recorded in the forms prepared by the researchers. Demographic characteristics including sex, age, body mass index (BMI) and years of education of the participants, as well as disease characteristics of the patients were recorded.

Outcome Parameters

Modified Ashworth Scale (MAS), 6-minute walking test (6MWT), Fatigue Severity Scale (FSS), Extended Disability Status Scale (EDSS), Berg Balance Scale (BBS), cardiopulmonary exercise test (CPET), and Multiple Sclerosis Quality of Life-54 (MSQoL-54) questionnaire were performed before and after the 6-week exercise program.

All the participants in this study were subjected to a 6MWT[19] and CPET to determine their aerobic capacity before the exercise program. Also, these tests were performed after treatment.

Cardiopulmonary exercises test was applied to each participant to determine their exercise capacity. Before the test, each participant was introduced to the device and an information form was given. The Care Fusion Type Master Screen-CPX device performed CPET with Bruce protocol on the treadmill. During the test, the patients continued to breathe with a mask fitted with a gas meter at the end, allowing the measurement of oxygen and carbon dioxide. During the test, electrocardiography was followed. The exercise test was terminated if the patient reported a degree of fatigue of 15-17 on the Borg Scale,[20] stated that participant could not continue exercising for any reason, or when the indications for completing the exercise test appeared. Maximum time, VO_2max, resting heart rate, maximum heart rate (HRmax), metabolic equivalent (MET), peak work rate (WRpeak) values achieved during the test were recorded.

Modified Ashworth Scale (MAS); was used for the assessment of spasticity and it was scored between 0-4.[21]

Kurtzke's Extended Disability Status Scale; describes the severity of disability in 8 functional systems in PwMS, and high scores represent higher levels of disability.[22]

Fatigue Severity Scale; consists of 9 questions (1-7 points) that measure the severity of fatigue and its effect on one's activities. High scores indicate severe fatigue.[23]

Berg Balance Scale; includes 14 general balance activities and scores between 0-4 by observing the patient's performance for each activity. Total score was calculated between 0 and 56 points.[24]

Multiple Sclerosis Quality of Life-54 questionnaire; consists of 2 main groups (Physical Health Composite [PHC], Mental Health Composite [MHC]), 13 subgroups and 2 independent items. The subscales evaluate health between 0 and 100 points (0:poor health conditions / 100: good health conditions).[25] In this study, main groups were scored separately.

Aerobic exercise program was prescribed to all the subjects according to the VO_2max obtained in the exercise tolerance test. Home exercise program was given to the outpatient group and the control group for 6 weeks, 5 days a week. In each exercise session, brisk walking with a maximum intensity of 60-80% of the maximum heart rate for 30 minutes between 5 minutes of warm-up and cooling periods (breathing, flexibility, posture, stretching, and balance exercises) was recommended. The patients were checked for their compliance with the exercises by calling the phone numbers given once a week, the necessary information was given, and they were motivated for the continuation of the exercises.

For the inpatient group, for a period of 6 weeks, 5 days a week, walking on a treadmill or cycling at the intensity of 60-80% of the maximum heart rate for 30 minutes between 5 minutes of warm-up and cooling periods in each exercise session was run. Patients were given breathing, flexibility, posture, stretching, and balance exercises under supervision, twice a day.

Statistical Analysis

The analysis of the data was done in SPSS for Windows 15.0 package program. Descriptive statistics were shown as mean±standard deviation for continuous variables and number of observations and (%) for nominal variables. During the analysis, it was evaluated whether there was a significant difference between the before and after values for each group. The percentage changes were taken as the basis when comparing the rates of change in the groups. Paired Sample t-test was used to compare the exercise program start and end values of the groups. Two samples t-test and Kruskal Wallis test were used to compare the rates of change between groups. $p < 0.05$ was considered significant for the results.

RESULTS

Twenty-seven healthy participants and 53 PwMS participated in the study. Comparison of the demographic data of the participants was given in **Table 1.** There was no significant difference between the groups except for the years of education.

According to the post-hoc Tamhane T2 results, a significant difference was found between the control group and both the outpatient group (p=0.002) and the inpatient group (p=0.000), due to the high educational years of the control group.

Table 1. Comparison of the demographic data of the patient and control groups

		Outpatient (n=26)	Inpatient (n=27)	Control (n=27)	p
Age mean (SD)		41.81 (9.20)	44.96 (9.70)	39.93 (10.76)	.222
Sex n (%)	male	4 (15.4%)	8 (29.6%)	5 (18.5%)	.414
	female	22 (84.6%)	19 (70.4%)	22 (81.5%)	
Education years mean (SD)		8.96 (4.20)	8.19 (4.30)	13.63 (5.09)	.000*
BMI mean (SD)		26.82 (5.74)	25.19 (5.60)	25.79 (3.42)	.343
Disease durations mean (SD)		8.08 (5.26)	9.81 (8.11)	.	.872a

SD: standard deviation, BMI: body mass index, *: p<0.05 Statistical method used: Kruskal Wallis, a: Independent Samples T-test

Comparison of 6MWT and CPET values before and after treatment, within and between healthy control, inpatient, and outpatient groups were presented in **Table 2**. The increase in 6MWT was significant for all groups [inpatient (p=0.010), outpatient (p=0.000), control (p=0.000)]. There was a significant increase in VO_2max (p=0.001), MET (p=0.009), time (p=0.000) and WRpeak (p=0.005) values in the inpatient group, and a significant increase in VO_2max (p=0.017), HRmax (p=0.003) and time (p=0.006) values in the outpatient group. There were also significant increases in VO_2max (p=0.000), HRmax (p=0.025), MET (p=0.000), duration (p=0.001) and WRpeak (p=0.000) in the healthy control group.

Changes in 6MWT and CPET data between groups, before and after treatment were evaluated with the Kruskal Wallis test. As a result of the analysis, a difference was found between the groups only in the change of CPET time, and according to the post-hoc Tamhane's T2 results, there was a difference between the control group and the inpatient group due to more change in inpatients (p=0.029).

Comparison of MAS, EDSS, FSS, BBS and MSQoL-54 (PHC and MHC) results before and after treatment, within and between inpatient and outpatient groups were shown in **Table 3.** Significant improvement was observed in the MAS (p=0.043), FSS (p=0.000), BBS (p=0.000), and MSQoL-54 PHC (p=0.000) scores in the inpatient group after treatment. Significant improvement was found in the EDSS (p=0.006), FSS (p=0.002), BBS (p=0.000), MSQoL-54 PHC (p=0.000), and MSQoL-54 MHC (p=0.022) scores in the outpatient group. When the post-treatment changes were compared between the outpatient and inpatient groups, no significant difference was found except for EDSS (p=0.036).

DISCUSSION

It is known that in the past, clinicians avoided exercise programs in PwMS, believing that it would increase spasticity. However, studies have shown that exercise program has positive effects such as increasing physical and motor functions, reducing spasticity, improving proprioception and balance.[9,26] In addition, aerobic exercise can improve physical, psychological, and mental health through various mechanisms that reduce pain and fatigue, the two main symptoms of MS.[9,13] In our study, it has been determined that fatigue, spasticity, and balance problems of the patients decreased with aerobic exercise. When the effect of the home program and the supervised exercise program was compared, no significant difference was found between the groups in terms of fatigue, spasticity, and balance changes. However, it was determined that the home program was significantly more effective in terms of EDSS change. The cause why there was no difference between the pre-treatment EDSS scores and more improvement in the home-exercise group may be that the individual continues his daily activities at the same time as the exercise program or is in his social life.

Table 2. Comparison of 6MWT and CPET data before and after treatment, within and between in- and outpatient groups and control groups

Variables	Control group (n=27) Mean (SD)			Inpatient Group (n=27) Mean (SD)			Outpatient Group (n=26) Mean (SD)			p**
	BT	AT	p	BT	AT	p	BT	AT	p	
6MWT (m)	526.30 (75.87)	558.89 (85.74)	.000*	373.15 (186.54)	397.96 (178.30)	.010*	408.46 (151.02)	443.85 (150.38)	.000*	.482
CPET VO_2max (ml/kg/mins)	1601.00 (358.01)	1766.22 (332.47)	.000*	820.93 (271.34)	1004.52 (333.28)	.001*	908.23 (491.22)	1001.54 (484.96)	.017*	.272
CPET rp (beats/mins)	85.85 (13.11)	86.37 (10.32)	.796	90.04 (17.16)	86.41 (11.72)	.266	88.31 (14.57)	90.08 (10.64)	.515	.429
CPET HRmax (beats/mins)	153.74 (23.31)	159.81 (24.15)	.025*	115.78 (21.55)	121.00 (24.09)	.187	116.12 (19.67)	125.27 (18.17)	.003*	.476
CPET MET	6.44 (1.74)	6.85 (1.80)	.000*	3.64 (1.47)	4.20 (1.84)	.009*	3.73 (1.77)	4.04 (1.68)	.094	.321
CPET time (mins)	8.79 (2.59)	9.87 (2.53)	.001*	5.27 (2.52)	7.22 (3.38)	.000*	5.52 (2.30)	6.85 (2.69)	.006*	.014*
CPET WRpeak (W)	169.59 (63.34)	197.93 (70.34)	.000*	38.52 (42.97)	56.30 (50.46)	.005*	60.27 (60.65)	70.65 (64.10)	.156	.293

BT: before therapy, AT: after therapy, 6MWT: 6 minutes walking test, CPET: cardiopulmonary exercise test, VO_2max: maximum oxygen consumption volume, rp: resting pulse, HRmax: maximum heart rate, MET: metabolic equivalent, WRpeak: peak work rate, min: minimum, max: maximum, mins: minutes, *: p<0.05, P**: comparison of changes between outpatient and inpatient groups. Statistical method used: Paired samples T-test and Kruskal Wallis test

Table 3. Comparison of MAS, EDSS, FSS, BBS and MSQoL-54 (PHC and MHC) results before and after treatment, within and between In- and Outpatient Groups

Variables	Inpatient Group (n=27) Mean (SD)			Outpatient Group (n=26) Mean (SD)			p**
	BT	AT	p	BT	AT	p	
MAS	1.26 (.45)	1.11 (.32)	.043*	1.15 (.46)	1.08 (.27)	.161	.318
EDSS	3.67 (1.54)	3.65 (1.53)	.574	4.17 (.71)	4.04 (.79)	.006*	.036*
FSS	22.81 (12.27)	18.30 (10.92)	.000*	21.19 (9.74)	15.96 (10.49)	.002*	.696
BBS	45.07 (9.70)	47.37 (8.17)	.000*	49.23 (5.60)	51.35 (4.51)	.000*	.372
MSQoL-54 PHC	55.53 (18.24)	62.25 (18.63)	.000*	57.77 (19.83)	66.94 (17.89)	.000*	.360
MSQoL-54 MHC	56.19 (18.15)	59.57 (18.58)	.120	55.01 (19.29)	62.40 (17.87)	.022*	.128

BT: before treatment, AT: after treatment, MAS: Modified Ashworth Scale, EDSS: extended disability status scale, FSS: Fatigue Severity Scale, BBS: berg balance scale, MSQOL-54: Multiple Sclerosis Quality of Life, PHC: Physical Health Composite, MHC: Mental Health Composite, min: minimum, max: maximum, * p <0.05, **: comparison of changes between outpatient and inpatient groups. Statistical method used: Paired samples T-test and Independent Samples T-test

As stated in previous studies, PwMS has a low QoL due to disease-related symptoms.[9] The effect of exercise on QoL is affected by many variables (age, gender, disease duration, disability level). It is thought that more experimental studies are needed in this area. In this study, we evaluated the quality of life in PwMS with a disease-specific scale.[27] In this study, when the MSQoL-54 data of PwMS treated as outpatient and inpatient were evaluated; significant improvements were found in PHC and MHC values in the outpatient group. There was a significant difference in PHC values in the inpatient group. When the change in the outpatient and inpatient groups was compared, there was no significant difference in MSQoL-54 data. After a regular aerobic exercise program, increased physical activity, decreased fatige, increased stability, increased functionality, and decreased disability can improve overall health perception and improved quality of life.

Walking disorder is a common and life-affecting parameter in PwMS. In studies have found a relationship between walking speed and muscle strength in PwMS, and it has been reported that PwMS has a lower walking speed than its healthy peers.[28-30] In line with these results, it was found in the current study that PwMS walked slower than healthy controls during the 6MWT. Studies have shown that aerobic exercise training improves walking resistance in PwMS.[9,31] Similarly, in this study, a significant improvement was observed in the 6-minute walking distance in patients and control groups after the aerobic exercise program. When the rates of change between the patient and control groups were compared, no significant difference was found between the three groups. The obtained data support the positive effects of the exercise program on walking speed, endurance, and ability in PwMS.

Previous studies have shown that VO_2max, HRmax, WRpeak data in PwMS are significantly lower than in healthy controls, and cardiopulmonary capacity can be improved with adequate time and intensity aerobic exercise training.[32-35] Similarly, in this study, VO_2max, HRmax, WRpeak were found to be lower in PwMS. Low VO_2max, HRmax, WRpeak levels in PwMS can generally be associated with low physical activity in these patients.[36] The reason for low physical activity may be due to the patient's current symptoms or may be due to their avoidance of physical activity, thinking that increased physical activity will cause the fatigue and weakness (37, 38). In addition, symptoms such as balance-coordination disorder, spasticity, muscle weakness, and cooperation disorder in PwMS may adversely affect the results obtained during the exercise test.[34,35] In addition, musculoskeletal disorders associated with obesity and aging may adversely affect the evaluation of CPET. The disadvantage of our study is that the age range of the participants was wide and additional issues related to aging were not evaluated. Despite randomization was performed in our study, no difference was found between the three groups in terms of age, gender, and BMI, and we accepted that additional issues related to aging and weight were similar between the groups.

When the change in CPET values of the patients and control groups was compared, the improvement in duration was greater in the inpatient group. There was no significant difference between all three groups in other CPET data. According to the results, the exercise program increased aerobic capacity in both the patients and control groups. When the changes in CPET values after treatment in outpatient and inpatient groups were compared, there was no significant difference to be found. According to these results, we can say that outpatient and inpatient groups benefit from aerobic exercise programs at similar rates. Considering that the home program and the supervised program have similar benefits, we may prefer the home exercise program first because of cost and easy accessibility. In addition, similar changes were obtained in the patient groups and the control group, suggesting that although PwMS have spasticity, balance disorder, or muscle weakness, they can benefit from a regular exercise program as much as healthy controls.

According to the data we obtained as a result of our study; aerobic exercise improves fatigue, quality of life, balance, spasticity, walking performance, and cardiopulmonary capacity in PwMS. Although the participants benefited from both programs (supervised exercise program and home program) at similar rates, the fact that the decrease in disability level was more common in the home program made the home program more advantageous in terms of both low cost and easy accessibility. In addition, we found that although the aerobic capacity was low in PwMS, a similar change in aerobic capacity could be achieved with the healthy controls by applying for the same exercise program.

The limitation of the current study is that patients with an EDSS score <5.5 were included in this study, so the effect of the exercise program on severely disabled patients could not be evaluated. In addition, a wide age range was included in this study, and geriatric problems caused by age were not considered, further studies are needed in which age groups are evaluated separately or additional diseases brought by age are specifically examined. Despite all this, we believe that the present study will make significant contributions to the literature. Because in previous studies, aerobic exercise program in PwMS was given as an inpatient or home program, but there are few studies in which both groups were included and compared. In our study, we found that both groups had similar effects and we think that it is more advantageous to prefer the home program first. Considering that MS is a lifelong disease, exercise programs should be made a lifestyle. Programs given under inpatient supervision may not be accessible every day of the year due to cost, hospital availability, workload, or social reasons, and may prevent the individual from continuing his daily life. However, with a home-based aerobic exercise program planned according to the person's capacity, the individual can both continue his daily life and protect himself against the negative symptoms of the disease.

CONCLUSION

Aerobic exercise has been observed to improve MS-related symptoms and functionality, in addition to increased cardiorespiratory capacity. Often exercise programs are given under supervision and are believed to be more successful; in this study, the home program was found to have similar benefits for patients. We think that home-based exercise program should be preferred primarily in terms of cost-effectiveness.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences, Ankara Dişkapi Yildirim Beyazit Health Research Center Ethics Committee (Date: 07.01.2019, Decision No: 58/22).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

The Role of Platelet Indices in Predicting Short-Term Mortality in Elderly Patients with Pulmonary Embolism

Pulmoner Embolisi Olan Yaşlı Hastalarda Kısa Süreli Mortaliteyi Öngörmede Trombosit İndekslerinin Rolü

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Abstract

Objective: This study aimed to investigate the role of platelet count, mean platelet volume (MPV), plateletcrit, platelet distribution width, platelet mass index (PMI), and MPV-to-platelet ratio (MPR) in predicting short-term mortality in patients aged 65 years and over with pulmonary embolism.

Material and Method: This retrospective, observational, cohort study included patients with computed tomography angiography-corrected pulmonary embolism. Demographics, clinical characteristics, platelet indices, and all-cause mortality data within 30 days after admission were noted. The receiver operating characteristic curve and multivariate analyses were performed to determine the discriminative ability of the platelet indices.

Results: A final analysis of 128 patients was performed. The mortality rate was 21.8%. There was no significant relationship in the multivariate analysis between mortality and platelet indices (Mann-Whitney U test). The area under curve values of the neutrophil-to-lymphocyte ratio, PMI, MPR, plateletcrit, platelet count, and MPV were 0.501, 0.640, 0.626, 0.642, 0.633, and 0.532, respectively.

Conclusion: Based on the results of our sample, the investigated platelet indices were not able to predict short-term mortality in elderly patients with pulmonary embolism.

Keywords: Blood platelets, pulmonary embolism, mean platelet volume, mortality

Öz

Amaç: Çalışmamızda 65 yaş ve üzeri pulmoner emboli hastalarında; trombosit sayısı, ortalama trombosit hacmi (OTH), plateletkrit, trombosit dağılım genişliği, trombosit kitle indeksi (TKİ) ve OTH-trombosit sayısı oranının (OTO) kısa dönem mortaliteyi öngörmedeki rolünü araştırmayı amaçladık.

Gereç ve Yöntem: Bu retrospektif, gözlemsel, kohort çalışmasında, bilgisayarlı tomografi anjiyografi ile doğrulanmış pulmoner emboli olan hastalar dahil edilmiştir. Başvurudan sonraki 30 gün içinde tüm nedenlere bağlı ölüm verileri, demografik, klinik özellikler ve trombosit indeksleri kaydedildi. Trombosit indekslerinin ölümü öngörebilirliğini belirlemek için alıcı karakteristik eğrisi ve çok değişkenli analizler yapıldı.

Bulgular: Toplam 128 hastanın son analizi yapıldı. Ölüm oranı %21,8 idi. Ölüm ile trombosit indeksleri arasında çok değişkenli analizde anlamlı bir ilişki yoktu (Mann-Whitney U testi). Nötrofil-lenfosit oranı, TKİ, OTO, plateletkrit, trombosit sayısı ve OTH'nin eğri altındaki alan değerleri sırasıyla 0,501, 0,640, 0,626, 0,642, 0,633 ve 0,532 idi.

Sonuç: Örneklemimizin sonuçlarına göre, trombosit indeksleri pulmoner emboli olan yaşlı hastalarda kısa dönem mortaliteyi öngörmede yeterli değildir.

Anahtar Kelimeler: Trombosit, pulmoner emboli, ortalama trombosit hacmi, mortalite

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INTRODUCTION

Pulmonary embolism (PE) is a common and often fatal disease. It is the third most common cause of cardiovascular deaths and the most common cause of patient death after surgery.[1] Rapid diagnosis and treatment significantly reduce mortality and long-term complications, such as chronic thromboembolic pulmonary hypertension and cor pulmonale.[2] The clinical features of pulmonary thromboembolism are variable and non-specific, making an accurate diagnosis and prognostication of poor outcome difficult. There is also no specific laboratory test. Many ancillary diagnostic tests are utilized because medical history and physical examination findings are not sufficient alone to diagnose PE.[2,3] Various clinical scoring systems, including pulmonary embolism severity index (PESI) and simplified PESI or laboratory parameters, such as cardiac troponin I and T, and B-type natriuretic peptide are used in the prognostic evaluation of PE.[3]

Platelets are granular cells with a diameter of 2-4 microns. They play a key role in hemostasis and coagulation.[4] The glycoprotein coat covering the platelet membrane surface ensures that the platelet adheres to the damaged vessel endothelium. This cover is especially responsible for binding to the damaged endothelial cells and the collagen released in the vessel wall.[4] In addition, phospholipids in the platelet membrane activate the intrinsic pathway in coagulation.[4] The risk of venous thromboembolism increases with age, and it is approximately 10 times greater in individuals aged over 80 years compared to those aged 45-50 years.[5] Based on this information, we hypothesized that platelet indices might be associated with prognosis in thromboembolic diseases, such as PE in the later decades of life.

In this study, we aimed to investigate the role of platelet count, mean platelet volume (MPV), plateletcrit, platelet distribution width (PDW), platelet mass index (PMI), and MPV-to-platelet ratio (MPR) in predicting short-term mortality in patients aged 65 years and over with PE.

MATERIAL AND METHOD

Study Design

Our retrospective observational study was conducted at the emergency department (ED) of a 721-bed tertiary education hospital receiving 961 ED admissions per day (annual average of the study period). The data of the patients presenting to the ED with PE signs and symptoms over the four-year study period (between June 15, 2017 and June 1, 2021) were gathered retrospectively.

Study Population

The population of this study consisted of patients presenting to our ED with PE signs and symptoms between June 15, 2017 and June 1, 2021. Patients under 65 years those for whom PE could not be confirmed with computerized tomography angiography (CTA), and those with missing data were excluded. **Figure 1** shows the flow chart of the study.

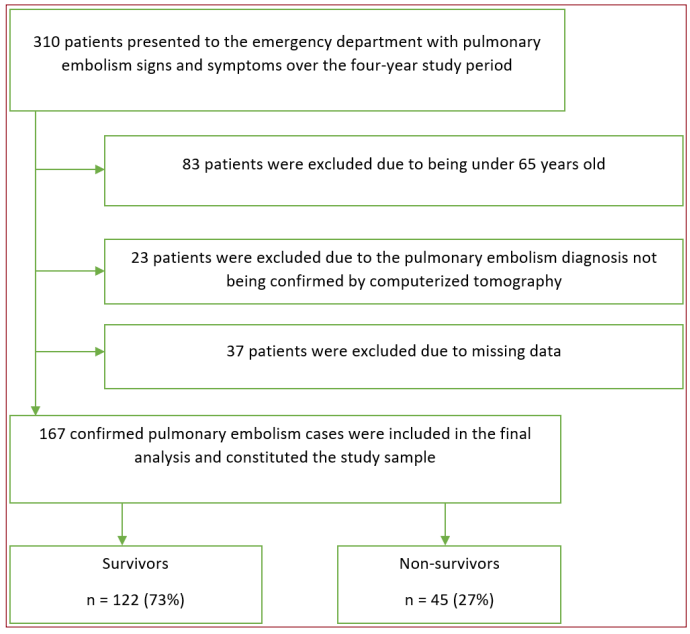

Figure 1. Flow chart of the study

Data Collection

The demographic data (age, gender), symptoms, ED triage tags, and laboratory parameters of the study sample were collected from the computer-based data system of the hospital. The symptoms of patients were noted as chest pain, hemoptysis, shortness of breath, weakness, muscle-joint pain (leg), back pain, stomachache, palpitation, nausea-vomiting, and syncope. The ED triage tags of the patients were recorded as red, yellow, and green. The following laboratory parameters were evaluated: white blood cell count, neutrophil count, neutrophil ratio, monocyte count, monocyte ratio, lymphocyte count, lymphocyte ratio, hemoglobin, hematocrit, mean corpuscular volume, red cell distribution weight, platelet count, MPV, plateletcrit, PDW, neutrophil-to-lymphocyte ratio (NLR), MPR, and PMI. The PMI values were calculated by multiplying the platelet count and MPV.

Statistical Analysis

Microsoft Excel was used for the frequency analysis, and the remaining statistical analyses were conducted using SPSS version 22.0 for Windows (SPSS Inc, Chicago, IL, USA). The conformity of data to the normal distribution was evaluated with the Kolmogorov-Smirnov test. Interquartile range (25th-75th percentile values) and median were used to present quantitative variables. The Mann-Whitney test was used to compare quantitative variables. To report the independent predictors of mortality, we performed a multivariate analysis of the factors determined to be significant in the univariate analyses and demographics.

The accuracy of the evaluated platelet indices in predicting short-term mortality was evaluated using the receiver operating characteristic (ROC) curves. The results of the ROC curves were presented as the area under the curve (AUC)

values. A good predictor should have an AUC value above 0.8. An AUC value closer to 1 indicates a better predictor. The optimal cut-off values of the platelet indices with the best specificity and sensitivity were determined using Youden's index. We used the DeLong equality test to test the differences between the AUC values of the platelet indices. P values below 0.05 were considered statistically significant.

Ethics

Approval for the study was obtained from the local ethics committee with (approval date: 08/25/2021, number 255). Due to the retrospective design of the study and the sample not including any personal data, informed consent was waived within the knowledge of the ethics committee.

RESULTS

A final analysis of 128 patients was performed after applying the inclusion and exclusion criteria. Forty-nine (38.3%) patients were male. The median age of the enrolled patients was 79 (IQR: 66-80) years. A total of 28 patients died, and the mortality rate was 21.8%. **Table 1** presents the baseline characteristics of the enrolled patients and the comparison of the characteristics between the survivor and non-survivor groups. The green triage tag was assigned to 23 (18%) patients had, the yellow triage tag to 30 (23.4%) patients, and the red triage tag to 75 (58.6%) patients. Of the surviving patients, 23 (23%) had the green triage tag, 28 (28%) had the yellow triage tag, and 49 (49%) had the red triage tag. Of the non-survived patients, none had the green triage tag, while two (7.1%) had the yellow triage tag and 26 (92.9) had the red triage tag. There was a statistically significant difference between the survivor and non-survivor groups in terms of the triage tag (chi-square test, p<0.001).

Table 2 shows the laboratory parameters of the enrolled patients and their comparison between the survivor and non-survivor groups. Significant differences were detected between the survivor and non-survivor groups in terms of platelet count [206 (149-259) versus 241 (192-317), p=0.033]. However, the relationship between platelet count and mortality was not significant according to the multivariate analysis (**Table 3**) (Mann-Whitney U test, p=0.756). The AUC values of NLR, PMI, MPR, plateletcrit, platelet count, and MPV were determined as 0.501, 0.640, 0.626, 0.642, 0.633, and 0.532, respectively (**Table 4, Figure 2**).

Table 1. Baseline characteristics of the enrolled patients and their comparison between the survivor and non-survivor groups

Variables	Total	Survivors	Non-survivors	p values
	n=128 (%, min-max)	n=100 (78.1%)	n=28 (21.9%)	
Age, years	79 (66-80)	76 (69-82)	81 (77-88)	0.305
Gender				0.573
Male	49 (38.3%)	37 (37%)	12 (42.9%)	
Female	79 (61.7%)	63 (63%)	16 (57.1%)	
Frequency of symptoms				0.961
Chest pain	14 (10.9%)	14 (14%)	0	
Hemoptysis	9 (7%)	7 (7%)	2 (7.1%)	
Shortness of breath	59 (46.1%)	46 (46%)	13 (46.4%)	
Weakness	9 (7%)	7 (7%)	2 (7.1%)	
Muscle-joint pain (leg)	7 (5.5%)	6 (6%)	1 (3.6%)	
Back pain	5 (3.9%)	5 (5%)	0	
Stomachache	3 (2.3%)	0	3 (10.7%)	
Palpitation	7 (5.5%)	5 (5%)	2 (7.1%)	
Nausea-vomiting	2 (1.6%)	2 (2%)	0	
Syncope	13 (10.2%)	10 (10%)	3 (10.7%)	
Triage tag				<0.001
Green	23 (18%)	23 (23%)	0	
Yellow	30 (23.4%)	28 (28%)	2 (7.1%)	
Red	75 (58.6%)	49 (49%)	26 (92.9)	

Table 2. Laboratory parameters of the enrolled patients and their comparison between the survivor and non-survivor groups

Variables	Total	Survivors	Non-survivors	p value
	Median (25th-75th percentile)	Median (25th-75th percentile)	Median (25th-75th percentile)	
White blood cell count	10.30 (8.41-13.88)	9.81 (8.12-12.85)	13 (10.12-17.28)	0.003
Neutrophil count	7.26 (5.63-10.87)	7.05 (5.55-10.21)	8.70 (6.35-13.43)	0.054
Neutrophil %	75 (66-82.3)	75.2 (66.4-86.9)	74.9 (57.6-87.2)	0.954
Monocyte count	0.66 (0.46-0.91)	0.66 (0.46-0.87)	0.81 (0.51 1.08)	0.077
Monocyte %	5.74 (5-7.7)	6 (5.2-7.8)	5.1 (4.3-6.8)	0.031
Lymphocyte count	1.58 (1.18-2.51)	1.56 (1.18-2.47)	1.98 (1.21-3.96)	0.172
Lymphocyte %	16.4 (10.3-24.1)	16.4 (16.4-23.7)	14.8 (7.6-33.1)	0.944
Hemoglobin	12.5 (10.8-13.7)	12.7 (11-13.7)	11.8 (9.67-13.55)	0.181
Hematocrit	37.6 (32.8-41.7)	38.8 (34.1-41.9)	36.4 (31-41.4)	0.242
Mean corpuscular volume	88.1 (85.1-92.1)	88.1 (85.6-91.3)	88.2 (83.3-94.5)	0.898
Red cell distribution weight	14.7 (13.4-16.7)	14.5 (13.3-15.9)	16.2 (14.2-18.6)	0.004
Platelet count	235 (178-293)	206 (149-259)	241 (192-317)	0.033
Mean platelet volume	9 (8.1-9.8)	9 (8.1-9.9)	9 (8.4-9.7)	0.611
Plateletcrit	0.21 (0.16-0.26)	0.22 (0.16-0.29)	0.18 (0.14-0.24)	0.022
Platelet distribution width	16.3 (16-16.9)	16.3 (15.9-16.8)	16.4 (16.2-16.9)	0.452
Neutrophil-to-platelet ratio	4.77 (2.73-7.61)	4.71 (2.81-7.32)	5.13 (1.75-11.61)	0.981
Mean platelet volume-to-platelet count ratio	0.038 (0.029-0.050)	0.038 (0.027-0.047)	0.045 (0.033-0.071)	0.042
Platelet mass index	2123.3 (1575.2-2584.4)	2171.5 (1609.5-2937)	1785.6 (1353.6-2345.9)	0.024

Table 3. Results of the univariate and multivariate logistic regression analyses

	Univariate Analysis		Multivariate Analysis	
	odds ratio (95% confidence interval)	p	odds ratio (95% confidence interval)	p
Age, years			1.025 (0.99-1.05)	0.093
Age, ≥75 vs. <75	2.928 (0.81-10.51)	0.099		
Gender			0.829 (0.32-2.13)	0.699
Platelet count			0.998 (0.98-1.01)	0.756
Platelet mass index			1.009 (0.99-1.02)	0.226

Table 4. Ability of the investigated laboratory parameters to predict 30-day all-cause mortality following admission to the emergency department

	AUC	Cut-off	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Accuracy	95% CI	p-value
NLR	0.501	>1.59	75	7.07	18.6	50.0	0.81	3.54	17.93	41.1-59.1	0.984
PMI	0.640	≤1966.2	64.3	61.6	32.1	85.9	1.67	0.58	25.90	55.0-72.4	0.019
MPR	0.626	>0.062	35.7	90.9	52.6	83.3	3.93	0.71	26.62	53.6-71.0	0.051
Plateletcrit	0.642	≤0.18	57.1	66.7	32.7	84.6	1.71	0.64	23.81	55.2-72.5	0.018
Platelet count	0.633	≤212	60.7	62.6	31.5	84.9	1.62	0.63	23.34	54.2-71.6	0.032
MPV	0.532	>8.28	82.1	33.3	25.8	86.8	1.23	0.54	15.48	44.1-62.1	0.609

AUC: area under the curve; PPV: positive predictive value; LR: likelihood ratio; CI: confidence interval; NPV: negative predictive value; NLR: neutrophil-to-lymphocyte ratio; PMI: platelet mass index; MPR: mean platelet volume-to-platelet count ratio; MPV: mean platelet volume

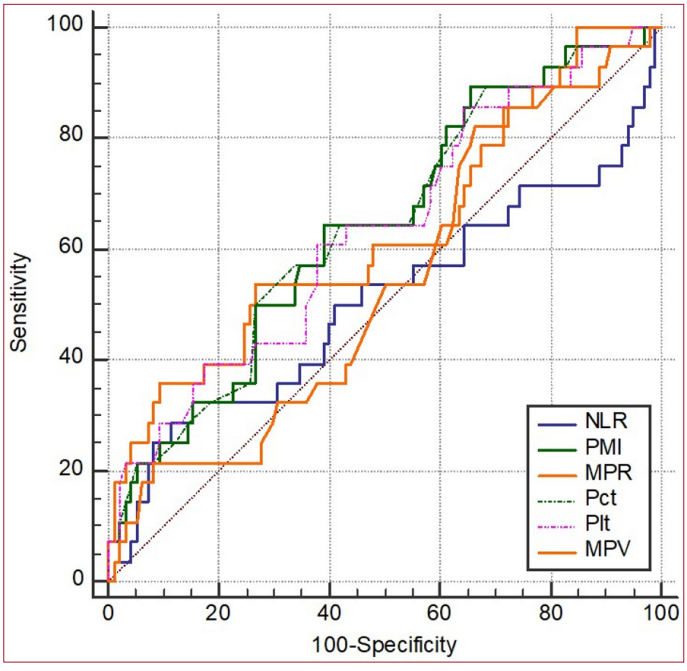

Figure 2. Receiver operating characteristic curves of the investigated laboratory parameters for the prediction of 30-day mortality in all patients aged 65 years and over with pulmonary embolism

DISCUSSION

This study examined the predictive ability of platelet indices for short-term mortality in elderly patients with PE and revealed no statistically significant difference between the survivor and non-survivor groups in the terms of any of the indices except for platelet count. To the best of our knowledge, this is the first study to investigate the predict ability of PMI in short-term mortality in elderly patients with PE.

Platelet count and MPV are inexpensive and easy-to-measure parameters used in most routine clinical practices. Platelet count and other platelet indices, including PDW, plateletcrit, and MPV increase in thromboembolic events.[6] Physiologically, there is an inverse relationship between MPV and platelet count.[6] There is evidence that MPV is an important risk factor for arterial thrombosis, acute myocardial infarction, diabetes, and venous thromboembolism.[7] It is also known that the MPV value is higher in the acute phase of venous and arterial thrombosis, and this leads to poor clinical outcomes.[6,7] It has been shown that larger platelets are younger, have contain granules, adhesion receptor expression, are more enzymatically and metabolically active, aggregate more rapidly with collagen, and therefore have increased thrombogenic properties.[8] This can be explained by the migration of platelets to a larger population and a higher proportion of immature platelets in peripheral blood.[9] Considering the high level of platelet turnover at the time of thrombus formation, platelets released into the circulation are more thrombogenic in their natural environment,[9] which is the reason for undesirable prognosis associated with higher levels of MPV in the PE setting.[10] Significantly increased MPV has been reported in different meta-analyses of various clinical conditions.[11] A meta-analysis reported significantly increased MPV and significantly decreased platelet count in thromboembolism.[11] However, further studies are required to determine whether increased MPV in thromboembolic events is the cause or result of venous occlusion.

PMI and MPR, which is a combination of platelet count and MPV, have been investigated in different clinical situations by different researchers.[12-16] It has suggested that low PMI and high MPR values may be associated with the inflammatory process. We consider that neither parameter being determined as a good predictor of mortality in our sample may be because platelet count and MPV were already resulted negatively in our sample.

Plateletcrit is the ratio of the volume of platelets to the total blood volume, and it is an indicator of total platelet mass.[17] It is generally correlated with MPV and PDW. Increased plateletcrit has been associated with poor prognosis in thromboembolic

events.[17,18] Possible explanations in the literature include thrombus formation due to exaggerated platelet activity and increased blood viscosity and aggregability resulting in increased plateletcrit.[18]

Since PDW is a specific platelet activation marker, it has been reported to increase in thromboembolic events.[19,20] Several other possible mechanisms have been suggested for the increase in PDW in thromboembolic events. One of the theories is platelets being larger in bone marrow due to increased platelet destruction. Another possible explanation is platelet enlargement secondary to hypoxemia and platelet activation.[20]

Limitations

The most important limitation of our study is that it was conducted retrospectively. Secondly, the single-center nature of our study reduces its generalizability. Another important limitation is that the PE cases could not be classified as high, intermediate, and low risk. Our study was a negative resulted study. However, the small sample size may be the reasons for from the absence of significant results; therefore, we recommend further multicenter studies with larger cohorts.

CONCLUSION

Based on the results of our sample, the evaluated platelet indices were not able to predict short-term mortality in elderly patients with PE. However, we recommend multicenter prospective studies with larger cohorts to validate the results of our study.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for the study was obtained from the local ethics committee with (approval date: 08/25/2021, number 255).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

Comparison of Individuals' Fear of COVID-19 Pandemic and Perceived Control in Turkey

Türkiye'de Bireylerin COVID-19 Pandemisi Korkusu ve Kontrol Algılarının Karşılaştırılması

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Abstract

Objective: This study was conducted to compare individuals' fear of novel coronavirus disease 2019 (COVID-19) pandemic and perceived control.

Material and Method: The sample of this descriptive study comprised 1749 individuals between 18 and 70 years of age living in various provinces in Turkey. Data were collected via an online questionnaire. The "Sociodemographic Information Form," "Fear of COVID-19 Scale (FCV-19S)," and "COVID-19 Perceived Control Scale (CV-19PCS)" were used to collect data for this study.

Results: It was determined that the FCV-19S mean total score of participants was 21.7±5.8 and the CV-19PCS mean total score was 35.6±5.6. There was a statistically significant correlation between the FCV-19S total score and CV-19PCS subdimension total scores, whereas no statistically significant effect of the CV-19PCS total score on the FCV-19S total score was found.

Conclusion: The results of the study revealed a partial relationship between the fear of COVID-19 pandemic and perceived control in the Turkish society.

Keywords: COVID-19 pandemic, midwifery, perceived control, fear

Öz

Amaç: Bu araştırma bireylerin COVID-19 pandemisi korkusu ile kontrol algılarının karşılaştırılması amacı ile yapılmıştır.

Gereç ve Yöntem: Tanımlayıcı tasarımda yapılan araştırmanın örneklemini Türkiye'nin çeşitli illerinde yaşayan 18-70 yaş arasındaki 1749 birey oluşturmaktadır. Veriler çevrimiçi anket yolu ile toplanmıştır. Araştırmanın verilerinin toplanmasında "Sosyodemografik Bilgi Formu", "COVID-19 Korkusu Ölçeği (COVID-19 KÖ)" ve "COVID-19 Kontrol Algısı Ölçeği (COVID-19 KAÖ)" kullanılmıştır.

Bulgular: Bireylerin COVID-19 KÖ toplam puan ortalaması 21,7±5,8, COVID-19 KAÖ toplam puan ortalaması ise 35,6±5,6 olarak bulunmuştur. COVID-19 KÖ toplam puanı ile COVID-19 KAÖ alt boyut toplam puanları arasında istatistiksel olarak anlamlı bir ilişki bulunurken; COVID-19 KAÖ toplam puanının COVID-19 KÖ toplam puanı üzerine istatiksel olarak anlamlı bir etkisi bulunmamıştır.

Sonuç: Araştırmanın sonuçları doğrultusunda Türk toplumunda COVID-19 pandemisi korkusu ile kontrol algısı arasında kısmen bir ilişki olduğu saptanmıştır.

Anahtar Kelimeler: COVID-19 pandemisi, ebelik, kontrol algısı, korku

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INTRODUCTION

Historically, humanity has had to go through several epidemic diseases, such as plague, Spanish flu, Ebola, and severe acute respiratory syndrome (SARS).[1,2] At present, we are faced with the novel coronavirus disease 2019 (COVID-19) pandemic that emerged in Wuhan, China, and rapidly spread worldwide.[3] While the COVID-19 virus that caused this pandemic results in only mild or moderate symptoms in several individuals, the symptoms of the disease follow a more severe course in the elderly or people with a chronic disease, leading to a large number of deaths worldwide.[4,5]

Epidemic diseases not only cause the death of individuals but also negatively impact the lives of individuals as well as societies. In literature, there are reports that epidemic diseases cause fear in the mind of individuals.[2,6-8] The fear that occurs due to the nature of the epidemic can affect an individual's relationships in daily lives. For example, there are reports that individuals who were quarantined on suspicion of having come into contact with a SARS patient would try to keep away from people who would sneeze or cough even weeks after quarantine and also avoid crowded or confined spaces, and public spaces. In addition, individuals who were quarantined and had a psychiatric history reported experiencing anxiety and anger even four or six weeks after the quarantine.[9-11] In the COVID-19 epidemic, people have experienced intense fear due to reasons such as having limited information about the disease, high levels of transmission, serious consequences on health, and lack of treatment.[11]

Fear or anxiety experienced during epidemics may not have harmful effects to some extent.[12] However, if the fear reaches an uncontrollable level, individuals may lose their perceived control and become unable to fight the epidemic. Therefore, the "perceived control," defined as "the perceived ability to change important situations or adapt to change," plays an important role in protecting health of individuals.[13,14] In addition, there are reports in literature that the perceived control mitigates the relationship between the severity of COVID-19 and mental health problems.[15,16] In particular, some studies demonstrated that the perceived control significantly affects both life satisfaction and perceived general health.[17,18] Therefore, in the COVID-19 pandemic, determination of how individuals perceive this situation and how they react to the disease is critical for both individuals and public health. In addition, it is important for health authorities to learn more about these behaviors so that they effectively respond to, and be prepared for, epidemics.[19] The knowledge of how midwives, nurses, and other health professionals, who are in close contact with society, function has influenced society and changed health behaviors to protect and promote both individual health and social health during the COVID-19 pandemic, which, in turn, has been critical for safeguarding and improving the health of individuals in particular and society in general.

In the literature review, studies on different topics such as depression, health anxiety, mental health and psychosocial problems, psychological effects of quarantine, and fear and anxiety levels during the COVID-19 pandemic were encountered.[1,8,20-23] However, there has been no study comparing the fear of the COVID-19 pandemic with the perceived control of the pandemic. For this reason, this study was conducted to compare individuals' fear of the COVID-19 pandemic and their perceived control of the pandemic.

MATERIAL AND METHOD

Study Design and Participants

The study employed the descriptive design. Accidental sampling method was used in the study. The population of the study consisted of individuals aged between 18 and 70 years living in various provinces of Turkey. The G*Power software (version 3.1.7) was used to determine the sample size of the study. While calculating the sample size, the correlation coefficients in the article titled "The reliability and validity of Turkish version of coronavirus anxiety scale" were taken into consideration and it was found that the study should be conducted with a minimum of 75 participants with a confidence level of 95% (1-α), test power of 95% (1-β), and effect size of ρ=0.4.[24]

Data were collected using Google Forms between November 9, 2020 and November 23, 2020. While collecting data, social media tools (such as WhatsApp, Instagram, and Facebook) were used via online surveys. As a result, 1749 people who completed the questionnaires in two weeks, were literate, and used social media tools, were included in the study. The data of the study were collected using the "Sociodemographic Information Form," "Fear of COVID-19 Scale," and "COVID-19 Perceived Control Scale".

Data Collection Tools

Sociodemographic Information Form, developed by researchers in line with the literature, consists of a total of 10 questions concerning the socioeconomic, educational, and employment status of all participants as well as statements about COVID-19.[20-24]

Fear of COVID-19 Scale (FCV-19S) was developed by Ahorsu et al. (2020) to measure individuals' levels of fear caused by COVID-19. The validity and reliability study of the Turkish version of the scale was conducted by Ladikli et al. The five-point Likert type scale consists of seven items. The total score obtained from all items of the scale reflects the level of COVID-19 fear experienced by an individual. The highest and lowest scores that can be taken from the scale are 7 and 35 points, respectively. High scores from the scale mean that individuals experience high levels of fear of COVID-19.[20,24,25] In the Turkish validity and reliability study of the scale, the Cronbach's alpha coefficient was reported as 0.86.[24] In the present study, the Cronbach's alpha coefficient of the scale was found to be 0.77.

COVID-19 Perceived Control Scale (CV-19PCS) was developed by Ekiz et al. (2020) to determine the perceived control of the COVID-19 epidemic. The 5-point Likert scale consists of three subdimensions (macro control, personal control, and inevitability) and 12 items. The lowest and highest scores that can be obtained from the scale are 12 and 60 points, respectively. Looking at the breakpoints of the scale, between 12 and 20 points are defined as a very low level of perceived control, while between 21 and 30 points, 31 and 40 points, 41 and 50 points, and 51 and 60 points are low, medium, high, and very high levels of perceived control, respectively. In the Turkish validity and reliability study of the scale, the Cronbach's alpha coefficient was specified as 0.72.[21] In the present study, the Cronbach's alpha coefficient of the scale was found to be 0.64.

Data Analysis

The data were analyzed with the IBM SPSS Statistics software (version 23), and compliance with normal distribution was examined using the Kolmogorov-Smirnov test. Spearman's rank correlation coefficient was used to examine the relationship between scores that were not normally distributed. Mean, standard deviation, median, minimum and maximum values were used in the evaluation of the data. Independent two-sample t-test was used to compare normally distributed data according to paired groups, and one-way analysis of variance was used for the comparison of normally distributed data according to three and more groups, and finally, the Kruskal-Wallis test was used for comparing the data that were not normally distributed. The effect of the FCV-19S scores on the CV-19PCS total and subdimension scores was analyzed using linear regression analysis. The statistical significance level was taken as $p<0.05$.

Ethical Issues

Prior to collecting research data, permission was obtained from the Social and Human Sciences Research Ethics Committee of a university, dated 04.11.2020 and numbered 01–11. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Before individuals started to fill out the questionnaire, they were required to approve the informed consent form section explaining the purpose of the study. In this way, informed consent was obtained from all individuals who participated in the study.

RESULTS

The average age of participants included in the study was determined to be 32.9±10.7. When the sociodemographic characteristics of participants and their FCV-19S total scores were evaluated, it was determined that there was a statistically significant difference between the FCV-19S total scores and the sociodemographic characteristics, such as gender, educational status, marital status, profession, family type, income status, place of residence, and status of contracting COVID-19. When the sociodemographic characteristics of participants and their CV-19PCS total scores were evaluated, it was determined that there was a statistically significant difference between the CV-19PCS total scores and the sociodemographic characteristics, such as educational status, marital status, family type, place of residence, status of employment during the COVID-19 pandemic and the status of contracting COVID-19 (**Table 1**).

The mean FCV-19S total score was found to be 21.7±5.8. Regarding the CV-19PCS scores, the macro control, personal control, and inevitability subdimension mean scores were found to be 10.4±3.5, 12.8±3.3, and 11.7±3.7 respectively, while the total mean score was found to be 35.6±5.6 (**Table 2**).

There was a statistically significant relationship between the FCV-19S total score and the CV-19PCS macro control perception subdimension total score. The increase in the FCV-19S CS total score created a very weak decrease in the macro control perception total score. There was a statistically significant relationship between the FCV-19S total score and the CV-19PCS personal control perception total score. The increase in the FCV-19S total score resulted in a very weak increase in the personal control perception total score. There was a statistically significant relationship between the FCV-19S total score and the CV-19PCS inevitability subdimension total score. The increase in the FCV-19S total score led to a very weak increase in the inevitability subdimension total score. No statistically significant relationship was found between the FCV-19S total score and the CV-19PCS total score (**Table 3**).

As the FCV-19S total score increased, the CV-19PCS macro control perception subdimension total score decreased, whereas, when the FCV-19S total score increased by one unit, the macro control subdimension total score decreased by 0.052 unit. As the FCV-19S total score increased, the CV-19PCS personal control subdimension total score increased, whereas, when the FCV-19S total score increased by one unit, the personal control subdimension total score increased by 0.107 unit. As the FCV-19S total score increased, the CV-19PCS inevitability subdimension total score increased, whereas, when the FCV-19S total score increased by one unit, the inevitability subdimension total score increased by 0.075 unit. There was no statistically significant effect of the FCV-19S total score on the CV-19PCS total score ($p=0.386$) (**Table 4**).

DISCUSSION

The COVID-19 pandemic has had a profound effect across several countries worldwide, including Turkey. At the time of writing this study, the deep impact of the pandemic was still underway. As a result, the relationship between the fear created by the pandemic and the perceived control that can be used by individuals to cope with the pandemic were discussed in the light of limited findings acquired from the literature.

Table 1. Comparison of FCV-19S and CV-19PCS scores based on the sociodemographic characteristics of participants

Characteristics	n	%	FCV-19S	CV-19PCS
Gender			**Mean±SD, Median (Min-Max)**	**Mean±SD, Median (Min-Max)**
Male	812	46.4	22.2±6.7, 21.0 (7.0–35.0)	35.8±5.3, 35.0 (21.0–49.0)
Female	937	53.6	21.3±4.9, 21.0 (7.0–35.0)	35.4±5.8, 35.0 (18.0–53.0)
Test and p-value			t=3.289, p=0.001	t=1.613, p=0.107
Educational status				
Primary school	152	8.7	20.0±5.1a, 19.0 (11.0–35.0)	35.7±5.9ab, 35.0 (21.0–53.0)
Middle School	119	6.8	22.1±4.4b, 22.0 (9.0–35.0)	35.2±5.6ab, 35.0 (24.0–53.0)
High school	355	20.3	22.0±6.5b, 20.0 (7.0–35.0)	36.5±5.4a, 37.0 (21.0–49.0)
University and above	1123	64.2	21.8±5.8b, 21.0 (7.0–35.0)	35.3±5.6b, 35.0 (18.0–50.0)
Test and p-value			F=6.130, p<0.001	F=4.260, p=0.005
Marital status				
Single	825	47.2	22.4±6.2, 21.0 (7.0–35.0)	35.9±5.6, 36.0 (18.0–49.0)
Married	924	52.8	21.1±5.4, 20.0 (7.0–35.0)	35.3±5.5, 35.0 (21.0–53.0)
Test and p-value			t=4.742, p<0.001	t=2.322, p=0.020
Profession				
Civil servant	609	34.9	21.9±5.8ab, 21.0 (7.0–35.0)	35.6±5.5, 36.0 (18.0–50.0)
Housewife	121	6.9	20.5±4.5a, 20.0 (10.0–35.0)	35.6±5.7, 35.0 (21.0–53.0)
Student	273	15.6	21.9±5.3ab, 21.0 (12.0–35.0)	35.5±5.7, 35.0 (23.0–49.0)
Private sector	121	6.9	22.9±5.9b, 22.0 (7.0–35.0)	36.8±5.2, 37.0 (23.0–47.0)
Self-employment	541	30.9	21.6±6.2ab, 20.0 (7.0–35.0)	35.5±5.7, 35.0 (20.0–53.0)
Unemployed	84	4.8	20.3±5.9a, 20.0 (7.0–35.0)	34.6±5.0, 34.0 (25.0–45.0)
Test and p-value			F=3.719, p=0.003	F=1.690, p=0.134
Family type				
Nuclear family	1386	79.2	21.9±5.8ab, 21.0 (7.0–35.0)	35.7±5.6a, 35.0 (18.0–53.0)
Extended family	290	16.6	20.9±5.5b, 20.0 (11.0–35.0)	35.5±5.4ab, 36.0 (21.0–53.0)
Broken family	73	4.2	21.4±7.0ab, 22.0 (7.0–35.0)	33.8±4.6b, 34.0 (22.0–42.0)
Test and p-value			F=3.448, p=0.032	F=4.028, p=0.018
Income status				
Income less than expense	556	31.8	21.0±5.4a, 20.0 (7.0–35.0)	35.3±5.4, 35.0 (20.0–53.0)
Income more than expense	324	18.5	22.7±6.0b, 22.0 (7.0–35.0)	35.9±5.8, 37.0 (22.0–49.0)
Income equal to expense	869	49.7	21.8±5.9b, 21.0 (7.0–35.0)	35.6±5.6, 35.0 (18.0–52.0)
Test and p-value			F=8.834, p, <0.001	F=1.000, p=0.368
Place of residence				
Village	217	12.4	21.8±6.0, 22.0 (7.0–35.0)	36.1±6.2, 36.0 (21.0–53.0), ab
Town	46	2.6	25.6±6.1, 25.0 (13.0–34.0)	35.9±3.2, 37.0 (25.0–42.0), ab
District	421	24.1	21.9±6.1, 21.0 (7.0–35.0)	36.0±5.5, 36.0 (18.0–52.0), b
Province	1065	60.9	21.4±5.6, 20.0 (7.0–35.0)	35.3±5.5, 35.0 (21.0–53.0), a
Test and p-value			F=8.253, p<0.001	χ2=11.525, p=0.009
Presence of a systemic disease				
Yes	216	12.3	21.0±5.4, 20.0 (10.0–35.0)	36.2±5.1, 37.0 (24.0–53.0)
No	1533	87.7	21.8±5.9, 21.0 (7.0–35.0)	35.5±5.6, 35.0 (18.0–53.0)
Test and p-value			t=-1.785, p=0.074	t=1.777, p=0.077
Status of employment during the COVID-19 pandemic				
Not working	467	26.6	21.6±5.6, 21.0 (7.0–35.0)	35.5±5.5a, 35.0 (18.0–53.0)
Works alternately	248	14.2	21.4±5.0, 20.0 (7.0–35.0)	35.1±5.2a, 36.0 (20.0–49.0)
Continues to work from home	222	12.7	21.8±6.0, 19.0 (12.0–35.0)	37.1±5.5b, 37.0 (22.0–49.0)
Unemployed during the epidemic	94	5.4	22.8±6.3, 23.5 (7.0–35.0)	34.3±5.1a, 35.0 (21.0–45.0)
Working like before the epidemic	718	41.1	21.7±6.1, 22.0 (7.0–35.0)	35.5±5.7a, 35.0 (21.0–53.0)
Test and p-value			F=0.995, p=0.410	F=6.252, p<0.001
Contracting COVID-19				
Yes	314	18	21.1±5.2, 20.0 (12.0–35.0)	34.5±4.8, 35.0 (22.0–52.0)
No	1435	82	21.8±5.9, 21.0 (7.0–35.0)	35.8±5.7, 36.0 (18.0–53.0)
Test and p-value			t=-2.253, p=0.025	t=-4.085, p<0.001

FCV-19S: Fear of COVID-19 Scale, CV-19PCS: COVID-19 Perceived Control Scale, t: Independent two-sample t-test statistics, F: Variance analysis test statistics, χ^2: Kruskal-Wallis test statistics, ac: There is no difference between groups with the same letter, mean±standard deviation, median (minimum–maximum).

Table 2. Descriptive statistics of FCV-19S and CV-19PCS

		X̄±SS	Median	Minimum	Maximum
FCV-19S		21.7±5.8	21.0	7.0	35.0
CV-19PCS	Macro Control Subdimension	10.4±3.5	10.0	4.0	20.0
	Personal Control Subdimension	12.8±3.3	13.0	6.0	20.0
	Inevitability Subdimension	11.7±3.7	12.0	5.0	20.0
	Total	35.6±5.6	35.0	18.0	530

Table 3. Examining the relationship between FCV-19S and CV-19PCS scores

		FCV-19S	
		r	p
CV-19PCS	Macro Control Subdimension	-0.119	<0.001
	Personal Control Subdimension	0.171	<0.001
	Inevitability Subdimension	0.115	<0.001
	Total	-0.039	0.101

r: Spearman's rank correlation coefficient

Table 4. Examining the effect of FCV-19S score on CV-19PCS total and subdimension scores by linear regression

The dependent variable		Beta	s. error	Non-standardized beta (95% CI)	P	F	P	R2	Adjusted R2
CV-19PCS Macro Control Subdimension	Constant	11.542	0.322	(10.912–12.173)	<0.001	13.032	<0.001	0.007	0.007
	FCV-19S	-0.052	0.014	-0.086 (-0.08–-0.024)	<0.001				
CV-19PCS Personal Control Subdimension	Constant	10.501	0.300	(9.912–11.089)	<0.001	64.402	<0.001	0.036	0.035
	FCV-19S	0.107	0.013	0.189 (0.081–0.133)	<0.001				
CV-19PCS Inevitability Subdimension	Constant	10.047	0.344	(9.372–10.722)	<0.001	24.143	<0.001	0.014	0.013
	FCV-19S	0.075	0.015	0.117 (0.045–0.105)	<0.001				
CV-19PCS Total score	Constant	35.996	0.514	(34.988–37.005)	<0.001	0.752	0.386	0.000	0.000
	FCV-19S	-0.020	0.023	-0.021 (-0.065–0.025)	0.386				

When the FCV-19S scores were analyzed according to the sociodemographic characteristics of participants, it was revealed that gender, educational status, marital status, profession, family type, income status, place of residence, and the status of contracting COVID-19 affected the fear of COVID-19, whereas the presence of a systemic disease and status of employment during the COVID-19 pandemic had no effect on the fear of COVID-19. Bakioğlu et al. (2020) studied the fear of COVID-19 and found that factors such as gender and having a chronic illness affected the fear of COVID-19, whereas educational status and place of residence had no effect on the fear of COVID-19. Memiş Doğan and Düzel (2020) examined the levels of fear and anxiety in the case of the COVID-19 pandemic. They deduced that gender, educational status, and profession had an effect on the fear of COVID-19. Gencer (2020) found that while gender and marital status affected the fear of COVID-19, the presence of a systemic disease and educational status did not affect the fear of COVID-19. Given these findings on sociodemographic characteristics in literature, the finding that gender, profession, and marital status had an impact on the fear of COVID-19 was supported by other studies.[1,20,26,27] It can be concluded that these findings in literature supported the present study's findings. When educational status was evaluated, there were studies that supported the present study's finding and other studies reporting the opposite result.[1,20,26] It can be said that this difference may have resulted from the fact that the studies were conducted in different periods of time during the pandemic. Bakioğlu et al. (2020) found that the place of residence did not affect the fear of COVID-19.[20] However, in the present study, it was determined that place of residence was an effective factor contributing to the fear of COVID-19. Thus, it was determined that those living in provinces had less fear of COVID-19. It is thought that this situation may have resulted from easier access to services in provinces. In the study of Bakioğlu et al. (2020), there were findings that the presence of a systemic disease increased the fear of COVID-19.[20] However, in the present study, no effect of a systemic disease on the fear of COVID-19 was found. It can be argued that this difference between the two studies stemmed from the difference in the sample groups studied. In the present study, it was found that family type had an effect on the fear of COVID-19. The lowest fear of COVID-19 mean score was found in the extended family. It can be thought that individuals in an extended family could receive support from their family elders without external support in matters such as child care, and they were less afraid of other working family members than they paid attention to individual measures. On the other hand, there was a higher mean score for the fear of COVID-19 in broken families. These individuals had to be in contact with more people as they had to get external support on issues, such as childcare and housekeeping. In this case, it may be argued that such individuals would have a greater fear of COVID-19, as it would increase the likelihood of contracting the disease. It was found that individuals with high income status had higher FCV-19S scores. This may be attributed to the fact that individuals with high income would have easier access to information and services, and they would be more aware of the seriousness of the situation. Considering the status of employment during COVID-19 pandemic, it was determined that those who were unemployed during the epidemic had higher mean scores for the fear of COVID-19, but it was not statistically significant. This may be due to the fact that unemployed individuals would believe that they would have difficulty in meeting their basic needs, and their immune

systems might be weakened, resulting in them contracting COVID-19 more quickly and hardly recovering from it. Such individuals would also have difficulty in meeting their expenses including health expenses. It was found that the status of contracting COVID-19 had an effect on the fear of COVID-19. This finding may be due to the difficulty in overcoming the symptoms of the disease, occasional need for advanced health support, and fear of infecting their relatives.

When the CV-19PCS scores were analyzed according to the sociodemographic characteristics of participants, it was found that educational status, marital status, family type, place of residence, status of employment during the COVID-19 pandemic, and status of contracting COVID-19 affected the perceived control of COVID-19, whereas gender, profession, income status, and presence of a systemic disease did not affect the perceived control of COVID-19. Ekiz et al. compared the levels of health anxiety with the perceived control of the COVID-19 pandemic, and observed that gender has an effect on the perceived control.[21] However, in the present study, it was determined that gender had no effect on the perceived control of COVID-19. This discrepancy may be due to fact that the perceived control levels of women and men may change depending on the differences in cultural life practices and gender roles. In the present study, it was determined that educational status had an effect on perceived control. The findings of Ekiz et al. (2020) support those of the present study.[21] In the present study, marital status was found to affect the perceived control of COVID-19. Since single individuals are not responsible for other people (such as children), it can be thought that they have a higher perceived control than married individuals. It has been found that the profession has no effect on the perceived control. However, family type was found to have an impact on perceived control of COVID-19. CV-19PCS score of individuals living in extended families in particular was found to be higher than groups in other family types. It can be argued that this was due to the higher social support individuals living in extended families could obtain. It was also determined that the place of residence affected the perceived control of COVID-19, and those living in villages had a higher perceived control than those living in provinces, districts, and towns. It can be said that COVID-19 perceived control scores of individuals living in villages were higher than those who resided in districts and provinces owing to reasons, such as villages are not very crowded and there are limited immigrants. It was found that the presence of a systemic disease state did not affect the perceived control of COVID-19, whereas individuals with a systemic disease had a moderate level of perceived control of COVID-19. It was found that the status of employment during the COVID-19 pandemic affected the perceived control of COVID-19, and those who continued to work from home had the highest perceived control of COVID-19 among other groups. It can be said that the perceived control of COVID-19 was higher than other groups, as individuals working from home did not have economic problems and did not come into contact with other people while going to work or in the workplace during the pandemic. It was determined that the status of contracting COVID-19 affected the perceived control of COVID-19. It was found that those who contracted COVID-19 had a lower level of perceived control of COVID-19 than those who did not contract COVID-19. This may be due to the fact that the individuals who contracted COVID-19 thought they had contracted COVID-19 as they were unable to control the pandemic conditions.

As the COVID-19 pandemic causes high loss of life in today's modern societies, fear can spread from an individual level to the social plane. In the present study, the FCV-19S total score of participants was above the median. Satıcı et al. (2020) and Duman (2020) reported results similar to those of the present study.[28,29] When the perceived control of the COVID-19 pandemic was evaluated, it was found that participants had a moderate sense of control. In their study on perceived control, Zeng et al. (2020) stated that participants had a low level of perceived control.[30] Their results partially supported the present study's results.

As perceived control acts as a protective factor against the psychological effects of COVID-19, there are studies in literature reporting that perceived control increases participants' ability to cope with stressors and changes the subjective experience of environmental stressors.[15,31,32] According to findings of the present study, in the macro control subdimension of the COVID-19 Perceived Control Scale, any increase in the fear of COVID-19 created a slight decrease in the perceived control of COVID-19. However, any increase in the fear of COVID-19 resulted in a slight increase in the personal control and inevitability subdimensions of FCV-19S (**Table 3**). These findings of the present study partially support the literature findings.[15,31,32] Despite these findings, when the relationship between FCV-19S and CV-19PCS total scores was evaluated, no correlation was found between the fear of COVID-19 and the perceived control of COVID-19.

In the literature, there are reports that perceived control plays a moderate role in the relationship between the severity of the pandemic and mental health problems. There are also reports that support the basic effects of perceived control on health, as well as those that state that perceived control has a buffering effect in adjusting the psychological consequences of individuals living in areas affected by the pandemic.[15,16,30-32] In the present study, it was revealed that as the fear of COVID-19 increased, perceived control of the macro control subdimension of CV-19PCS decreased, but the total scores of the personal control and inevitability subdimensions increased. The results of the present study partially support the results of the previous studies, which indicate that perceived control has an effect on balancing of the psychological conditions experienced in the pandemic.[16,30,31] However, when the FCV-19S and CV-19PCS total mean scores were evaluated, no correlation was found between the perceived control of COVID-19 and the fear of COVID-19.

CONCLUSION

As a result of this study conducted with the aim of determining the effect of the fear of COVID-19 on the epidemic control perceptions of individuals, it was determined that individuals' fear of COVID-19 and perceived control of COVID-19 were close to the median, whereas there was a partial correlation between the fear of COVID-19 and perceived control of COVID-19. However, results of the present study contribute significantly to the literature on understanding the psychological effects of the COVID-19 epidemic, such as fear and perceived control.

Limitations

As with any research, this study has some limitations. First on-site research could not be conducted due to the pandemic, and electronic tools were used for data collection. Individuals with no or limited access to these tools and illiterate could not be included in the scope of the study. Another limitation is that the answers given to the questionnaires are based on the self-report of individuals. In this case, some biases toward social desires may have been reported.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval with the registration number 01–11 and dated 04.11.2020 was received from the Social and Human Sciences Research Ethics Committee, Tokat Gaziosmanpaşa University.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

Lightning Related Deaths in Istanbul, Between 2007-2012

İstanbul'da 2007-2012 Yılları Arasında Yıldırım Çarpmasına Bağlı Ölümler

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Abstract

Objective: Lightning injuries can cause a variety of injuries including "integumentary system, cardiac system, central nervous system, eyes and ears", in which some of them may cause death. In this study, it was aimed to evaluate crime scene findings, autopsy findings and histopathological findings by presenting 9 cases that died due to lightning strike.

Material and Method: Nine cases (0.3%) included this study were obtained from the screening of a total 24,755 cases that were performed autopsy at the Council of Forensic Medicine, Istanbul between 2007 – 2012. All cases' age, gender, crime scene, circumstances during the event, witness statement, skin lession, autopsy findings, histopathological findings were evaluated.

Results: Three (33.3%) cases were female and six (66.7%) cases were male, and the mean age was 39.66±13.36 (min: 18, max: 56). Fatal lightning strike occurred between April and September, but mostly in May. At autopsy, an external examination was revealed an electrical exit wound in 4 cases, burn areas on the skin in five cases, a Lichtenberg figure on the skin in two cases, and a burn in the hair surface in four cases.

Conclusion: Nonspecific findings are frequently detected in autopsies performed due to lightning strikes. However, crime scene investigation and the testimony of the witness may be the crucial indicative evidence for forensic investigators in getting an accurate diagnosis in cases of suspected lightning strikes. In addition, examining the clothes worn by victims provides important clues in diagnosis.

Keywords: Lightning strike, death, autopsy, forensic medicine

Öz

Amaç: Yıldırım yaralanmaları, "örtü sistemi, kalp sistemi, merkezi sinir sistemi, gözler ve kulaklar" dahil olmak üzere bazıları ölüme neden olabilen çeşitli yaralanmalara neden olabilir. Bu çalışmada yıldırım çarpması sonucu ölen dokuz olgunun sunularak, olay yeri bulguları, otopsi bulguları ve histopatolojik bulguların değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya dahil edilen dokuz olgu (%0,3) 2007 - 2012 yılları arasında İstanbul Adli Tıp Kurumu'nda otopsi yapılan toplam 24.755 olgunun dosyalarının retrospektif taranmasından elde edildi. Tüm olguların yaşı, cinsiyeti, olay yeri, olay sırasındaki koşullar, tanık ifadesi, deri lezyonları, otopsi bulguları, histopatolojik bulgular değerlendirildi.

Bulgular: Olguların üçü (%33,3) kadın, altı (%66,7) olgu erkekti ve ortalama yaş 39,66±13,36 (min: 18, maks: 56) idi. Ölümcül yıldırım düşmesi Nisan ve Eylül ayları arasında, ancak çoğunlukla Mayıs ayında meydana geldi. Otopside 4 vakada elektriksel çıkış yarası, beş vakada ciltte yanık alanları, iki vakada ciltte Lichtenberg figürü ve dört vakada saçta yanık tespit edildi.

Sonuç: Yıldırım düşmesi nedeniyle yapılan otopsilerde spesifik olmayan bulgular sıklıkla saptanmaktadır. Bununla birlikte olay yeri incelemesi ve tanık ifadeleri bu olgularda doğru tanı koymada adli araştırmacılar için önemli argümanlardır. Ayrıca kişinin giydiği kıyafetlerin incelenmesi de tanı koymada önemli ipuçları sağlayabilir.

Anahtar Kelimeler: Yıldırım çarpması, ölüm, otopsi, adli tıp

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INTRODUCTION

Lightning, following a zigzag way as branches when goes downward, is the electrical potential discharge between the cloud and the earth.[1] Lightning can emit more than 1 million volts of energy, thus more than 200,000 amperes of current may occur.[2] The air surrounding the lightning can heat up to 25,000 to 30,000 °C. However, it does not always cause serious injury, as lightning contact is very short (2 msec).[3] Lightning-related worldwide mortality rate is estimated to be 0.2-1.7 deaths/million people.[4] The idea that lightning will only strike during a storm is a myth. In fact, the most risky interval that a fatal injury due to ligtning strike may occur is the interval preceding the storm. Moreover, as the ligtning can travel horizontally as far as 10 miles and more, it may ocur when the weather is still sunny.[5] Another myth is that ligtning strike is always lethal. On the contrary, the literature shows that the mortality rate is 10-30% due to lightning strikes.[2,4,5] The electric current in lightning strike is direct current (DC) and the amount of DC current transmitted due to lightning strike is far higher than that produced by alternative current (AC).[4] There are seven different ways in which lightning can interact with human body: "direct strike, side flash (splash), touch (contact) voltage, step voltage (ground strike, stride potential, ground current), subsequent stroke, connecting leaders and shock waves".[6] Lightning incidents may cause a variety of injuries including "integumentary system, cardiac system, central nervous system, eyes and ears", in which some of them may cause death.[4-8] In this study, it was aimed to evaluate crime scene findings, autopsy findings and histopathological findings of cases that died due to lightning strike in İstanbul.

MATERIAL AND METHOD

The study was carried out with the permission of Bolu Abant Izzet Baysal University Clinical Researches Ethics Committee Approval Date: 17/10/2020, Decision No: 423. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In Istanbul, a population of more than 18 million, all forensic autopsies are performed in the Morgue Department of The Ministry of Justice Council of Forensic Medicine. All referred judicial cases undergo autopsy at the Morgue Department. In this study, the achive files of 24,755 autopsy cases between the dates 1st January, 2007 and 31st December, 2012 which had been referred to the İstanbul Morgue Department of The Ministry of Justice Council of Forensic Medicine for determining the cause of death were retrospectively analyzed and the cases that had defined been to be lightning related deaths were included in the study and reviewed in a detailed way. The demographical, judicial and clinical data of the cases included in the study were evaluated through the parameters of age, gender, crime scene, circumstances during the incident, witness statement, skin lession, autopsy findings and histopathological findings. SPSS 21.0 (Armonk, NY) statistics program was used for data analysis of the study. Descriptive statistics were presented with frequency, percentage, mean (mean), standard deviation (SD), minimum (min), maximum (max) values.

RESULTS

Screening of a total 24,755 cases revealed nine cases (0.3%) of lightning strike deaths. Three (33.3%) cases were female and six (66.7%)cases were male, and the mean age was 39.66±13.36 (min: 18, max: 56). It was determined that six (66.7%) cases were engaged in farming in the field, two (22.2%) cases had been having a picnic in the picnic area, and one (11.1%) case had been hunting in the forest during the ligtning strike incident (**Table 1**). Three cases in the field were on the tractor in the event of lightning strike. In seven cases, it was found that there were witness who saw a lightning strike at the scene (**Table 1**). These fatal lightning strikes occured between April and September, but mostly in May (**Table 1**). At autopsy, an external examination was revealed an electrical entry-exit wound in four cases (**Figure 1**), burn areas on the skin in five cases (**Figure 2**), a Lichtenberg figure on the skin in two cases (**Figure 3**), and burn in the hair surface in four cases (**Figure 4**) (**Table 2**). At autopsy, As an internal examination was revealed nonspecific findings in all cases, including widespread subpleural petechial hemorrhage at the lungs in eight cases (**Figure 5**), subepicardial hemorrhage in two cases, petechial hemorrhage on the heart in two cases, lung parenchyma and visceral pleura tears in one case, focal subarachnoidal hemorrhage in one case (**Table 3**). In all cases, intraalveolar fresh bleeding was detected in histopathological examination of the lungs (**Table 3**). In five cases, cutaneous changes compatible with electrical flow and heat affect (intraepidermal - subepidarmal seperation, elongation in the basal layer in spinal cells in the epidermis, fusiform shape, diffuse homogenization in the collagenous fibers of the dermis) were detected on histopathological examination of the skin (**Table 3**).

Table 1. Personality and environmental features of victims who died due to lightning strikes.

Case	Age	Gender	Circumstance During the Event	Crime scene	Month	Witness Statement
1	48	Woman	Farmer	Field	8	+
2	19	Man	Farmer	Tractor trailer	7	+
3	45	Woman	Farmer	Field	4	+
4	56	Man	Farmer	Tractor	6	-
5	46	Woman	Picnicker	Picnic area	9	+
6	45	Man	Picnicker	Picnic area	5	+
7	33	Man	Farmer	Field	5	-
8	18	Man	Farmer	Tractor	5	+
9	47	Man	Hunter	Woodland	9	+

Table 2. External findings at autopsy in victims who died due to lightning strikes.

Case	Electric Entry – Exit Wound	Electrical Burn	Lichtenberg Figures	Singed Hairs
1	-	-	-	-
2	-	-	-	-
3	-	-	+	-
4	+	+	-	+
5	-	+	-	+
6	+	+	-	+
7	+	+	-	-
8	+	-	-	-
9	-	+	+	+

Table 3. Autopsy and histopathological findings in victims who died due to lightning strikes.

Case	Autopsy Findings	Histopathological Lung Sign[1]	Histopathological Skin Sign[2]	Other Findings
1	+	+	-	-
2	+	+	-	Subepicardial hemorrhage
3	+	+	-	-
4	+	+	+	Subepicardial hemorrhage
5	+	+	+	-
6	+	+	+	-
7	+	+	+	Petechial bleeding in the heart, Focal subarachnoidal hemorrhage in the brain
8	+	+	+	
9	+	+	-	Petechial bleeding in the heart

[1]Intraalveolar fresh bleeding, [2]Cutaneous changes compatible with electrical flow and heat affect (intraepidermal – subepidarmal seperation, elongation in the basal layer in spinal cells in the epidermis, fusiform shape, diffuse homogenization in the collagenous fibers in the dermis)

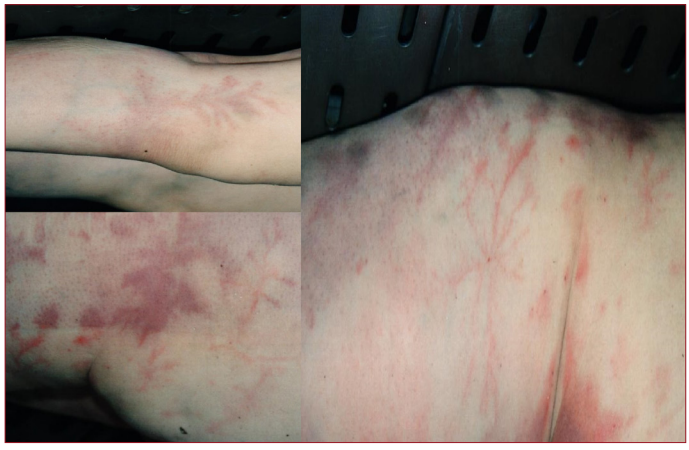

Figure 3. Lichtenberg figures on thighs, hips, and abdomen in Case 3.

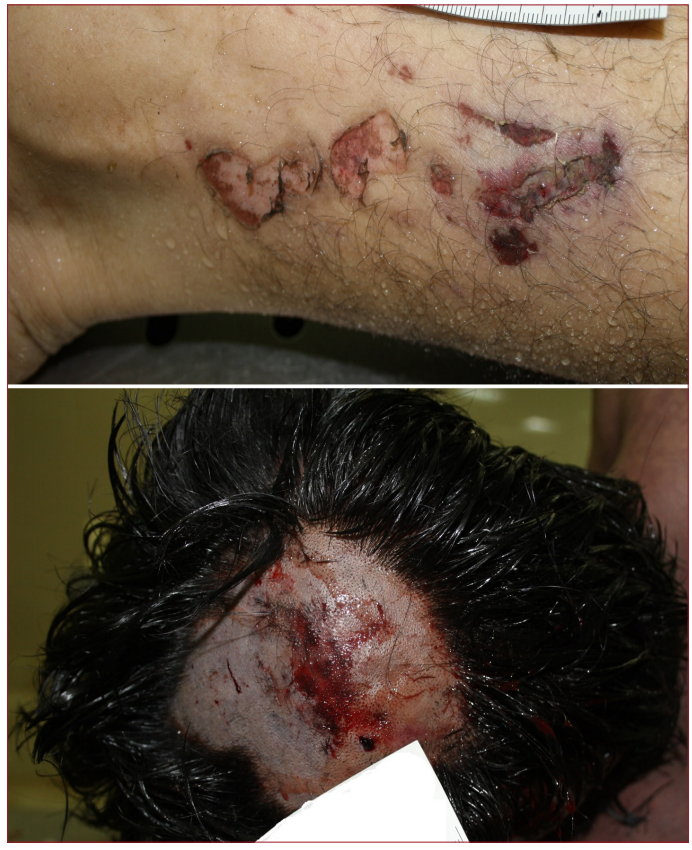

Figure 1. The electric entry wound on the scalp in the parietooccipital region and exit wound on the inner side of the right ankle in Case 7.

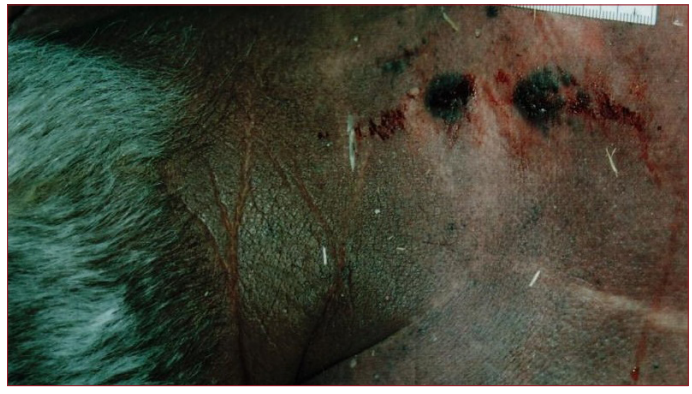

Figure 2. Point-shaped burn areas on the back in Case 5

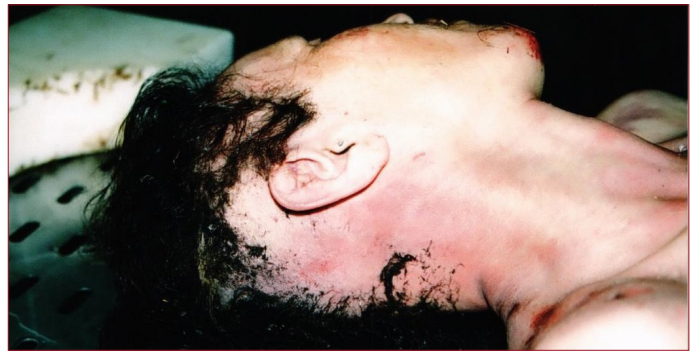

Figure 4. Burn in the hair surface in Case 6.

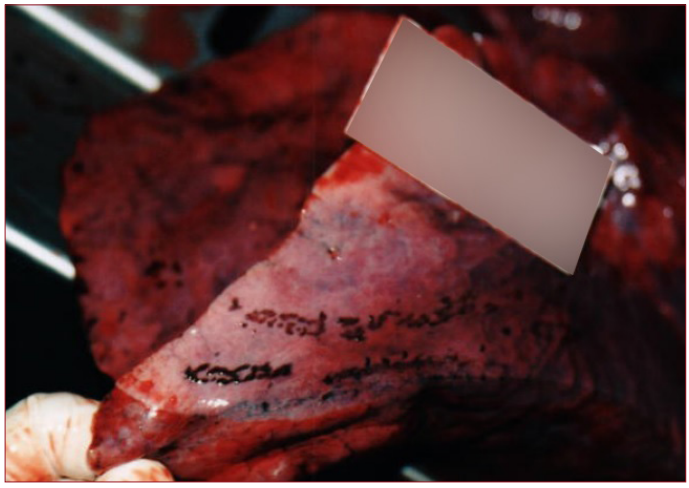

Figure 5. Linear subpleural petechial hemorrhages in the lung consistent with the passage of electric current

DISCUSSION

General Knowledges of Lightning

Approximately 10-30% of lightning injuries may result in death.[4,5] Seven different ways in which lightning can interact with human body are "direct strike, side flash (splash), touch (contact) voltage, step voltage (ground strike, stride potential, ground current), subsequent stroke, connecting leaders and shock waves".[6] Various injuries can occur through these mechanisms. Direct strike is generally seen in less than 5% of cases and is often fatal.[9] Side flash (splash) injuries can be seen as a result of the lightning current jumps to a less resistant individual through a nearby object (the most common example; a tree) due to the potential differences.[5,10,11] Touch (contact) injuries occur when the person is in contact with the object struck by lightning.[5,10] Step voltage (stride voltage, ground current) injuries can be seen in cases where the lightning targets "the ground or any object in contact with the ground" near the person.[5] Here lightning current enters the body through one foot and leaves through the other.[10] An upward connecting leader is also explained as a current rising from the ground after a lightning strike, which struck the head or other upper body parts.[6] Tympanic membrane perforation and blunt traumatic injuries can also be determined due to shock waves generated by lightning.[5,11] Occasionally, after the first lightning near the person, the second strike can directly target the person, in which case the lightning can injure the person with both "step voltage" due to the first strike and with direct affect due to the subsequent one.[6]

Gender

The percentage of males that died due to lightning strikes in the United States between 2006 and 2016 was 91%.[12] All of the cases exposed to the lightning strike presented by Nagesh et al were male and under the age of 35 (9). 55.5% of the cases exposed to lightning strikes within 10 years at a Swiss Trauma Center were reported to be male, and 44.5% female.[13] In a study involving 47 cases died by lightning strike, 70.2% of the cases were male.[14] Likewise, 79% of the deaths due to lightning strikes in South Africa were male.[15] In a study conducted in the east of Turkey, 90.1% (1/11) of the cases died due to lightning strikes were reported to be male.[16] In addition, it was stated that 87.5% of the cases in Eskisehir were male.[17] In the present study, three (33.3%) cases were female and six (66.7%) cases were male.

Age

In the study of 47 cases died as a result of lightning strike, 33 of the cases were reported to be in 11-30 age range.[14] In South Africa, the average age of the cases that died due to lightning strikes was 36.[15] In another study involving 54 cases in New Mexico, the mean age was reported to be 34.[18] In the study of Hekimoglu and et al., the average age of cases died due to lightning strike was 23.5.[16] The mean age of the cases in the present study was 39.66±13.36 (min: 18, max: 56).

Scene

In the United States, approximately two-thirds of deaths due to lightning strikes between 2006 and 2016 occurred during outdoor leisure activities (fishing, camping, beach, boat tour etc.).[12] In a study conducted in New Mexico was reported that 27.8% of cases died a result of lightning strikes while working in a job (working in the field, grazing sheep, etc.), and a larger part (72.2%) in non-working activities (sport outdoors, fishing, camping, boating, etc.).[18] In the study of 47 cases died by lightning strike, 48.9% of the cases were reported to be farmers.[14] In the study of Hekimoglu et al., was reported that 36.4% of cases were soldier and 36.4% were farmer.[16] In the present study, during the event, it was determined that six (66.7%) cases were engaged in farming in the field, two (22.2%) cases had been having a picnic, and one (11.1%) case had been hunting in the forest.

It has been shown that close proximity to metal objects such as bicycles, trains and motor vehicles during a lightning incidents.[18] It is claimed that approximately 10% of lightning strikes are related to motor vehicles.[13] The most likely places exposed to lightning strikes in car are "antenna, windshield and bonnet".[19] Pfortmueller et al. reported that two out of nine cases injured by lightning while driving.[13] Three cases we presented were on the tractor in a field when the lightning strike.

Session

Lightning strikes have been reported to occur frequently in wet seasons in Malawi.[20] Gadge and Shrigiriwar reported that deaths due to lightning strikes occured mostly in June, July and August.[14] In New Mexico, 63% of 54 cases died as a result of lightning strikes were attacked in the summer.[18] In the study of Hekimoglu et al., five cases (45.5%) died in the summer and five cases died in the autumn.[16] In the study of Turan et al., all deaths were in summer.[21] In the present study, fatal lightning strike incidents were between April and September, but mostly in May.

Witness Testimony

In cases found death due to lightning strikes, the testimony of the witness is one of the most important proofs that facilitates the decision in medicolegal investigations. In some studies conducted in Turkey, all cases have the testimony of the witness.[16,21] In the present study, there was a witness who had saw a lightning strike at the scene in seven of nine cases. Moreover, although there was no external examination finding in the first and second cases, it was determined by the testimony of the witness that death due to a lightning strike occurred.

Skin Lesions

Linear burns, spot burns, singed hair, thermal burns and their combination can be seen due to lightning strikes.[4,5] It is estimated that linear burns between 1 and 4 cm in diameter are caused by evaporation of sweat due to thermal overloading on body surface. Linear burns, usually seen as first or second degree burn; often detected on the chest, armpit and under the breast.[4,5] Multiple and closely spaced full layer spot burns, usually smaller than 1 cm, can be seen on the tiptoes and edges of the plantar surface, as the "tip toe sign".[4,22] In singed hair findings, epidermis and dermis layers are often normal, but there is a singed appearance on the body surface hair.[4] Thermal burns occur due to overheating of metal objects such as necklaces and bracelets by the lightning.[4,23] At postmortem cases, "skin burns, signed hair, torn clothes, melting of metal objects worn on the body such as belt buckles - jacket zipper - necklace, burnt cigarette box in the pocket" can be considered in diagnosis.[10,18] In addition, lightning - related entry and exit lesions can also be seen on the skin.[24] Pfortmueller et al. reported three of nine cases were injured as a result of lightning strike had skin findings, one of those three cases had mild skin lesions, while the other two had entry and exit lesions together with second and third degree burn areas.[13] In the study involving 47 cases died by lightning strike, burns on the skin in 80.8% of the cases and singed hair in 42.5% of the cases were detected.[14] In the autopsy study of lightning strikes in South Africa, thermal burns in 89.5% of cases (28% first degree, 73% second degree, 47% third degree), singed hair in 68% of cases and tears in clothes in 26% of cases were determined.[15] In New Mexico study, it was shown that 16 cases had an entrance wound and 20 cases had an exit wound.[18] In the study of Hekimoglu et al. linear burns in six cases (54.5%), punctate burns in four cases (36.4%), burns due to melting metal object in three cases (27.3%), thermal burns in two cases (18.2%) and burns due to the direct effect of lightning in three cases (27.3%) have been found.[16] Turan et al. showed that 71% singed hair, 63% traumatic lesions, 57% thermal burns and 14% electrothermal lesions were observed in seven cases died as a result of lightning strikes.[21] In another study, 85.7% of the cases (6/7) had skin burns of varying degrees and 42.8% of cases (3/7) had electrical entry and exit lesions.[17] In the present study at autopsy, an external examination was revealed an electrical entry-exit wound in four cases (**Figure 1**), burn areas of varying degrees on the skin in five cases (**Figure 2**), and burn in the hair surface in four cases (**Figure 4**) (**Table 2**). Also, in five cases, cutaneous changes compatible with electrical flow and heat affect (intraepidermal - subepidarmal seperation, elongation in the basal layer in spinal cells of the epidermis, fusiform shape, diffuse homogenization in the collagenous fibers of the dermis) were detected on histopathological examination of the skin.

"Lichtenberg figures" are considered pathognomonic for lightning strikes, but they often develop in the first hours after the lightning strike and disappear within 24 hours.[22] Also, it is rarely detected in autopsy in postmortem cases.[15] It is estimated that "Lichtenberg figures" may occur due to erythrocyte flow to the superficial skin layer in capillaries through the electrical deterioration and electric flux density on the skin.[25] Blumenthal reported that none of the 38 cases who died due to lightning strike had a lichtenberg figure at autopsy.[15] In New Mexico study, only 11.1% (6/54) of the cases were reported to have "Lichtenberg figure".[18] In the postmortem studies from Turkey, "Lichtenberg figures" were observed in between 29% and 63.6% of the cases died due to lightning strikes[16,17,21] while in the present study it is observed in two cases (%22.2) (**Figure 3**).

Cardiac effects

Among the proposed mechanisms for the effects of lightning strike on the heart; there are "induction of coronary artery spasm, catecholamine storm, direct thermal damage, ischemia secondary to arrhythmia and coronary artery ischemia due to widespread vascular damage".[26] A strong continuous contraction develops due to the simultaneous depolarization of the whole myocardium.[27] The most common cause of death due to lightning strike is asystolic cardiac arrest or ventricular fibrillation.[4] For ventricular fibrillation, lightning must occur just in time at the peak of the T wave, so asystole is predicted to be more frequent than ventricular fibrillation.[28] However, secondary cardiac arrest may also develop as a result of deep hypoxia due to paralysis of respiratory muscles or inhibition of respiratory centers.[4,5] "Ventricular fibrillation, asystole, hypertension, tachycardia, nonspecific ST and T wave changes, prolonged QT interval, premature ventricular contractions" can be seen due to lightning strikes.[5] In addition, severe stunned myocardium and acute myocardial infarction can rarely be seen due to lightning strikes.[3,8] Postmortem macroscopic heart alterations due to lightning strike are fairly seldom.[18] Soft tissue bleeding in front of pericardium at autopsy was reported in only one (4.7%) of 21 cases died due to lightning strikes in New Mexico.[18] In the present study, macroscopic cardiac damage was observed as subepicardial hemorrhage in two cases(22.2%) and petechial bleeding in two cases (22.2%).

Lungs Effects

Petechial hemorrhages can be seen on the pleural and epicardial surfaces as postmortem findings due to lightning strike.[29] In addition, macroscopically intense pulmonary edema and congestion, histopathologically intense pulmonary edema and hemorrhage can also be seen.[29,30] Burns in the chest area, lung and heart contusions can be occured especially such as necklaces worn on the chest area.[23] Aspiration bronchopneumonia, diffuse alveolar damage and pulmonary edema were detected at autopsy in 6 of 21 cases (28.5%) died due to lightning strikes.[18] Akkaya et al. detected lung contusion in 85.7% (6/7) of the autopsy cases.[17] In two of the three cases presented by Dogan et al, detected lung contusion findings.[31] Eight out of nine cases we presented had widespread subpleural petechial hemorrhage (**Figure 5**) and lung parenchyma and visceral pleura tears in one case. Also, in all cases, intraalveolar fresh bleeding was detected in histopathological examination of the lungs.

Brain Effects

It's important to discuss also the nervous system injuries due to the lightning strikes. Keroneuroparalysis is a transient condition due to lightning strikes in survivors characterized by limb paralysis, sensory paralysis, pulseless, pallor or cyanosis, motor or sensory loss.[32] The nervous system, has been reported the most commond injury area due to lightning strikes in Switzerland.[13] Epidural and subdural hemorrhage, respiratory center paralysis, intraventricular hemorrhage, petechiae and dural tears may be seen due to lightning current.[5] Bone fractures, brain hemorrhage and internal organ injuries can be revealed as a result of burst effect of lightning.[2,33] Bilateral or unilateral basal ganglia bleeding due to lightning strikes may also be seen.[7,34] In the postmortem study of Pincus et al, was reported cerebral edema, subarachnoid, subgaleal and periosteal hemorrhage may be seen due to lightning strikes.[18] In the study of Hekimoglu et al., craniocerebral trauma findings were detected in two of the victims.[16] Likewise, Akkaya et al. detected contusion in the barin in three of the autopsy cases.[17] In the present study, brain damage was observed as subarachnoid hemorrhage in only one out of nine cases.

CONCLUSION

As a result, nonspecific findings are frequently detected in autopsies performed due to lightning strikes. However, crime scene investigation and the testimony of the witness may be the crucial indicative evidence for forensic investigators in getting an accurate diagnosis in cases of suspected lightning strikes cases. In addition, examining the clothes worn by victims provides important clues in differential diagnosis.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Bolu Abant Izzet Baysal University Clinical Researches Ethics Committee Approval Date: 17/10/2020, Decision No: 423.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

Working with Older People: A Qualitative Study of X and Y Generation Nurses' Perceptions

Yaşlı Bireylerle Çalışmak: X ve Y Kuşağındaki Hemşirelerin Algılarının Nitel Değerlendirilmesi

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Abstract

Aim: This study aimed to compare the perceptions and working experiences of two age cohorts of nurses' about care of older people.

Material and Method: A qualitative descriptive study was used. The research sample consisted of 68 internal medicine and surgery nurses representing X and Y generations. Data were collected using a demographic form and a semi-structured interview form. Data were subjected to thematic analysis.

Results: The general themes for generation X were: care time, emotional responses, and provide resources for older patients. The general themes for generation Y were: increasing workload and time problems, categorization of older people, and finally, the need for holistic care.

Conclusions: All nurses experienced that caring for elderly is difficult. However, they emphasized the needs of older people. This may be an essential component in organizing older people care. It is recommended regulation of working conditions to reduce the difficulties experienced by nurses in care of older people.

Keywords: Generation, nursing care, aging, perception

Öz

Amaç: Bu çalışma, iki yaş grubundaki hemşirelerin yaşlıların bakımı hakkındaki algılarını ve çalışma deneyimlerini karşılaştırmayı amaçlamaktadır.

Gereç ve Yöntem: Bu çalışmada nitel tanımlayıcı araştırma deseni kullanılmıştır. Araştırmanın örneklemini X ve Y kuşaklarını temsil eden 68 dahiliye ve cerrahi hemşiresi oluşturmuştur. Veriler, demografik bilgi formu ve yarı yapılandırılmış görüşme formu kullanılarak toplanmıştır. Verilerin değerlendirilmesinde tematik analiz yapılmıştır.

Bulgular: X kuşağı için genel temalar; bakım süresi, duygusal tepkiler ve yaşlı hastalar için kaynak sağlamadır. Y kuşağının genel temaları; artan iş yükü ve zaman sorunu, yaşlıların sınıflandırılması ve bütünsel bakıma duyulan ihtiyaçtır.

Sonuç: Tüm hemşireler yaşlılara bakmanın zor olduğunu belirtmekle birlikte yaşlıların ihtiyaçlarını vurguladılar. Çalışma sonuçları yaşlı insanların bakımını organize etmede yarar sağlayabilir. Yaşlıların bakımında hemşirelerin yaşadıkları zorlukları azaltmak için çalışma koşullarının düzenlenmesi önerilir.

Anahtar Kelimeler: Kuşak, hemşirelik bakımı, yaşlanma, algı

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INTRODUCTION

Older people are generally defined according to a range of characteristics including: chronological age, change in social role and changes in functional abilities. Older people may be defined as those over 60 years.[1,2] The number of older people is expected to reach 2 million by the year 2050 in the world.[3] Similarly, the Turkish population is increasingly aging. In 2016, 8.3% of the overall population was older than 65 years old. Predictions are that this rate will increase to 20.8% in 2050.[4] These estimates have stimulated research and discussions around aging, chronic disease management, and care of older people.[5,6] Also, these growing numbers of older persons increased the need for qualified nurses to provide specialised care.

Nurses are the health personel who play an active role in the identification of older patients' needs, care, and rehabilitation. Nurses can develop positive or negative attitudes towards care for older people. Quantitative studies have detected that nurses attitudes toward aging are multi-dimensional and influenced by many factors, including each individual's experiences, culture, values, and beliefs. At the same time age is an important demographic variable in studies investigating perception towards the elderly.[2,7,8] Higgins et al. reported that nurses prefer working with young people to work with older people.[9] However, Coffey, & Whitehead (2015) reported that health care assistants have a positive attitude towards the elderly care.[10]

Attitudes toward older people vary with changing societies and generations, and health personnel are influenced by these transformations.[6,11] Individuals growing up in different generations represent the values of their own generation. Members of generation X (39–51 age group) are unconventional and open to new ideas. They try to balance parenthood roles, such as being a partner and a mother. In this time period, when women entered the workforce more frequently than before, individuals prioritized their families. Members of generation Y (24–38 age group) were raised during the welfare period. They are sociable and sharing. They grew up in an environment where family values were concentrated on children. These individuals were raised by more attentive families, and they prioritize balancing work and family life.[12-14] Finally, perception of older people is shaped by cultural values. In some societies, the elderly person is perceived as a burden because needs for health and care services increase with aging. In other societies, older person is viewed as a positive process accompanied by growth in wisdom and maturity.[2,15] Turkish society has always valued and protected older people. Because older people form an essential element of the Turkish family ideal, meeting the needs of older people remains the family's responsibility: the family continues to be the primary psychological and social support system.[5,15] At the same time, downsizing of families and consumerism increases along with industrialization, the escalating number of people with chronic disease that accompanies longevity, and the increased need for care, can lead to weakened family ties and problems associated with older people care.[2,16,17] Studies have been conducted to examine the views of nurses toward their job and profession.[7,8] Also, studies were conducted about ageism and nurses' view for elderly. But there are only limited nursing about nurses' perceptions and working experiences care of older people in Turkish society.[18-22] Generation refers to specific groups of people with a major characteristic in common. Understanding the differences between generations is crucial to improving care in geriatric clinics. For this reason, the research question in the study was: What are two age chorts of nurses' perceptions and working experiences about care for the elderly. The aim of this study was to determined different age groups clinical nurses' perceptions and working experience towards care for older people in Turkey.

MATERIAL AND METHOD

Study Design

The study was conducted the qualitative approach to compare perceptions and working experiences of clinical nurses in different generation about caring for the older people (65+ years).

Study Site

Participants were nurses working with older people in internal medicine and surgery clinics. We condected the research at the internal medicine and surgery clinics because of deficiencies in geriatric care clinics, most of nurses give care to older people in most of clinics in hospitals in Turkey. A thematic-based analysis was used to examine whether nurses' perceptions and experiences on working with older people vary by generation.

Participants

The age groups are divided into generations, which in this research is Generation X and Generation Y. The nurses included in generation Y group were born between 1980 and 1994, ages 24 to 38 years old. The nurses included in the generation X group were born between 1965 and 1979, ages 39 to 51.[22] The inclusion criteria is to become as a nurse in Turkey, be working in internal medicine and surgery clinics, nurses with at least 1 year experience, prior experience caring for older people and age groups representing the X and Y generations. Nurses who did not give consent for voice recording (n=26), who only worked night shifts (n=20), or who had less than one-year experience (n=10) were not included in the study. Further, nurses working in pediatrics, the intensive care unit, bone marrow transplantation units, psychiatry units or polyclinics were excluded from the study. In our study, no sample selection was made, and the saturation of the data was taken account.[23] Specifically, the research sample consisted of 68 nurses working at a university hospital.

Data Collection

The study was conducted between May 2018 and July 2018 at the clinics of a university hospitals in the city center of Ankara. A short demographic questionnaire was used. A demographic form consisted of 7 questions including gender, age, years of

experience, and clinic base. A semi-structured interview form was developed by two the researchers on the basis of their reviews of the relevant literature.[9-11,14,22] This form consisted of questions on nurses' perceptions and working experiences toward care for older people. Open-ended interview questions were as follows:

- What images do you have about older people in hospital?
- What are your feelings about working with older people?
- What are your experiences about providing care for the older people?
- How do you think older people health services should be?

Data were collected in the clinic environment during and after work hours. Voice recorders and note-taking were used during the interviews. Each interview took approximately 30–40 minutes for each participant. Each participant was interviewed once. Face-to-face interviews were carried out in a meeting room. Data were collected by researcher who has clinical experience and researches in gerontology.

Data Analysis

SPSS 21 was used for the statistical analysis of quantitative data. Percentage and mean values were calculated. The Braun and Clarke (2006) approach for conducting thematic analysis of qualitative data was used.[24] This approach consists of several steps as detailed here. (i) Familiarizing yourself with the data: Voice recordings of the in-depth interviews were fully transcribed verbatim. Participants' verbal expressions read and reread data to ensure understanding of the content. Age groups were analyzed separately. (ii) Generating initial codes: Data were grouped based on content, and accuracy with the original version was maintained and interpreted on the basis of the research questions. Then the codes were collated into potential themes in independently by two of the authors. (iii) Searching for themes: All codes were grouped into categories based on how they were related and themes and subthemes were found by two of authors. Internal and external consistency principles were considered during thematic coding. Within the overarching themes, subthemes were identified for each group. (iv) Reviewing themes: Lastly, each theme was analysed in detail based on their importance in answering the research questions. Subthemes supported by direct quotations that could most accurately emphasize/identify nurses' perceptions and working experiences. (v) Defining and naming themes: The names of themes were created. (vi) Finally, the report was produced.

The trustworthiness of the findings was considered. İnterview questions were reviewed by three experts (Turkish education expert, academician and qualitative analyst) and revised in light of the expert views. Then the interview question was tested, by the first author and one nurse ahead of the interviews to assure confirmability. Participants' verbal expressions were transferred to a separate Microsoft Word document without adding any comments. All the interviews were conducted by a researcher with clinical experience and research experience in gerontology for credibility of the study.

Ethics

Ethical consent was obtained Yıldırım Beyazıt University Social and Humanities Ethics Committee (Date: 09.12.2016, Decision No: 398). The study was carried out according to the principles of the Helsinki Declaration. Data were collected from nurses who gave informed consent and voluntarily participated in the study.

RESULTS

Nurses' sociodemographic characteristics are shown in **Table 1.** Three themes were decided upon as a result of the qualitative analyses for each group. While X generation nurses seems to have accepted that older people are difficult to care for both negative and positive emotional responses. There remained problems with the care time working with older people. It is stated that X generation nurses try to understand older people through empathy and that better conditions for older people should be provided. When Y generation nurses gave care to older people, they experienced ambivalent feelings and they categorized the elderly in workload and felt that improvements in the health care system as well as employment conditions should be made. Three subthemes for generation X and Y are shown in **Table 2**. Words frequently repeated by participants were grouped using the word cloud method during voice recording. Members of generation X emphasized the words 'care' and 'insufficient', whereas generation Y nurses repeated "care" and "dependent".

Table 1. Characteristics of nurses (n=68)

Characteristics	Frequency	Percentage
Sex		
Female	63	93.1
Male	5	6.9
Generation		
X generation	33	48.5
Y generation	35	51.5
Education status		
Bachelor's degree	56	82.4
Higher education graduate	12	17.6
Marital status		
Married	48	70.6
Single	20	29.4
Clinic stationed at		
Internal medicine	36	52.9
Surgery	12	26.5
Any children		
Yes	46	67.6
No	12	32.4
Living with elderly people		
Yes	8	12.4
No	60	87.6

Table 2. Themes for different generation nurses

Themes for X generation nurses
Emotional responses
Care time
Provide resources for older patients
Themes for Y generation nurses
Categorized of older people
İncreasing workload and problem of time
Need for holistic care

Themes for Y Generation

The general themes of generations Y were: increasing workload and time problems, categorization of older people, and finally, the need for holistic care.

Increasing workload and the problem of time: Nurses reported that working with older individuals is difficult and increases workload. There were many reasons for the difficulties experienced by nurses. Due to time problems and other intensive nursing practices, older people are increasing nurses' workload. Additionally, older people had many chronic diseases, dependency of elderly people to others and physical limitations are reported as the causes of workload. Generation Y nurses noted that because older people need more care, nurses' workload has increased and they have had problems keeping up with other nursing practices that also need to be managed.

"There are many differences between providing care for an individual who is 20–30 years old and for individuals who are 60 years old and above. This is because there are many complications involved in elderly diseases. For instance, if the elderly patient is admitted to the cardiology clinic, other units such as internal medicine, nephrology, and endocrine monitor the patient too. Following up all these influences our workload" (34 years old, female).

Categorization of older people: Nurses stated that individual differences of the elderly affect their perception of care. Most of nurses reported that they tried to empathize. However, the nurses have reported that they have been exhausted. Nurses defined categories in relation to older people. Nurses stated that caring for some older people is difficult and more demanding than caring for other patients and some people change in their personalities through the process of disease and development of physical problems. Some older people are no different to others.

"Sometimes during the process of aging, people feel lonely and useless. They are dependent on care, and sometimes they may try to attract the attention of other individuals surrounding them….. But some older people are no different than others and are so cute" (26 years old, female).

Need for Holistic Care: Most of the nurses considered that health services for the elderly were insufficient. Nurses experienced difficulties in the care of the elderly because of the conditions in the hospitals. Generation Y nurses emphasized the importance of holistic care for older people and the need for recruiting personel in this area. Because of multiple needs, it was considered necessary to provide holistic care and to provide teamwork with trained personnel.

"Care programs for the elderly should be organized holistic approach. However, since there is no space in geriatric services, such care cannot be provided. Care programs should include both medical treatments and activities that cannot be carried out due to physical inadequacies (all forms of logistic support including eating, cleaning, shopping, and a telephone hotline") (32 years old, female)

Themes for X Generation

The general themes of generations X were: care time, emotional responses, and provide resources for older patients.

Care time: Nurses stated that they are aware of the needs of older people. This awareness affects workload positively so the elderly did not increase their workload. However, nurses explained that they had time problems while caring for elderly people. They must have more time to look after older people. Because diseases increased in line with aging so the elderly often were dependent on care. However, nurses reported that nurses don't have enough time for older people care because of other intensive nursing activities.

"The elderly cannot immediately carry out what they are told. For example, you tell her 'take your medicine', but she cannot open the box and take it. Most of the time, she needs help in standing up. It is not difficult to support them but you have to spend for more time for older people. Sometimes because of the time problem, we are not as interested in their needs" (42 years old, female).

Emotional responses: Nurses had positive and negative emotional of working with older people. Nurses reported that they tried to empathize with older people and that they mostly felt happy and pleased. Some nurses said that elderly people became in need of care and fond. Nurses defined the feeling of pity and sadness when they gave care to these patients and that they thought they could be like this when they got older.

"First, I put myself in their shoes. For sure, I empathize with other patients too, but the part when I envision myself getting older makes the elderly more important for me. Second, I feel pleased feel happy while giving them care. Sometimes I feel sadness for them because I think older people feels insufficient in meeting her needs, gets exhausted easily, needs help" (50 years old, female).

Provide resources for older patients: Nurses aware of the needs of the elderly. However, participants experienced insufficient working circumstances while caring for older people. Generation X nurses noted that care programs for the elderly should be organized according to the needs and care of the patient and elderly home care services should be improved. Nurses believed that elderly are better cared for in old people's homes. They needed activities to diminish dependency of the older persons.

"It became better over the last few years, but still the number of elderly home care services should be increased. There should be frequent medical examination and controls. Health services should be easily accessed. There should be support for transportation, shopping, and care of the elderly" (44 years old, female)

DISCUSSION

Although general attitudes toward older people were found to be positive, views regarding care at hospitals may be negative as a result of health problems, hospitalization processes, functional regression, and accompanying comorbidities.[25] In our study nurses had positive and negative perceptions towards older people care. Similar to our study. Higgins et al. reported that

nurses prefer working with young people to work with older people.[9] However, in the other study, were found that the attitudes of nurses generally were positive.[26] Perceptions can be negatively influenced by the under resourced care environments experienced when working with older people. In our study, both generations nurses described older people are difficult to care for. Life changes arising from chronic diseases were considered to affect both older people and their caregivers. Hospitalization for the older person can represent the beginning of functional decline and increased dependency. For this reason, nurses interpreted older people with chronic disease as increasing the burden of care. Health workers are interested in pathological aging rather than healthy aging. In this case, it is seen that they work more patient-centered than individuals.

Nurses from both generations in our study emphasized increasing workload and nurses noted that the problem of time is due to this workload increase. Contexts such as physical and mental loss, dependency, and the need for another person in daily care make aging an uneasy period. Similar to our study Smythe at al. expressed lack of time to care.[27] In the study by Higgins and colleagues, nurses did not pay attention to the care of older people and perceived it as a waste of time.[9] It has also been determined that nurses cannot provide the required care for older people due to time limitations.[28] İntensive workload and inadequate role preparation may cause challenges in young nurses. Also generation X nurses have time management problems. Generation Y nurses don't like to waste time.[22]

Although nurses in our study empathized working with older people, and nurses experienced more feelings of ambivalece, sadness, happy, and exhaustion. Smythe and colleagues carried out a study on nurses working with dementia patients.[27] Under the themes of responsibilities and vacancies, nurses explained that they felt sorry for limiting the extent of their relationships with the older people, as well as providing less than attentive and person-focused care due to other priorities such as administering medications and catheterization.[27] The study condected by Kae and Gyeong was identified wisdom and maturity as one of the four themes among the perceptions of aging.[29] It ıs stated in a systematic review that nurses' have coexisting positive and negative attitudes towards older adult care.[30] Generation X nurses, did not have any preconceived ideas and mentioned the emotional responses to older people. They felt happy and empathic when giving care due to the respect and attention given to older people. However, generation Y nurses evaluated elderly people by categorically dividing them according to workload. One possible reason why generation Y nurses expressed exhaustion more often could be related to members of this group being less willing to work and belief in having a more flexible working method.

All nurses expressed insufficient health care for elderly in our study. Nurses mentioned that care services for older people were inadequate and advised developing a holistic care service for patients and increasing home care services as well as increased personnel recruitment. Members of generation X mentioned home-care services more frequently because they wanted to work in environments with specific boundaries. Generation Y nurses highlighted the concept of recruitment in response to their belief in team-work. Likewise, in the qualitative study carried out by Hunter and colleagues, nurse assistants emphasized the need to develop a holistic care approach and to provide psychological support for the elderly.[31] Organizing the health care system to care to for the needs of the population of older people is important in view of the health problems and difficulties that arise from aging. In Turkey, necessary arrangements should be made for developing new service models that can meet the problems and needs of an increasingly aging society. Older people should be supported with live-in care and professional assistance. Findings of our study reveal the current short comings in this area in Turkey.

CONCLUSION

Nurses perceptions towards older people care are complex and contradictory. Age as a demographic variable emerged as influences on nurses' attitudes and nurses' approaches to older patients care. This study determined the perceptions of different generation nurses' on caring for older people. Whereas respect, protection, and importance given to older people in Turkish society are still safe guarded, aging-related diseases and the burden of care are regarded as problems. This research determined differences between generations of nurses in their care of older people. We suggest that focus should be given to the development of work force support and supervision. The number of older people in need of care is expected to increase as the population continues to age and politicians both nationally and internationally emphasize the goal of quality of care for older people. Findings suggest that improved organization of health care services and greater opportunities for continuing education related to care of older people and working conditions should be implemented in Turkey to improve nursing care.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical consent was obtained Yıldırım Beyazıt University Social and Humanities Ethics Committee (Date: 09.12.2016, Decision No: 398).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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Orjinal Araştırma / Original Article

B-Type Natriuretic Peptide and Calcium Score in Angina Pectoris Patients

Angina Pektoris Hastalarında B-Tipi Natriüretik Peptit ve Kalsiyum Skoru

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Abstract

Objective: The purpose of this study is to look into the relationship between coronary artery disease evaluated with multislice computed tomography (MSCT) findings and B-type natriuretic peptide (BNP) and calcium score (CaS).

Material and Method: The study included 83 patients who were administered to our center and who had asymptomatic and stable angina pectoris. Blood samples were collected for BNP testing, and the Abbott AxSYM System kit was used for measurements. Calcium scoring was performed on each of the four main coronary arteries, and the total "Agatston" score was calculated for each patient by summing up the results. MSCT angiograms were studied at the three-dimensional operating base.

Results: Coronary artery disease (CAD) was found in 51 (61.4%) patients, while the coronary arteries of 32 (38.6%) patients were deemed normal. While patients with CAD had a median BNP of 33.9 (0–834), those without CAD had a median of 19.2 (0–185), which was statistically significant (p=0.011). Furthermore, there was a positive correlation between the number of vessels involved and BNP (r=0.364, p=0.001). BNP levels were found to be significantly higher in hypertensive patients (p=0.008). The CaS and BNP median of the group with three-vessel involvement were significantly higher (p < 0.001 and p=0.007, respectively). According to the multivariate logistic regression results, BNP and age were not found to be associated with presence of CAD, but CaS was found to be associated.

Conclusion: CaS was found to be associated with presence of CAD. Further studies should be conducted to confirm aforementioned associations.

Keywords: Coronary artery disease, B-type natriuretic peptide, Coronary artery calcium

Öz

Amaç: Bu çalışmanın amacı, çok kesitli bilgisayarlı tomografi (ÇKBT) bulguları ile değerlendirilen koroner arter hastalığı ile B tipi natriüretik peptit (BNP) ve kalsiyum skoru (KaS) arasındaki ilişkiyi incelemektir.

Gereç ve Yöntem: Merkezimize başvuran asemptomatik ve stabil angina pektorisli 83 hasta çalışmaya alındı. BNP testi için kan örnekleri alındı ve ölçümler için Abbott AxSYM Sistem kiti kullanıldı. Dört ana koroner arterin her biri için kalsiyum skorlaması yapıldı ve sonuçlar toplanarak her hasta için toplam "Agatston" skoru hesaplandı. ÇKBT anjiyogramları, üç boyutlu işlem tabanında çalışıldı.

Bulgular: 51 (%61,4) hastada koroner arter hastalığı (KAH) saptanırken, 32 (%38,6) hastanın koroner arterleri normaldi. 17 hastada (%20,5) tek damar tutulumu, 18 hastada (%21,7) iki damar tutulumu, 16 hastada (%19,3) üç damar tutulumu saptandı. KAH olan hastaların medyan BNP'si 33,9 (0-834) iken, KAH olmayanların medyan değeri 19,2 (0-185) idi ve bu istatistiksel olarak anlamlıydı (p=0,011). Ayrıca tutulan damar sayısı ile BNP arasında pozitif bir korelasyon vardı (r=0,364, p=0,001). Hipertansif hastalarda BNP düzeyleri anlamlı olarak yüksek bulundu (p=0,008). Üç damar tutulumu olan grubun KaS ve BNP medyanı anlamlı olarak daha yüksekti (sırasıyla p<0,001 ve p=0,007). Çok değişkenli lojistik regresyon sonuçlarına göre BNP ve yaş KAH varlığı ile ilişkili bulunmazken CaS ilişkili bulundu.

Sonuç: CaS, KAH varlığı ile ilişkili bulundu. Yukarıda belirtilen ilişkileri doğrulamak için daha fazla çalışma yapılmalıdır.

Anahtar Kelimeler: Koroner arter hastalığı, B tipi natriüretik peptit, Koroner arter kalsiyum

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INTRODUCTION

Cardiovascular diseases consist of ischemic heart disease, stroke, heart failure, peripheral artery disease, and a variety of other cardiac and vascular conditions. These diseases are among the leading causes of death and morbidity worldwide, with ischemic heart disease being the leading cause of death in countries of all income groups.[1,2]

Multislice computed tomography (MSCT) angiography is a noninvasive screening method used to diagnose coronary artery atherosclerosis.[3] Moreover, MSCT coronary angiography has become more popular in recent years. In addition, it has been reported that it outperforms the standard invasive method in the evaluation of some parameters such as the degree of calcification.[4]

Evaluation of coronary artery calcification by computed tomography is equivalent to the total coronary atherosclerosis burden and cardiovascular event risk.[5] The Agatston method is the most widely used for calculating the calcium score (CaS).[6] CaS has been shown to be an independent risk marker for cardiac events, cardiac mortality, and all-cause mortality, and it adds prognostic information to other cardiovascular risk markers.[7]

B-type natriuretic peptide (BNP) is another parameter whose level increases in heart failure caused by several heart diseases, including ischemic heart disease, and is used as a prognostic indicator.[8] In addition to BNP elevation having a prognostic value, a decrease in BNP levels during hospital follow-up was also used as an indicator of a favorable prognosis.[9] Although MSCT and BNP levels and CaS are used in the evaluation of coronary artery diseases (CAD), there have been few studies that compare the two.

The purpose of this study is to investigate the relationship between coronary artery disease as determined by MSCT findings and BNP and CaS.

MATERIAL AND METHOD

The study was approved by the Research Ethics Committee of Marmara University Faculty of Medicine (No: B.30.2.MAR.0.01.00.02/AEK-258). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

The study included 83 patients who were administered to our center between September 1, 2006, and December 21, 2006. After being informed about the aim of the study, all patients provided written informed consent.

Inclusion Criteria

The study included patients with asymptomatic and stable angina pectoris.

Exclusion Criteria

1. Patients who refuse to participate in the study
2. With mental/physical disabilities who are unable to provide written consent
3. Those who have an atrial fibrillation rhythm
4. Those suffering from chronic obstructive pulmonary disease
5. Who have had myocardial infarction, percutaneous transluminal coronary angioplasty, and coronary artery bypass graft
6. Those who describe unstable angina pectoris

Measurements

Just prior to the shooting, vascular access was established in the right arm. Blood samples were collected for BNP and high-sensitivity C-reactive protein (hsCRP) using Abbott AxSYM System kit for measurements.

After the image for calcium scoring (Agatston) was taken, 90 cc of nonionic contrast material was administered, and the shooting was completed within 10 seconds. The topogram image was obtained while the patient was lying in supine position. Then, to minimize heart movements, all examinations were performed, including the whole heart from the aortic root, with a breath-holding time of 3–5 seconds and ECG triggering at 80% R-R interval.

Four major coronary arteries were examined for the presence of calcified lesions throughout their traces: the left main artery, left anterior descending (LAD) artery, circumflex artery (Cx), and right coronary artery. All numerical data with homogeneous variances were evaluated: systolic tension arterial (STA), diastolic tension arterial, heart rate, left ventricular ejection fraction, interventricular septum end-diastolic thickness, interventricular septum end-systolic thickness, lateral septum end-diastolic thickness, lateral septum end-systolic thickness, pulmonary vein mean diameter (PVMD), right pulmonary artery diameter, and left pulmonary artery diameter.

The "Agatston" score was calculated for calcification in the coronary arteries using the SYNGO software (Siemens Medical Systems). According to the scoring system, lesions with a CT density of more than 130 HU in 2–3 pixels adjacent to each other, in an area larger than 1 mm^2, were interpreted as calcification. The CaS was calculated for each calcified lesion by multiplying the lesion area by the intensity score determined by lesion density. Calcium scoring was performed on each of the four main coronary arteries, and the total "Agatston" score was calculated for each patient by adding the scores.[6]

MSCT angiograms were studied at the three-dimensional operating base (Aquarius, TeraRecon, San Mateo, California).

The participants in the study were divided into two groups: those who had CAD and those who did not. In addition, they were also divided into four groups (normal coronary arteries, single-vessel involvement, two-vessel involvement, and three-vessel involvement) based on the number of vessels involved.

Statistical Analysis

For the analyses, SPSS v20 (SPSS Inc., Chicago, IL, USA) was used. The Shapiro-Wilk test was used to determine the normality. According to the normality check, data are presented as mean±standard deviations or median (minimum-maximum) for continuous variables and as frequency (percentage) for categorical variables. While normally distributed variables were analyzed using the student t-test and one-way ANOVA test, non-normally distributed variables were analyzed using the Mann-Whitney U test and Kruskal-Wallis H test. Moreover, the chi-square tests or Fisher's exact tests were used to analyze categorical variables. To evaluate the relationships between continuous variables, Spearman correlation coefficients were calculated. Multivariate logistic regression model were constructed. The dependent variable was presence of CAD. Independent variables were selected from the factors showed statistically significant relationship with presence of CAD. In addition, $p<0.05$ was regarded as statistically significant.

RESULTS

The study group consisted of 59 (71.0%) men and 24 (29.0%) women, with a mean age of 52.6±12.5.

All patients had a median BNP of 31.1 pg/ml (0–834). Moreover, male patients had a median BNP of 30.9 pg/ml (0–693), whereas female patients had a median BNP of 39.0 pg/ml (0–834), (p=0.227). The hsCRP median was 1.8 mg/l (0.3–19.0). **Table 1** shows some characteristics of the study group.

Table 1. Distribution of some characteristics of men and women

	Male	Female	Total	p
Age	49.0 (25-89)	56.5 (40-81)	50.0 (25-89)	0.004
BMI (kg/m²)	26.7 (21.3-37.9)	26.6 (22.1-35.2)	26.6 (21.3-37.9)	0.726
BNP (pg/ml)	30.9 (0-693)	39.0 (0-834)	31.1 (0-834)	0.227
hsCRP (mg/l)	1.7 (0.3-19.0)	2.1 (0.4-14.3)	1.8 (0.3-19.0)	0.713
Smoking history	33 (78.6%)	9 (21.4%)	42 (100%)	0.128
Hyperlipidemia history	33 (71.1%)	13 (28.3%)	46 (100%)	0.883
Hypertension history	27 (60.0%)	18 (40.0%)	45 (100%)	0.015
Diabetes Mellitus history	11 (64.7%)	6 (35.3%)	17 (100%)	0.515

While CAD was detected in 51 (61.4%) patients, the coronary arteries of 32 (38.6%) patients were found to be normal. Single-vessel involvement was detected in 17 (20.5%) patients, two-vessel involvement in 18 (21.7%) patients, and three-vessel involvement in 16 (19.3%) patients. The most involved artery was the LAD. Furthermore, 18 (21.7%) patients had exertional angina. When BNP, hsCRP, and CaS levels in patients with exertional angina were compared, all three were found to be significantly higher than asymptomatic patients (p=0.020, p=0.034, and p=0.008, respectively).

The median age of patients with CAD was 53.0 (36–89), which was significantly higher than those without CAD (p=0.002). When the number of vessels involved was considered, the median age of the group with three-vessel involvement was significantly higher than the group without CAD (p=0.002).

While the median BNP of patients with CAD was 33.9 (0–834), those without CAD had a median of 19.2 (0–185) (p=0.011). In addition, there was a positive correlation between the number of vessels involved and BNP (r=0.364, p=0.001). The relationship between BNP level and smoking, hyperlipidemia, hypertension, and DM history was also investigated. While BNP levels were found to be significantly higher in hypertensive patients (p=0.008), there was no significant difference between other variables and BNP levels (p>0.05 for each).

CaS values ranged from 0.0 to 1471.0. The CaS mean was 104.6±240.5 (median value 0.0). Further, CaS was measured above 0 in 41 patients. The median CaS of patients with CAD was 48.9 (0–1471), which was significantly higher than those without CAD (p<0.001). When the number of vessels involved was considered, the CaS median of the group with three-vessel involvement was significantly higher than the other groups (p<0.001). In terms of median hsCRP, there was no significant difference between groups (p=0.222). **Table 2** and **Table 3** show some characteristics of the study group.

According to the multivariate logistic regression analysis, only factor affecting the CAD was found to be as CaS (p=0.049). BNP and age were found to be non-significant in multivariate analysis (**Table 4**).

Table 2. The distribution of some characteristics of the study group according to whether they have CAD or not.

	CAD absence	CAD presence	p
Age	47.0 (25.0-68.0)	53.0 (36.0-89.0)	0.002
BMI	26.7 (24.2-37.2)	26.5 (21.3-37.9)	0.438
BNP	19.2 (0-185)	33.9 (0-834)	0.011
CaS	0 (0-38.0)	48.9 (0-1471)	<0.001
hsCRP	1.5 (0.3-19.0)	1.9 (0.4-15.0)	0.222
STA	139.2±14.6	140.4±20.7	0.763
DTA	81.1±11.0	80.7±10.5	0.849
HR	73.5±9.2	71.1±8.6	0.228
LVEF	57.5±6.9	57.1±7.9	0.828
ISEDT	10.3±1.5	10.9±1.6	0.090
ISEST	13.4±1.5	13.8±1.8	0.334
LSEDT	9.6±1.6	9.8±2.2	0.618
LSEST	14.8±2.1	15.4±3.1	0.388
PVMD	12.7±1.4	13.2±1.5	0.181
RPAD	20.9±2.6	21.7±2.6	0.191
LPAD	21.2±1.9	21.5±2.6	0.639

Table 3. The distribution of some characteristics of the study according to the number of vessels involved.

	CAD absence	single-vessel involvement	2-vessels involvement	3-vessels involvement	p
Age	47.0 (25.0-68.0	49.0 (37.0-69.0)	50.5 (36.0-81.0)	62.0 (41.0-89.0)	0.002
BMI	26.7 (24.2-37.2)	24.9 (21.3-33.3)	27.3 (23.2-37.9)	27.3 (22.6-36.6)	0.369
BNP	19.2 (0-38.0)	26.3 (0-235)	31.0 (0-403)	86.6 (10.6-693)	0.007
CaS	0 (0-38.0)	0 (0-158)	52.6 (0-403)	201.7 (2.9-1471)	<0.001
hsCRP	1.5 (0.3-19.0)	1.8 (0.4-11.7)	2.6 (0.6-15.0)	1.6 (0.8-7.4)	0.334
STA	139.2±14.6	131.2±17.9	140.0±22.4	150.8±17.6	0.023
DTA	81.1±11.0	77.0±10.4	83.6±12.0	81.4±7.8	0.323
Nds	73.5±9.2	68.7±8.4	72.1±7.4	72.5±9.9	0.352
LVEF	57.5±6.9	59.1±5.7	56.9±7.1	54.3±11.1	0.436
ISEDT	10.3±1.5	10.6±1.7	11.3±1.1	10.9±2.0	0.244
ISEST	13.4±1.5	13.6±2.0	14.2±1.7	13.8±1.9	0.617
LSEDT	9.6±1.6	9.5±2.8	9.9±1.6	10.1±2.3	0.838
LSEST	14.8±2.1	15.0±3.8	16.0±1.5	15.1±3.8	0.585
PVMD	12.7±1.4	12.4±0.8	13.9±1.7	13.5±1.4	0.021
RPAD	20.9±2.6	20.8±1.5	21.5±2.0	23.3±4.0	0.069
LPAD	21.2±1.9	21.3±2.6	21.2±2.9	22.7±2.2	0.684

Table 4. Multivariate regression results for the factors affected the coronary artery disease

	B	S.E.	Sig.	Exp(B)	95% CI for EXP(B)	
					Lower	Upper
Age	0.034	0.032	0.299	1.034	0.971	1.102
BNP	0.002	0.004	0.725	1.002	0.993	1.010
CaS	0.087	0.044	0.049	1.091	1.000	1.190
Constant	-2.201	1.551	0.156	0.111		

Dependent variable: Presence of CAD, Nagelgerke R2: 0.507

DISCUSSION

In this study, we analyzed 83 patients who had asymptomatic or stable angina pectoris and had their cardiac findings evaluated with MSCT. The following were the major findings:(1) CAD was found in 51 (61.4%) of the patients. (2) Those with CAD had significantly higher BNP levels. (3) There was a positive correlation between the number of vessels involved and BNP. (4) BNP levels were found to be significantly higher in hypertensive patients. (5) CaS levels were higher in CAD patients. (6) Exertional angina patients had higher levels of BNP, hsCRP, and CaS than asymptomatic patients.(7) Multivariate analysis showed CaS levels were associated with presence of CAD, but BNP were not.

In recent studies, many mechanisms, including myocardial ischemia, have been shown to contribute to BNP release, and BNP level has also been shown to be a useful clinical indicator in the diagnosis and prognosis of cardiovascular diseases.[10-13] Furthermore, it has been reported that BNP has vasodilator effects on the coronary artery system and that BNP primarily acts on both epicardial coronary arteries and coronary microvessels.[10,12] Due to its release in response to increased wall tension, it represents a higher degree of myocardial dysfunction in acute coronary syndrome patients with low left ventricular ejection rate and high BNP levels, with a high risk of congestive heart failure and mortality.[14] BNP level was found to be higher, particularly in patients with three-vessel involvement. In addition, when compared to asymptomatic patients, BNP levels were significantly higher in patients with exertional angina. However in multivariate analysis, there was no significant relationship between CAD and BNP.

For a long time, there has been a relationship between hypertension and CAD. In the current study, the STA of patients with three-vessel involvement was significantly higher than in patients with single-vessel involvement. Furthermore, those with a history of HT had higher BNP levels.

The presence of calcium in the coronary arteries indicates the presence of atherosclerosis, and the extent of coronary calcium corresponds to the burden of atherosclerotic plaque.[15-17] In addition, in asymptomatic individuals, coronary artery calcification has been shown to be the most predictive cardiovascular risk marker.[18,19] A study found that when CaS is added to traditional risk factors, it improves risk stratification for the prediction of coronary disease events in an asymptomatic population.[20] In symptomatic patients, the CaS score can be interpreted as a screening tool to facilitate diagnosis. Therefore, it was reported that using CaS score alone in symptomatic patients is limited.[7] During an 11-year follow-up in a population-based study of older adults without known cardiovascular disease, individual coronary artery calcium score was shown to provide better discrimination than chronological age for atherosclerotic coronary heart disease.[21] In our study, total CaS was found to be greater than 0 in 38 (71.6%) of those with CAD. In addition, CaS was found to be significantly higher in CAD patients with three-vessel involvement. Also, CaS was found to be associated with presence of CAD in multivariate logistic regression analysis. The results confirm that a high level of CaS is associated with the presence and severity of CAD. However, values greater than 0 in some patients with normal coronary arteries indicate that total CaS may not be a reliable predictor of the presence of CAD.

There were several limitations in this study. First, our results were limited to the experience of a single center, and the sample size was relatively small. Second, in this study, only circulating BNP levels were measured. Measuring plasma BNP levels in the coronary sinus may have been more precise in determining the relationship between BNP level and CAD. Third, changes in CaS resulting from medical treatment and/or lifestyle changes were not evaluated in this study. Therefore, these changes may have influenced the results.

CONCLUSION

CAD was detected in more than half of the study participants. The most involvement was determined to be from a single-vessel, with LAD being the most involved vessel. CaS levels were significantly higher in those with CAD, and there was a positive correlation between the number of vessels involved and BNP. Further studies should be performed to confirm these conclusions.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Research Ethics Committee of Marmara University Faculty of Medicine (No: B.30.2.MAR.0.01.00.02/AEK-258)

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

Screening Nutritional Status of Hospitalized Patients with Nutritional Risk Screening 2002 and Subjective Global Assessment Tools

Hastanede Yatan Hastaların Beslenme Durumlarının Nutrisyonel Risk Skoru 2002 ve Subjektif Global Değerlendirme ile Taranması

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Abstract

Aim: The assessment of the nutritional status of hospitalized patients is important to detect individuals who are under malnourishment risk and malnutrition-related conditions. The present study aimed to screen the nutritional status of hospitalized patients with Nutritional Risk Screening 2002 (NRS-2002) and Subjective Global Assessment (SGA) and to compare the results of two screening methods in predicting malnutrition.

Material and Method: NRS-2002 and SGA were administered to 134 non-critical service patients within the first days of hospital admission. Tool performance in predicting malnutrition and the association with length of hospital stay (LOS) were analyzed.

Results: 22.4% (n=30) of the patients were at nutritional risk when screened with NRS-2002; when screened with SGA, 35.8% (n=48) of the patients were found to be malnourished (p=0.015). The hospital LOS (day) of malnourished patients and non-malnourished patients according to NRS-2002 were similar. However, according to SGA, the hospital LOS of malnourished patients was longer than non-malnourished patients (17.90±16.93 vs 10.79±11.23) (p=0.004). In both screening tools, most of the malnourished patients were overweight or obese (the total overweight and obese patients rate 70% and 75% according to NRS-2002 and SGA; respectively). Factors associated with malnutrition were only age and hospital LOS (p<0.05).

Conclusion: Considering current criteria for nutritional risk, NRS-2002, as an objective and remarkably powerful tool, seems to provide a better yield for an objective assessment. Besides this, adding subjective parameters to the assessment by applying SGA could increase the capability of detecting the nutrition risk of hospitalized patients for a comprehensive nutritional assessment.

Keywords: Malnutrition, nutritional assessment, nutritional risk screening 2002, subjective global assessment.

Öz

Giriş: Hastanede yatan hastaların beslenme durumlarının değerlendirilmesi, malnütrisyon riski altında olan hastaların ve malnutrisyonla ilişkili diğer durumların tespit edilmesi için önemlidir. Çalışmada, hastanede yatan hastaların beslenme durumlarının Nutrisyonel Risk Skoru 2002 (NRS-2002) ve Subjektif Global Değerlendirme (SGD) tarama araçları ile taranması ve malnütrisyonun belirlenmesinde iki tarama yönteminin sonuçlarının karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: NRS-2002 ve SGD, hastaneye kabulün ilk günlerinde 134 kritik olmayan servis hastasına uygulanmıştır. Malnütrisyonun tespitinde tarama aracının etkinliği ve hastanede kalış süresi ile ilişkisi analiz edilmiştir.

Bulgular: NRS-2002 ile tarandığında hastaların %22,4'ü (n=30) beslenme riski altında olduğu, SGA ile tarama yapıldığında hastaların %35,8'inin (n=48) malnütrisyonlu olduğu saptanmıştır (p=0,015). NRS-2002'ye göre yetersiz beslenen hastaların ve yetersiz beslenen hastaların hastanede kalış süreleri (gün) benzerdi. Ancak SGD taramasına göre malnütrisyonlu hastaların hastanede kalma süreleri malnütrisyonsuz hastalara göre daha uzundu (sırasıyla; 17,90±16,93 ve 10,79±11,23) (p=0,004). Her iki tarama aracında da yetersiz beslenen hastaların çoğu aşırı kilolu veya obezdi (toplam aşırı kilolu ve obez hastalar NRS-2002 ve SGD'ya göre sırasıyla; %70 ve %75). Malnütrisyon ile ilişkili bulunan faktörler sadece yaş ve hastanede kalış süresiydi (p<0,05).

Sonuç: NRS-2002, beslenme riski için mevcut kriterler göz önüne alındığında, son derece güçlü bir araç olarak, nesnel bir değerlendirme için iyi bir verim sağlamaktadır. Bunun yanı sıra, SGD uygulanarak değerlendirmeye subjektif parametrelerin eklenmesi, kapsamlı bir beslenme değerlendirmesi için hastanede yatan hastaların beslenme riskini tespit etme kabiliyetini artırabilir.

Anahtar Kelimeler: Malnutrisyon, beslenme durumunun değerlendirilmesi, nutrisyonel risk skoru 2002 (NRS-2002) ve subjektif global değerlendirme (SGD)

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INTRODUCTION

Malnutrition is an important health problem among patients of all healthcare settings around the world. Disease-related malnutrition is more common in malign disease and chronic diseases (cardiovascular disease, respiratory disease, liver disease, and renal disease) and is associated with higher hospital admission rates, increased length of stay in hospital, mortality and morbidity.[1,2]

Hospitalization is also a factor leading to malnutrition due to poor feeding procedures and insufficient intakes of macro and micronutrients. The assessment of the nutritional status of hospitalized patients is important to detect individuals who are under malnourishment risk and malnutrition-related conditions. The American Society for Parenteral and Enteral Nutrition (ASPEN) recommends a nutritional screening for all patients at the beginning of the hospitalization.[3] In guidelines published by ASPEN, it is stated that a nutrition screening should be a component of the initial evaluation of all patients in all care settings (hospital, home) and that the screen should incorporate objective data such as height, weight, weight change, primary diagnosis, and presence of comorbidities.[4] Applying screening tools is accepted as an effective method for nutritional screening. European Society for Parenteral and Enteral Nutrition (ESPEN) recommends Nutritional Risk Screening (NRS) 2002 to consider the nutrition risk of hospitalized patients.[5] The NRS 2002 is a remarkably powerful nutritional screening tool: it is rapid, easy to administer, and does not require highly trained health care professionals. The Subjective Global Assessment (SGA) is a simple and effective tool to assess nutritional status of hospitalized patients by subjective assement that evaluates abnormalities in food intake, gastrointestinal symptoms, functional capacity, diseases related to nutritional requirements and body composition. SGA is a diagnostic tool which determines the presence of a problem in the nutritional status of patients.[6] It was reported that no single parameter was effective to determine malnutrition and the multitude of factors that influence nutritional status in all patients.[7] To overcome the limitations of a single indicator, it has been recommended that more than two indicators of nutrition status be used to detect malnutrition in hospitalized patients. The objective and subjective parameters should be considered together for a comprehensive nutritional assessment.[8] The Academy of Nutrition and Dietetics recommends that added to a nutritional screening by tool, receive patients appropriate nutritional monitoring and evaluation by health care professionals to avoid false negative or positive results on nutritional risk of patients.[6] The capability of detecting nutrition risk may increase by this comprehensive assessment containing subjective parameters.

The present study aimed to access the nutritional status of hospitalized patients screening with two different tools, NRS 2002 and SGA, which are commonly used in clinics. Additionally to compare the results of two screening methods in predicting malnutrition of hospitalized patients and to observe their association with body mass index (BMI) and length of hospital stay (LOS).

MATERIAL AND METHOD

Participants

The study was conducted with 134 adult patients (male/female: 59/75) who were hospitalized in the clinics (hematology, neurology, gastroenterology, nephrology, endocrine, pulmonary disease and cardiology) of Malatya Training and Research Hospital Hospital between January 1 and August 30, 2016.

The sample size was calculated as the minimum of 88 patients based on the primary outcome variable: the detection of a 5% difference between the nutritional status and NRS 2002 and SGA tools and statistical power of 95%.

The exclusion criteria included: patients were (i) < 18 years old, (ii) hospitalized due to surgical operation, (iii) pregnant women, (iv) breastfeeding women, (v) bed-dependent, (vi) suffered an advanced disease that required palliative care.

The study was conducted in accordance with the Declaration of Helsinki Principles. Ethical approval Clinical Research Ethics of Erciyes University, Faculty of Medicine (2016/144). Written informed consent was obtained from the patients.

Study Design

In the cross-sectional study demographic data (age, gender), BMI, cause of hospitalization and hospital LOS were recorded. For the nutritional assessment, all patients were screened with NRS 2002 and SGA within the first days of admission to the patients. And also the edema and the acid were evaluated by the physician. The primary predictors of interest in our study were the NRS 2002 and SGA results of patients.

In the beginning, 168 patients were included to study but 34 patients did not complete the screening process by the reason of missing data and were excluded from the study. Finally, 134 patients completed the nutritional screening (**Figure 1**).

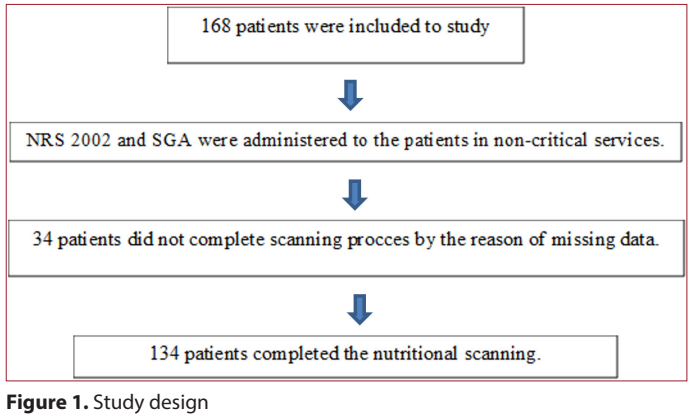

Figure 1. Study design

BMI Classification

BMI as an objective measurement, refers to the weight for height, which is valid for both genders and all age groups. BMI classification according to WHO refers to, <16.5 kg/m^2 severe malnourished, 18.5 kg/m^2 malnourished, 18.5-24.9 kg/m^2 normal weight, 25-29.9 kg/m^2 overweight, ≥30 kg/m^2 obese in adults 9. ESPEN recognises malnutrition as, patient has (i) weight loss >10–15 % of body weight in last 6 months; (ii) BMI <18.5 kg/m^2; (iii) level B and C (mild-to-moderate and severe malnourished) Accordig to SGA or score ≥3 according to NRS 2002; (iv) serum albumin <30 g/L (out of hepatic and renaldysfunction) 10.

Nutritional Status

The nutritional status of all patients was screened both NRS 2002 and SGA within the first days of admission to the patients by a trained dietician.

The patients were classified as being nutritionally risk (NRS+): total score ≥ 3 or nutritionally risk-free (NRS-): total score < 3 according to NRS 2002 results.

The SGA screening normally provides three alternative categories for nutritional classification: well nourished (A); mild-to-moderately malnourished (B); or severely malnourished (C).

To facilitate the analysis of the influence of the nutritional status on the outcomes, to allow comparison with the NRS 2002 and SGA, patients were grouped as being either non-malnourished (A) or malnourished (B or C; included mild-to-moderately malnourished and severely malnourished according to SGA results). In addition, according to the results of two screening tools, patients were grouped as being malnourished [included patients on (NRS+) or SGA (B or C)] and non-malnourished [included patients on (NRS-) or SGA (A)].

Statistics

Continuous variables were expressed as the mean and standard deviation. Statistical differences between groups were assessed using Chi-Square and Fisher exact tests for categorical variables, while the Student's t-test was used for continuous variables.

In order to analyze which variables affected the prevalence of malnutrition, a logistic regression analysis was performed, in which malnutrition according to the NRS 2002 and SGA was considered the dependent variable separately. The level of significance used was 0.05. Statistical analysis was carried out with IBM SPSS Statistics 22.0.

RESULTS

Nutritional Screening NRS 2002 and SGA Scores Frequencies

A total of 134 adult patients (59 men/75 women) were included in to study with a mean age of 64.58±16.08 years. **Table 1** shows the results in terms of both nutritional screening tools. According to SGA, 86 (64.2%) of the patients were classified as well nourished, 48 (35.8%) were classified as malnourished (B or C; 47 of them were mild-to-moderately malnourished and 1 of them was severely malnourished). According to NRS 2002, 104 (77.6%) were nutritional risk-free (or non-malnourished), 30 (22.4%) of the patients were classified as nutritionally risk (or malnourished).

Table 1. The nutritional status of the patients according to NRS 2002 or SGA

Nutritional status	NRS 2002		SGA		p
	n	%	n	%	
Malnourished	30	22.4	48	35.8	
Non-malnourished	104	77.6	86	64.2	0.015*
Total	134	100	134	100	

*p<0.05

The main data related to the nutritional status of patients in terms of both nutritional screening tools are shown in **Table 2**. Malnourished patients according to both nutritional screening tools have similar profiles in terms of gender and BMI to those of non-malnourished patients. There are different results in age profile of patients among tools. Although the mean the age of malnourished patients is similar with non-malnourished patients according to SGA, the mean age of malnourished patients was higher than non-malnourished patients according to NRS 2002 (74.83±12.50 vs 61.63±15.82) and most of them (malnourished patients) are ≥65 years (25 vs 5) (p<0.001).

BMI Classification and Nutritional Status

In both screening tools most of the malnourished patients were overweight or obese (BMI >25 kg/m^2) (the total overweight and obese patient rate 70% and 75% according to NRS 2002 and SGA; respectively) and only 6.7% of the malnourished patients, the BMI levels were below the18.5 kg/m^2 (p>0.05) (**Table 2**). According to SGA assessment weight loss in the last 6 months was higher in men than women (3.97±5.85 kg and 2.16±3.66 kg, respectively; p=0.041) (data not shown in table).

Length of Hospital of Stay and Nutritional Status

The hospital LOS (day) of malnourished patients and non-malnourished patients according to NRS 2002 were similar. However, according to SGA screening the hospital LOS of malnourished patients was longer than non-malnourished patients (17.90±16.93 vs 10.79±11.23; p=0.004) (**Table 3**).

Factors Associated with Malnutrition

A logistic regression analysis was performed, which considered malnutrition as a dependent variable and age, gender, BMI, hospital LOS (day) as independent variables. Only age was associated with malnourishment according to NRS 2002 (OR: 0.92; OR CI: 0.88-0.96; p<0.001) and only hospital LOS was associated with malnourishment according to SGA (OR:1.03; OR CI: 1.00-1.06; p<0.021) (**Table 4**).

Table 2. Main data related to the nutritional status

	NRS 2002			SGA		
	Malnourished (n=30)	**Non-malnourished (n=104)**	**p**	**Malnourished (n=48)**	**Non-malnourished (n=86)**	**p**
Gender (male/female)	15/15	44/60	0.455	25/23	34/52	0.161
Age (years, mean±SD)	74.83±12.50 (44-92)	61.63±15.82 (18-90)	<0.001*	67.31±15.64 (20-92)	63.06±16.20 (18-90)	0.142
Age range (n, %)						
<65	5 (16.6%)	52 (50%)	<0.001*	17(35.4%)	40(46.5%)	0.213
≥65	25 (83.3%)	52 (50%)		31(64.5%)	46(53.4%)	
BMI (kg/m²) (mean±SD, (min-max)	28.03±6.80 (15.49-49.08)	28.04±6.31 (13.67-45.58)	0.992	29.17±5.70 (18.26-49.08)	27.40±6.71 (13.67-45.58)	0.126
BMI classification kg/m²						
(< 18.5)	2 (6.7%)	5 (4.8%)	0.720	1 (2.1%)	6 (7.0%)	0.278
(18.5-24.9)	7 (23.3%)	33 (31.7%		11 (22.9%)	29 (33.7%)	
(25-29.9)	11 (36.7%)	29 (27.9%)		16 (33.3%)	24 (27.9%)	
(≥ 30)	10 (33.3%)	37 (35.6%)		20 (41.7%)	27 (31.4%)	
Cause of hospitalization (n, %)						
Hematologic diseases	3 (10.0%)	11 (10.5%)	0.038	5 (10.4%)	9 (10.4%)	0.671
Neurologic problems	6 (30.0%)	5 (4.8%)		5 (10.4%)	6 (6.9%)	
Pulmonary disease	5 (16.6%)	38 (36.5%)		17 (35.4%)	26 (30.2%)	
Gastrointestinal disease	4 (13.3%)	20 (19.2%)		7 (14.5%)	17 (19.7%)	
Renal disorders	4 (13.3%)	5 (4.8%)		5 (10.4%)	4 (4.6%)	
Metabolic problems	4 (13.3%)	17 (16.3%)		5 (10.4%)	16 (18.6%)	
Cardiovascular diseases	4 (13.3%)	8 (7.6%)		4 (8.3%)	8 (9.3%)	

*p<0.05

Table 3. Length of hospital stay and the nutritional status with NRS 2002 or SGA

Hospital LOS (day)	NRS 2002			SGA		
	Malnourished (n=30)	**Non-malnourished (n=104)**	**p**	**Malnourished (n=48)**	**Non-malnourished (n=86)**	**p**
(mean±SD), (min-max)	17.10±15.20 (2-60)	12.25±13.41 (2-81)	0.093	17.90±16.93 (2 – 81)	10.79±11.23 (2 – 75)	0.004*
0-9 day (n,%)	13 (16.7%)	65 (83.3%)	0.194	21 (26.9%)	57(73.1%)	0.002*
10-19 day	9 (25.7%)	26 (74.3%)		12 (34.3%)	23(65.7%)	
20-29 day	4 (36.4%)	7 (63.6%)		8 (72.7 (%)	3 (27.3%)	
≥30 day	4 (40.0%)	6 (60.0%)		7 (70.0%)	3 (30.0%)	

*p<0.05

Table 4. The factors of associated with malnutrition

Variable	Malnourished NRS 2002			Malnourished SGA		
	Odds Ratio (OR)	**OR CI (%95)**	**p**	**Odds Ratio (OR)**	**OR CI (%95)**	**p**
Age	0.92	0.88-0.96	<0.001*	1.01	0.99-1.04	0.220
Gender (male)	0.92	0.37-2.29	0.871	1.38	0.65-2.93	0.397
BMI	1.01	0.95-1.09	0.592	1.03	0.97-1.09	0.248
Hospital LOS (day)	0.97	0.94-1.00	0.099	1.03	1.00-1.06	0.021*

Logistic regression model. OR CI: Odds ratio confidence interval, *p<0.05

DISCUSSION

Screening the nutritional status of hospitalized patients, in the beginning, provides positive results on patients outcomes and on avoiding comorbidities. Malnutrition is a well-known factor that increases the length of stay in hospital, morbidity and morbidty.[2] Determination of nutritional status helps physicians and clinical nutritionists to decide on the best regimen which should be prescribed for a patient.[11] Although many nutritional screening tools have been developed, there is no screening tool considered to be the best standard for defining nutritional risk. Most methods are cumbersome and time-consuming and therefore not performed on a routine basis. NRS 2002 is the most commonly used screening method in hospitalized patients and ESPEN recommends the NRS 2002 for nutritional assessment. Patients are evaluated and scored for malnutrition and disease severity in NRS 2002 to take into consideration the patient's nutrition risk at the time of assessment and used to identify hospitalized patients who may benefit from nutrition support. It is relatively easy to calculate and does not require a significant amount of time or data points.[12] SGA is also a simple and effective screening tool which has been developed to evaluate the physiological symptoms observed in functional capacity and malnutrition or the conditions involved in malnutrition. Different from NRS 2002, subjective parameters are used in the assessment. Screening tools contain different objective and subjective parameters and this may lead to determine malnutrition rates at different levels. Therefore, there are many studies comparing these screening tests in the literature and they also found different malnutrition rates among tools. In a cohort study, 7973 adult patients from 47 hospitals scanned

to determining nutritional status and the rate of malnourished patients was found 36.9% by NRS 2002 and 44.9% by SGA.[13] Fernández et al.[14] found malnutrition rate 35.8% according to NRS 2002 and 62.1% according to SGA in hospitalized patients. Konturek et al.[15] scanned 815 hospitalized patients and found a malnutriton rate of 44.6 % according to NRS 2002 and 44.6 % according to SGA. In a study conducted by Olivares et al.[16] 21.3% of the hospitalized patients were malnourished according to NRS 2002; and 19.5% of the patients were malnourished according to SGA. Raslan et al.[17] conducted a study with the aim of evaluating the ability of NRS 2002 and SGA to predict malnutrition related to poor clinical outcomes. They found that of the patients screened, 27.9% were at nutritional risk (NRS+) and 38.9% were malnourished (SGA B or C). In the current study, we found that malnutrition rates were 22.4% according to NRS 2002 and 35.8% according to SGA. Consistent with most of the other study results, in our study; the rate of malnourished patients among NRS 2002 was lower than among SGA. This result may be related to subjective parameters included in SGA. Because objective and subjective parameters alone have some limitations on determining nutritional status, it is recommended that objective and subjective parameters should be used together for a comprehensive nutritional assessment.[7] Among objective parameters, anthropometric measurements, are effective in the diagnosis of malnutrition. BMI is one of the most commonly used anthropometric measurements in the clinic but it is not sufficient alone to determine malnutrition. Malnutrition is also detected at a normal weight or even in overweight patients. There are also studies reporting that the BMI of malnourished patients is higher than the BMI of non-malnourished patients. In a study conducted by Borek et al.[18] 292 patients with renal disorders in Poland, were screened by using NRS 2002 and SGD methods, they found that 38% of the patients determined on nutritional risk were weighted or obese and only 8.4% of the patients with BMI below 18.5 kg/m^2 at risk of malnutrition. In the University Hospital of Haukeland Norway, 3279 patients were screened by using NRS 2002, 12% of overweight patients and 11% of obese patients were found on nutritional risk.[19] In the current study, we found that among NRS 2002 screening, malnourished patients 36.7% of them were overweight and 33.3% were obese. These rates for SGA screening, were 33.3% and 41.7% for overweight and for obese, respectively. All these results show that weigh status and BMI of the patients, as a single parameter, did not alone reflect completely the nutritional status and malnutrition risk of hospitalzed patients.

Age, prolonged hospital stay and increased complications are among the independent risk factors of malnutrition. The prevelence of malnutrition is 5 times higher in patients over 80 years of age than in patients under 50 years of age.[20] Raslan et al.[21] screened hospitalized patients with NRS 2002 and detected malnutrition prevelance 42% in elderly patients (>65y old), and 27.9% in all patients. In a study, malnutrition was found 53% of patients over the age of 64 according to SGA screening and 46% according to NRS 2002 screening.[22] In our study, according to NRS 2002 results, the rate of malnourished patients was found 8.8% of the patients aged <65 years and 32.5% of the patients aged ≥65 years (<0.001). In SGA results, the rate of malnourished patients was found 29.8% of the patients aged <65 years and 40.3% of the patients aged ≥65 years (p>0.05).

Length of hospital stay is an important independent factor affecting malnutrition. A prolonged length of hospital stay is related to deterioration of the nutritional status of patients and increased malnutrition rates. Previous studies have shown the impact of nutritional status on LOS.[15,23,24] In a study conducted in Spain with the aim of assessing the nutritional risk of hospitalized patients using SGA, found a significantly relationship between nutritional risk and length of hospital stay. Correia et al.[23] demonstrate that malnourished patients had significantly longer length of hospital stay than well nourished patients (16.77±24.5 days and 10.17±11.7 days, respectively). In a study conducted by Velasco et al.[25] according to the NRS 2002 screening, the mean length of hospital stay was 8.9±7.9 days in patients without risk of malnutrition and 13.7±9.5 days in patients with risk of malnutrition and according to SGA screening, it was found to be 8.8±7.7 days in non-malnourished patients and 13.7±9.7 days in malnourished patients. Olveira et al.[24] conducted a multicenter prospective study, they scanned patients by SGA and found that the mean duration of hospital stay was 30.9±28.3 days for malnourished patients and 37.3±27.2 days for malnourished patients. In a study conducted by Konturekt et al.[15] it was found that the length of hospital stay was significantly shorter in the well-fed patients (4.0±4.2 days) compared to the malnourished patients (7.8±7.7 days) according to the NRS 2002 screening. We found that the hospital LOS (day) of malnourished patients and non-malnourished patients according to NRS 2002 screening were similar. But according to SGA screening the hospital LOS of malnourished patients was longer than non-malnourished patients (17.90±16.93 vs 10.79±11.23) (p=0.004). And in patients with the hospital, LOS is more than 30 days, 40% of them were malnourished according to NRS 2002 results and 70% of them were malnourished according to SGA results. In our present study, hospital LOS was associated with malnourishment according to SGA. This result gives a supportive finding that prolonged length of hospital stay increases malnutrition risk in hospitalized patients.

Study Limitations

The main limitation of this study was the group of patients was heterogeneous and have a different cause of hospitalization. There are so many previous studies accessing the nutritional status of patients in intensive care units. However, we studied with patients among the different causes of hospitalization with the aim of assessing patients' nutrition status in all hospitalized patients in different clinics. Another limitation could be related to the impact of malnutrition on the outcomes. The results for readmission rates and mortality could not be followed up which were evaluated in some other studies related to nutritional screening.

CONCLUSION

Our study showed that SGA identified higher rates of malnourished patients than NRS 2002. Screening tools have different characteristics and capabilities in detecting malnutrition. The NRS 2002, as an objective, remarkably powerful and modern instrument that was developed for hospital settings and is recommended by the European Society of Parenteral and Enteral Nutrition, seems to provide a better yield for an objective assessment. Besides this, adding subjective parameters to the assessment could increase the capability of detecting nutrition risk of hospitalized patients. Applying objective and subjective parameters together in nutritional evaluation provides positive results for a comprehensive nutritional assessment. Althought these different results of the screeing tools, nutrional risk or malnutrition should be detect as early as possible in all hospitalized patients to avoid possible outcomes of malnutrition.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permissionof Clinical Research Ethics Committee of Erciyes University, Faculty of Medicine (2016/144).

Informed Consent: Written informed consent was obtained from the patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Orjinal Araştırma / Original Article

Has the Approach of Healthcare Workers to Influenza Vaccine Changed due to the Pandemic? What are their Perspectives on COVID-19 Vaccine?

Pandemi Nedeniyle Sağlık Çalışanlarının İnfluenza Aşısına Yaklaşımı Değişti mi? Covid-19 Aşısına Bakış Açıları Nelerdir?

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Abstract

Objectives: Increasing influenza vaccine intake in healthcare workers during the pandemic period will benefit the management of respiratory tract infections. This study aimed to investigate the effects of COVID-19 pandemic on influenza vaccination and COVID-19 vaccine.

Material and Method: Healthcare workers were questioned over a survey about their status of having received the previous influenza vaccine and the influenza vaccine and COVID-19 vaccine this year. Their relationship with occupation, working in risky conditions and demographic characteristics of the individuals was investigated.

Results: 768 healthcare workers participated in our study. While the rate of those who received the influenza vaccine in 2019 was 19.1% (n=147) this rate was 27.5% (n=211) in 2020 (p<0.001). While 101 of the 221 people who were vaccinated in 2020 were vaccinated in 2019, 110 people agreed to be vaccinated in 2020 even though they were not vaccinated in 2019. Those who received the influenza vaccine in 2019 accepted to receive the vaccine in 2020 as well (p<0.001) and it was observed that those who did not receive the vaccine in 2019 did not receive it in 2020, either (p<0.001). The rate of physicians who accepted both vaccines was higher than the rate of the other groups. When those who accepted to receive the COVID-19 vaccine were analyzed it was observed that the rate of those who accepted to receive the influenza vaccine in 2019 and 2020 was significantly higher than the rate of those who did not (p<0.001).

Conclusion: It has been understood with the COVID-19 pandemic, how important the vaccine is, and this awareness has also increased the vaccination rates of influenza in healthcare workers. In this period, we should encourage health workers for higher vaccination rates. One of the most important factors for vaccination is that get individuals to accept vaccination once.

Keywords: Influenza vaccine, COVID-19 pandemic, healthcare workers, COVID-19 vaccine

Öz

Amaç: Pandemi döneminde sağlık çalışanlarında influenza aşısı alımının arttırılması solunum yolu enfeksiyonlarının yönetimine fayda sağlayacaktır. Bu çalışma, COVID-19 pandemisinin influenza aşısı ve COVID-19 aşısı üzerindeki etkilerini araştırmayı amaçlamıştır.

Gereç ve Yöntem: Sağlık çalışanlarına, önceki yılki influenza aşısı ve bu yıl influenza aşısı ve COVID-19 aşısı yaptırma durumları hakkında bir anket hazırlandı. Bireylerin demografik özellikleri, meslek ve riskli birimlerde çalışma durumları ile ilişkileri araştırıldı.

Bulgular: Çalışmamıza 768 sağlık çalışanı katıldı. 2019 yılında influenza aşısı olanların oranı %19,1 (n=147) iken 2020 yılında bu oran %27,5 (n=211) idi (p<0,001). 2020'de aşılanan 221 kişiden 101'i 2019'da aşılanırken, 110 kişi 2019'da aşı olmamasına rağmen 2020'de aşı olmayı kabul etti. 2019'da influenza aşısı olanların tamamı 2020'de de aşı olmayı kabul etti. (p<0,001) 2019 yılında aşı yaptırmayanların 2020 yılında da yaptırmadığı görüldü (p<0,001). Her iki aşıyı da kabul eden hekim oranı diğer gruplara göre daha yüksekti. COVID-19 aşısını yaptırmayı kabul edenler incelendiğinde 2019 ve 2020 yıllarında influenza aşısı olmayı kabul edenlerin oranının yaptırmayanlara göre anlamlı derecede yüksek olduğu görüldü (p<0,001).

Sonuç: COVID-19 pandemisi ile aşının ne kadar önemli olduğu anlaşılmış ve bu farkındalık sağlık çalışanlarında influenza aşılama oranlarını da artırmıştır. Bu dönemde sağlık çalışanlarını daha yüksek aşı oranları için teşvik etmeliyiz. Aşılamanın en önemli faktörlerinden biri de aşıyı bir kez kabul ettirmektir.

Anahtar Kelimeler: İnfluenza aşısı, COVID-19 pandemisi, sağlık çalışanları, COVID-19 aşısı

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INTRODUCTION

Influenza is an acute viral infection with high infectivity and mostly seen from the late fall to early spring.[1] Although the influenza vaccine is recommended to the healthcare workers by the Centers for Disease Control and Prevention (CDC) every year the rates of vaccination are observed to be low.[2] Healthcare workers are at high risk in terms of influenza and they can be a source of infection especially for immunocompromised patients.[3]

Coronavirus disease 2019 (COVID-19) was defined as a severe viral respiratory tract agent in the late 2019.[4] COVID-19 disease was declared a global pandemic by the World Health Organization (WHO) in March, 2020.[5] COVID-19 and influenza are viral infection agents that are transmitted through similar routes and that can show similar clinical symptoms such as fever, coughing and shortness of breath. Studies have revealed that coexistence of these two infections can cause severe clinical course and complications and fatal results.[6,7]

Both the healthcare workers and patients are protected with the influenza vaccine received by healthcare workers. Influenza-like diseases seen in patients and the length of stays in the intensive care unit and hospital decrease as well.[2] It is not possible to decrease influenza due to low vaccination rates each year; however, the deficiency in vaccination will be more apparent this year due to the pandemic.[2] Influenza and COVID-19 are together in circulation especially in winter months and have similar symptoms, which will cause difficulties in diagnosing.[1] High vaccination rates not only decrease the influenza-associated mortality but also are of great importance in decreasing the load that can occur in the healthcare system due to COVID-19. When the safety of healthcare workers and patient health are considered reaching higher vaccination rates must be the national priority in the coexistence of COVID-19 and influenza.[2]

This study aimed to investigate the changes in attitudes and behaviors of the healthcare workers toward influenza vaccine due to pandemic and their attitude toward COVID-19 vaccine.

MATERIAL AND METHOD

Our study is a descriptive survey study and was performed on the healthcare workers between the 22nd and 28th of February 2021. After obtaining informed consent from participants, the questionnaire including 12 questions was sent to the healthcare workers over a survey. The participants were asked to anonymously complete the questionnaire. In the questionnaire, the healthcare workers were questioned about their demographic characteristics (age, occupation, gender, educational status, and chronic diseases), whether they worked for a unit with COVID-19 risk, whether they received the influenza vaccine last year or not, whether they received the influenza vaccine this year or not (yes or no), and whether they received the COVID-19 vaccine or not.

The healthcare workers who would like to receive the influenza vaccine received it until the end of December 2020 in our country. After COVID-19 vaccine was emergently approved by the Turkish Pharmaceuticals and Medical Devices Agency the first dose of vaccination was initiated for the healthcare workers in January 2021. When we started our study influenza vaccination of the healthcare workers was completed and the first dose of COVID-19 vaccine was administered. The study was prospectively performed and approved by the ethics committee of Mustafa Kemal University, Tayfur Ata Sokmen Faculty of Medicine (No:03 from february 18, 2021). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Categorical data in the study were expressed as numbers and percentiles. While Chi-Square Test was used in the comparisons between independent groups of the categorical variables Mc Nemar's Test was used in comparisons between the dependent groups. The analyses were performed with IBM SPPSS Package Software Program Version 24.0 (IBM Corporation, Armonk, NY, USA). Statistical significance level was $p<0.05$.

RESULTS

A total of 768 healthcare workers including 516 women (67%), 252 men (33%), 472 physicians (61%), and 214 nurses (27%) participated in the study. Median age of the participants in the study was 36.5 years.

When the status of having received the COVID-19 vaccine in 2020 was compared with the other factors stated in the table it was found that there was a statistically significant relationship in terms of occupation (While 23.4 % of those who receive COVID-19 vaccine were nurses, 66.1% of those who received the COVID-19 vaccine were physicians.), rates of having received the influenza vaccine in 2019 (While 8.1% of those who did not receive the COVID-19 vaccine received the influenza vaccine in 2019 21.8% of those who received the COVID-19 vaccine received the influenza vaccine in 2019.) and rates of having received the influenza vaccine in 2020 (While 7.4% of those who did not receive the COVID-19 vaccine received the influenza vaccine in 2020 32.3% of those who received the COVID-19 vaccine received the influenza vaccine in 2020.) ($p<0.001$) (**Table 1**). In addition, 132 (88.6%) out of 149 individuals who did not accept to receive the COVID-19 vaccine did not receive the vaccine although they worked in a unit at risk for COVID-19.

While the rate of those who received the influenza vaccine in 2019 was 19.1% (n=147) this rate was 27.5% (n=211) in 2020 ($p<0.001$). While 101 (68.7%) out of 147 individuals who received the influenza vaccine in 2019 received the vaccine in 2020 46 (31.3%) did not receive the vaccine. On the other hand, while 110 (17.7%) out of 621 individuals who did not receive the influenza vaccine in 2019 received the vaccine in 2020 511 (82.3%) did not receive the vaccine (**Table 2**).

Table 1. Comparison of the state of having received the COVİD-19 vaccine in 2020 with age, gender, occupation, chronic disease, suspected disease contact, institution they worked for (private/public) and the state of having received the influenza vaccine in 2019 and 2020

	COVİD-19 vaccine		p
	Those who didn't receive the vaccine (n;%)	Those who received the vaccine (n;%)	
Age (year)			0.207*
20-29 years	40 (27.0)	179 (28.9)	
30-39 years	67 (45.3)	236 (38.1)	
40-49 years	36 (24.3)	159 (25.7)	
50 years and above	5 (3.4)	45 (7.3)	
Gender			
Female	108 (72.5)	408 (65.9)	0.125*
Male	41 (27.5)	211 (34.1)	
Occupation			**<0.001***
Physician	63 (42.3)	409 (66.1)	
Nurse	69 (46.3)	145 (23.4)	
Other healthcare workers	9 (11.0)	65 (10.5)	
Chronic Disease			0.452*
No	120 (80.5)	481 (77.7)	
Yes	29 (19.5)	138 (22.3)	
Suspected COVİD contact			0.452*
No	17 (11.4)	58 (9.4)	
Yes	132 (88.6)	561 (90.6)	
2019 (influenza)vaccine			**<0.001***
No	137 (91.9)	484 (78.2)	
Yes	**12 (8.1)**	**135 (21.8)**	
2020 (influenza)vaccine			**<0.001***
No	138 (92.6)	419 (67.7)	
Yes	**11 (7.4)**	**200 (32.3)**	
Total	149 (19.1)	619 (80.6)	

* Chi-square Test

Table 2. Comparison of those who received and who did not receive the influenza vaccine in 2019 and 2020

			2019 (influenza)		Total	p
			No	Yes		
2020 (influenza)	No	N	511	46		<0.001*
		Row %	91.7%	8.3%	100.0%	
		Column %	82.3%	**31.3%**	72.5%	
	Yes	N	110	101	211	
		Row %	52.1**%**	47.9%	100.0%	
		Column %	17.7%	**68.7%**	27.5%	
Total		N	621	147	768	
		Row %	80.9%	**19.1%**	100.0%	
		Column %	100.0%	100.0%	100.0%	

* McNemar's Test

An increase in the rates of having received the influenza vaccine was observed in 2020 compared to 2019, however, this increase was statistically significant only in the group including the ages of 30-39 and 40-49, male individuals, physicians, and those without a chronic disease (p<0.05). On the contrary, it was not significant in the ages of 20-29 and ≥50, female individuals, nurses and the other healthcare workers, and those with a chronic disease (p>0.05) (**Table 3**).

The most common reason of the participants who received the influenza vaccine in 2020 was the pandemic at a rate of 34% (shown in **Figure 1**).

Table 3. Comparison of those who received the influenza vaccine in 2019 and 2020 in terms of age, gender, occupation, presence of a chronic disease, and the institution they worked for (private/public)

	N	Influenza vaccine		P
		2019 (n;%)	2020 (n;%)	
Age (year)				
20-29 years	219	40 (18.3)	48 (21.9)	0.332*
30-39 years	303	55 (18.2)	87 (28.7)	<0.001*
40-49 years	195	34 (17.4)	55 (28.2)	<0.001*
50 years and above	50	18 (36.0)	21 (42.0)	0.508*
Gender				
Female	516	92 (17.8)	138 (26.7)	0.253*
Male	252	55 (21.8)	73 (29.0)	0.027*
Occupation				
Physician	472	119 (25.2)	165 (35.0)	<0.001*
Nurse	214	19 (8.9)	29 (13.6)	0.064*
Other healthcare workers	82	9 (11.0)	17 (20.7)	0.077*
Chronic Disease				
Yes	601	103 (17.1)	162 (27.0)	<0.001*
No	167	44 (26.3)	49 (29.3)	0.500*
Total	768	147 (19.1)	211 (27.5)	<0.001*

* McNemar's Test

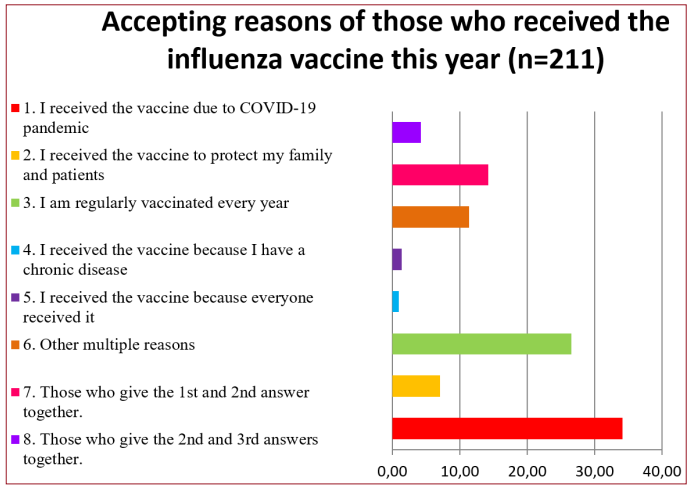

Figure 1. Accepting reasons of those who received the influenza vaccine this year

DISCUSSION

While most of COVID-19 patients have influenza-like symptoms such as fever, coughing and fatigue about 5% of these patients show rapid progression and are hospitalized in the intensive care unit due to acute respiratory distress syndrome (ARDS), septic shock and multiple organ failure.[7] If the condition that influenza and COVID-19 with similar clinical features are together in circulation especially in winter months is considered it is very important to determine strategies not to experience difficulties in diagnosing or to be able manage the treatments that will be used in the coexistence of these two viruses. According to a study by Simin Ma et al. in China, 44 (about 50%) out of 95 COVID-19 patients were infected with influenza and most of them were caused by influenza A. It was

considered that the coexistence of these two viruses causing the same clinical symptoms caused false negative COVID-19 test results and that these results would cause difficulties and delays in diagnosis and increase in the spread of COVID-19. In the same study, it was considered that cytokine storm and organ damage would occur earlier in case of the coexistence with influenza in patients infected with COVID-19.[7] According to some studies, the influenza vaccine may have mechanisms that could affect the pathogenicity of COVID-19.[8,9] Although influenza vaccination has importance every year its importance during the pandemic becomes more obvious due to all these reasons.

In studies, the rate of seasonal influenza vaccination in healthcare workers ranges from 9% to 92%.[10] In a study we assessed the influenza vaccination of 12,475 healthcare workers in our country, while only 6.7% of the healthcare workers were regularly vaccinated 18.8% stated that they were sometimes vaccinated[11] In the study by Kul et al. in our country, 371 individuals were questioned about whether they received the influenza vaccine or not and it was found that 134 (36.1%) of the participants were vaccinated at least once in their lifetime.[12] Of the healthcare workers, 20% have an influenza-like disease in the influenza season[13] and more than 41% keep working although they are infected.[14] As a result of this, healthcare-associated influenza epidemics occur. In a study in China, influenza vaccination rates increased during 2009-2020 H1N1 pandemic, but decreased to the rates of 2008-2009 season in 2010-2011 season. However, in a study in Hong Kong, although the WHO declared a second degree alarm vaccination rates did not change.[15] Therefore, how the COVID-19 pandemic will affect the influenza vaccination in healthcare workers is not completely certain. In our study, while the rate of those who received the influenza vaccine in 2019 was 19.1% (n=147) this rate was 27.5% (n=211) in 2020 among healthcare workers ($p<0.001$). In the study assessing the attitudes of nurses toward influenza vaccine during the pandemic in Hong Kong, Wang et al. found that the vaccination rates were similar in 2019 and 2020, but the nurses who did not receive the vaccine in 2019 changed their minds about receiving the vaccine more or being undecided in 2020 and this change was statistically significant ($p<0.001$).[16] In our study, the most common reason to receive the vaccine was COVID-19 pandemic (34%). The main reason of that is probably the increasing awareness on respiratory tract viruses due to the pandemic.

Vaccine hesitancy was declared one of the first ten threats on global health by the World Health Organization in 2019.[17] The reasons of vaccine hesitancy are complicated, but the most common reason of vaccine hesitancy in the healthcare workers is seen to be having insufficient and lacking information about safety of the vaccine.[18] Overcoming the false information and beliefs about the vaccination and convincing people to receive the vaccine should actually be among the main goals. According to the previous studies, it is known that those who accepted the vaccination once kept receiving the vaccines in the following years.[15,19] In our study, it was observed that those who received the influenza vaccine in 2019 accepted vaccination in 2020 as well ($p<0.001$), but if they did not receive the vaccine in 2019 they did not receive it in 2020, either ($p<0.001$). According to our study, while influenza vaccination revealed an increase in all occupation groups from 2019 to 2020 the most significant difference was observed in physicians. The rate of COVID-19 vaccination was found to be higher among physicians compared with the other healthcare workers like in the other studies ($p<0.001$).[20] The reasons may be that physicians have higher level of education, that diseases that can be prevented by vaccine are known better and that the consequences of influenza are known more due to the pandemic.

While 80.6% (619) of the participants in our study received the COVID-19 vaccine 19.1% (149) did not accept to receive the vaccine. It was observed that those who accepted to receive the influenza vaccine in 2019 and 2020 accepted to receive the COVID-19 vaccine and were statistically significantly different from those who did not accept to receive the influenza vaccine ($p<0.001$). It observed in the study by Wang et al. that those with previous influenza vaccine history were more intended to accept the COVID-19 vaccine (OR: 0.19, 95%CI: 0.11-0.32).[16] Similarly, in two separate studies on the healthcare workers and family physicians in Malta, having received the influenza vaccine before was an important determinant in accepting the COVID-19 vaccine.[20,21] Accepting to receive the vaccine is a way of behavior for the individuals[22] and due to this way of behavior, receiving the vaccine is more expected in these individuals in case of diseases with similar transmission routes or similar clinics. Another important point we noticed in our study was that 132 (88.6%) out of 149 individuals who did not accept to receive the COVID-19 vaccine did not receive the vaccine although they worked in a unit at risk for COVID-19. Similarly, although it was expected for those working at high-risk units to accept to receive the vaccine more compared with those working at low-risk units in the study by Wang et al. no significant difference was found between the groups.[16] It is important to investigate the reasons why those working at high-risk units refuse the vaccination and carry out activities encouraging this group with high risk of transmission for vaccination.

Protection of the healthcare workers during the pandemic was defined as the major component of the phase of preparation for the pandemic.[23] As is known all over the world how many people the vaccine reaches as well as the effectiveness of it are among the main goals in vaccination.[24,25] According to our study, the pandemic has positive effects on receiving the influenza vaccine among healthcare workers. However, it is necessary to determine new strategies to convince and encourage those who still have suspects about the influenza and COVID-19 vaccines.

The strengths of our study are as follows: The questions in the questionnaire were asked to the individuals after influenza and COVID-19 vaccinations started in our country. Not their intents but real data were obtained. The weaknesses of our study can be as follows: The population group was not very large and there was no equal distribution between the occupation groups and age groups.

CONCLUSION

Many diseases and pandemics worldwide have been overcome thanks to the vaccines. Therefore, it is possible that several pandemics that will occur in the future can end with the discovery of vaccines. The COVID-19 pandemic we experience today have revealed how the presence of a vaccine can affect the whole world. It is observed that even anti-vaxxers wait for the COVID-19 vaccine and state their requests to return to normal life in all platforms. It is important to develop especially evidence-based vaccination strategies for the healthcare workers. Future studies are needed to remove the hesitations on receiving the influenza vaccine, investigate the changes in accepting to receive the influenza vaccine due to pandemic and investigate the behavioral patterns in the intent of accepting to receive the COVID-19 vaccine.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was prospectively performed and approved by the ethics committee of Mustafa Kemal University, Tayfur Ata Sokmen Faculty of Medicine (No: 03 from February 18, 2021).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

Anxiety, Depression, Social Anxiety, Anxiety Sensitivity, and Perceived Stress in Psoriasis Patients

Psoriasis Hastalarında Anksiyete, Depresyon, Sosyal Anksiyete, Anksiyete Duyarlılığı ve Algılanan Stres

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Abstract

Objective: Psoriasis is a chronic inflammatory skin disease, and psychiatric comorbidities are common in these patients. Skin lesions can cause shame, anxiety, social avoidance, irritability and depressive symptoms in psoriasis patients. This study aimed to investigate anxiety, depression, social anxiety, anxiety sensitivity and perceived stress in patients with psoriasis and their relationship with disease severity and duration.

Material and Method: Forty patients and 40 healthy controls were included in our study. Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Liebowitz Social Anxiety Scale (LSAS), Perceived Stress Scale (PSS-14), and Anxiety Sensitivity Index (ASI-3) were administered to all participants. In patient group, PASI was applied for disease severity.

Results: Anxiety, depression, social anxiety, perceived stress and anxiety sensitivity were significantly higher in psoriasis patients than in healthy controls. There was no correlation between PASI scores and BAI, BDI, LSAS, PSS-14 and ASI-3 scores. Also, no correlation was found between disease duration and BAI, BDI, LSAS, PSS-14 and ASI-3 scores.

Conclusion: Our results show that anxiety, depression, social anxiety, anxiety sensitivity and perceived stress were high in psoriasis patients regardless of disease duration and severity. This is the first study to examine anxiety sensitivity in psoriasis patients to the best of our knowledge. Clinicians should consider the possible psychiatric comorbidity at all stages of the disease in patients with psoriasis. Collaboration between the disciplines of dermatology and psychiatry is necessary to ensure full recovery and maintain patient well-being.

Keywords: Perceived stress, anxiety, anxiety sensitivity, depression, psoriasis, social anxiety

Öz

Amaç: Psoriazis kronik inflamatuar bir deri hastalığıdır ve bu hastalarda psikiyatrik komorbiditeler sıktır. Deri lezyonları psoriasis hastalarında utanç, kaygı, sosyal kaçınma, sinirlilik ve depresif belirtilere neden olabilir. Bu çalışmada psoriazis hastalarında anksiyete, depresyon, sosyal anksiyete, anksiyete duyarlılığı ve algılanan stresin hastalık şiddeti ve süresi ile ilişkisinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Çalışmamıza 40 hasta ve 40 sağlıklı kontrol dahil edildi. Tüm katılımcılara Beck Anksiyete Envanteri (BAE), Beck Depresyon Envanteri (BDE), Liebowitz Sosyal Anksiyete Ölçeği (LSAÖ), Algılanan Stres Ölçeği (ASÖ-14) ve Anksiyete Duyarlılık İndeksi (ADI-3) uygulandı. Hasta grubuna hastalık şiddeti için PASI uygulandı.

Bulgular: Psoriazis hastalarında anksiyete, depresyon, sosyal anksiyete, algılanan stres ve anksiyete duyarlılığı sağlıklı kontrollere göre anlamlı derecede yüksekti. PASI puanları ile BAÖ, BDÖ, LSAÖ, ASÖ-14 ve ADI-3 puanları arasında korelasyon yoktu. Ayrıca hastalık süresi ile BAÖ, BDÖ, LSAÖ, ASÖ-14 ve ADI-3 puanları arasında ilişki bulunmadı.

Sonuç: Sonuçlarımız, hastalık süresi ve şiddetinden bağımsız olarak, psoriazis hastalarında anksiyete, depresyon, sosyal anksiyete, anksiyete duyarlılığı ve algılanan stresin yüksek olduğunu göstermektedir. Bildiğimiz kadarıyla, bu çalışma, psoriasis hastalarında anksiyete duyarlılığını inceleyen ilk çalışmadır. Klinisyenler, psoriazis hastalarında hastalığın tüm evrelerinde olası psikiyatrik komorbiditeyi göz önünde bulundurmalıdır. Dermatoloji ve psikiyatri disiplinleri arasındaki işbirliği, tam iyileşmeyi sağlamak ve hastanın iyiliğini sürdürmek için gereklidir.

Anahtar Kelimeler: Algılanan stres, anksiyete, anksiyete duyarlılığı, depresyon, psoriasis, sosyal anksiyete

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INTRODUCTION

Psoriasis is a chronic inflammatory skin disease characterized by erythematous, scaly plaques that present with remissions and relapses.[1] Genetic, environmental and immunologic factors are thought to play a role in pathogenesis.[1,2] However, psychosocial factors and stress also play a crucial role in developing and exacerbating the disease.[1-3] Stress has also been defined as an important factor in the onset, development and recurrence of psoriasis.[3,4] The skin is the most important cosmetic organ; moreover, lesions on the skin can cause stigma and significantly affect the patient's daily functioning and psychological well-being.[5] Apart from the difficulty of coping with a chronic disease, patients may encounter problems with interpersonal relationships, such as the negative impact of psoriatic lesions on their external appearance, worry about being accepted by others, other people's fear of the lesions, disgust, the thought that they may be contagious and negative comments about the disease.[6-8] These problems in daily life lead to the development of guilt, shame, hopelessness, internalized stigma and low self-esteem in psoriasis patients and increase the chronic stress caused by the disease. Psychiatric comorbidity, particularly depression and anxiety disorders are common in psoriasis patients.[1,3,4] In addition, social anxiety and social avoidance are commonly observed, especially in patients with lesions located on daily exposure areas; face,arms etc.[6,7] Psychiatric symptoms that develop in psoriasis patients are significant because they influence the course and severity of the disease as well as the quality of life of patients.[9,10] Perceived stress refers to individuals' feelings or thoughts about how stressed they are at a particular time or period.[11] Stress has been defined as an independent risk factor for both psychiatric disorders and psoriasis.[12] It plays a role in both the onset and exacerbation of psoriasis.[13] Depression and anxiety symptoms are quite common in psoriasis and can occur independently, along with the disease, or secondary to the disease.[14-16] In one study; anxiety and depression were found in 39.7% and 27.1% psoriasis patients, respectively.[17] Social anxiety disorder is characterized by an extreme fear of being negatively evaluated and disapproved of in social settings or situations requiring performance; patients with this disorder experience intense anxiety and exhibit avoidance behaviors in social settings that they perceive as dangerous.[18] Several studies have shown that 33-46% of dermatology outpatients experience significant social anxiety symptoms.[19-21] Since psoriasis is a disease that affects external appearance, it is closely associated with social anxiety.[1,22] In another study, social anxiety and avoidance behaviors were associated with lower quality of life in psoriasis patients.[23]

Anxiety sensitivity is a transdiagnostic factor that influences mental health and refers to the tendency to be overly anxious about anxiety's bodily sensations and symptoms. People with high anxiety sensitivity fear that the somatic symptoms associated with anxiety will have negative consequences, immediately go into a state of alarm and tend to catastrophically misinterpret bodily sensations associated with benign arousal.[24,25] High anxiety sensitivity may be associated with more severe anxiety symptoms, particularly social anxiety in dermatological diseases. A previous study reported higher anxiety sensitivity in patients with a psychodermatological disease than in patients without the disease.[26]

The first aim of this study is to compare the severity of anxiety, depression, anxiety sensitivity, perceived stress, and social anxiety in psoriasis patients with healthy controls. The second aim is to investigate the association between anxiety, depression, anxiety sensitivity, perceived stress and social anxiety levels and the severity and duration of the disease in psoriasis patients.

MATHERIAL AND METHOD

Study Design and Participants

40 patients diagnosed with chronic plaque psoriasis who presented to the Dermatology outpatient clinic of Abant İzzet Baysal University Medical Faculty between January 2016 and May 2016, and 40 healthy volunteers who matched the patient group in age and sex were included in this study. Informed consent was obtained from all participants. Study permission was obtained by the Ethics Committee of Abant İzzet Baysal University Faculty of Medicine (2016/8). Individuals with hypertension, diabetes mellitus, coronary artery disease, heart failure, hepatic and renal dysfunction, malignant diseases, cerebrovascular diseases, endocrine diseases, autoimmune diseases and systemic inflammation, dementia, mental retardation, autism, substance use or addiction other than smoking, head trauma, neurological diseases causing organic brain disorders such as epilepsy and individuals who received psychiatric treatment within the last month were excluded. In addition, subjects with psoriasis types other than plaque psoriasis, a diagnosis of psoriatic arthritis, other dermatologic diseases, individuals who had received systemic treatment for psoriasis in the past three months and subjects who currently received phototherapy were not included in the patient group.

Dermatological examinations were performed on all patients, and disease severity was assessed with the Psoriasis Area Severity Index (PASI). Subsequently, all participants received a socio-demographic form from a psychiatrist that measured anxiety severity with the Beck Anxiety Inventory (BAI), depression severity with the Beck Depression Inventory (BDI), anxiety sensitivity with the Anxiety Sensitivity Index (ASI-3), perceived stress level with the Perceived Stress Scale (PSS 14), and social anxiety severity with the Liebowitz Social Phobia Scale (LSPS).

Assessment Instruments

Socio-demographic Form: This form contains information about participants' age, sex, education level, smoking, and alcohol consumption.

Beck Anxiety Inventory (BAI): It consists of 21 questions that assess the severity of anxiety and is scored between 0-3. The total scale score ranges from 0-63, with high scores indicating high anxiety severity.[27] The Turkish validity and reliability study was conducted by Ulusoy et al.[28]

Beck Depression Inventory (BDI): The scale that assesses the severity of depression consists of 21 questions, with each question scored between 0 and 3. The total scale scores range from 0 to 63, with higher scores indicating more severe depression symptoms.[29] The Turkish validity and reliability study of the scale was conducted by Hisli et al.[30]

Liebowitz Social Anxiety Scale (LSAS): It is a 24-item scale consisting of two subscales measuring anxiety and avoidance in different social situations, where each item can be scored between 1 and 4. Higher scores indicate more severe social anxiety and social avoidance.[31] The Turkish validity and reliability study of the Liebowitz Social Anxiety Scale was conducted by Soykan et al. in 2003.[32]

Anxiety Sensitivity Index-3 (ADI-3): The ADI-3 measures anxiety sensitivity or fear of anxiety-related emotions. The scale consists of 18 items. It tests three dimensions: social, cognitive, and physical. The total score that can be obtained from the scale ranges from 0 to 72.[33] Mantar et al. demonstrated the validity and reliability of the Turkish version of the ADI-3. The internal consistency coefficient of the scale was found to be 0.93.[34]

Perceived Stress Scale-14 (PSS-14): Perceived stress scale was developed to assess a person's perceived stress. The total score of the scale ranges from 0 to 56.[35] The Turkish validity and reliability study was conducted by Eskin et al. The internal consistency coefficient of the scale was found to be 0.84.[36]

Statistical analysis

Normality of the distribution of continuous variables was tested using the Shaphiro Wilk test. Mann-Whitney U test was used to compare two independent groups for abnormal data. Chi-square test was applied to examine the relationship between 2 categorical variables, and Spearman rank correlation analysis was performed to evaluate the correlations between numerical variables. Statistical analysis was performed using SPSS for Windows version 24.0, and a p-value of <0.05 was considered statistically significant.

RESULTS

40 psoriasis patients (patient group) and 40 age- and sex-matched controls (control group) enrolled in this study. The patient (psoriasis) group consisted of 22 males and 18 females, and the control group consisted of 19 males and 22 females. The mean age of the patient group was 35.85±10.79 years and that of the control group was 33±6.67 years. There was no statistically significant difference between the two groups in terms of age, sex, education level, smoking and alcohol consumption (p>0.05). However, there was a statistically significant difference between the two groups in terms of marital status (p<0.01) (**Table 1**).

Table 1. Comparison of patient and control groups in terms of categorical variables

Variables (n(%))	Psoriasis (n=40)	Control (n=40)	P
Age	35.85±10.79	33±6.67	0.159**
Sex			0.502
Female	18 (45)	21 (52.5)	
Male	22 (55)	19 (47.5)	
Marital status			0.001*
Married	31 (77.5)	16 (40)	
Single	9 (22.5)	24 (60)	
Education level			0.077
Primary education	20 (50)	11 (27.5)	
High school	11 (27.5)	12 (30)	
University	9 (22.5)	17 (42.5)	
Smoking			0.228
Yes	15 (37.5)	10 (25)	
No	25 (62.5)	30 (75)	
Alcohol consumption			0.077
Yes	3 (7.5)	0 (0)	
No	37 (92.5)	40 (100)	

*Significant at 0.05 level; Chi-square test. ** Mann-Whitney U test.

Table 2. Medication use and psychiatric disease and psychiatric treatment history in psoriasis patients

		n (%)
Methotrexate	Yes	9 (22.5)
	No	31 (77.5)
Cyclosporine	Yes	1 (2.5)
	No	39 (97.5)
Acitretin	Yes	4 (10)
	No	36 (90)
Topical treatment	Yes	38 (95)
	No	2 (5)
Psychiatric disease history	Yes	10 (25)
	No	30 (75)
Psychiatric treatment history	Yes	9 (22.5)
	No	31 (77.5)
Family history of psychiatric disease	Yes	3 (7.5)
	No	37 (92.5)

Topical treatment was used in 38 (95%) of psoriasis patients, methotrexate in 9 (22.5%), cyclosporine in 1 (2.5%) and acitretin in 4 (10%). Of the psoriasis patients, 10 (25%) had a psychiatric disease history, 9 (22.5%) had a psychiatric treatment history. The mean PASI score of the patients was 8.84±6.44, the mean total disease duration was 12±9.25, and the mean age at disease onset was 23.85±12.74 years (**Table 3**).

Table 3. Mean age at disease onset, disease duration, and PASI scores in psoriasis patients

Variables	Descriptive statistics (n=40)	
	Mean±SD	Median (Min-Max)
Age at disease onset	23.85±12.74	21 (4-52)
Disease duration	12±9.25	11.5 (0.5-37)
Psoriasis Area Severity Index	8.84±6.44	7.25 (2-27.6)

The comparison of scale scores of psoriasis and control group is shown in **Table 4**. Accordingly, Beck Depression Inventory and Beck Anxiety Inventory scores were statistically significantly higher in psoriasis patients than in healthy controls (p=0.001, respectively). Similarly, Anxiety Sensitivity Index and Perceived Stress Scale scores were statistically significantly higher in psoriasis patients than in the control group (p=0.001, p=0.003). In addition, social anxiety, social avoidance and total scores on Liebowitz Social Anxiety Scale were statistically significantly higher in the psoriasis group than in the healthy controls (p=0.006, p=0.020, p=0.005, respectively).

Table 4. Comparison of patient and control groups in terms of anxiety, depression, anxiety sensitivity, social anxiety, and perceived stress

	Psoriasis (n=40)	Control (n=40)	P
Beck Depression Inventory	11.43±8.57	1.68±1.97	0.001*
Beck Anxiety Inventory	7.6±8.32	2.2±2.21	0.001*
Perceived Stress Scale	21.35±10.71	14.4±7.61	0.003*
Liebowitz Social Anxiety Scale Anxiety	41.63±13.64	33.6±8.39	0.006*
Liebowitz Social Anxiety Scale Avoidance	40.38±14.13	33.18±7.38	0.020*
Liebowitz Social Anxiety Scale Total	82±26.55	66.78±15.44	0.005*
Anxiety Sensitivity Index	33.08±12.33	17.15±8.1	0.001*

*Significant at 0.05 level; Mann-Whitney U test.

When variables were compared by sex in psoriasis patients, PASI scores were statistically significantly higher in males (p=0.009). However, there was no difference between males and females in age at disease onset, mean disease duration, and scale scores (p>0.05, respectively) (**Table 5**).

No statistically significant correlation was noted between PASI scores, disease duration, age at disease onset and Beck anxiety, Beck depression, perceived stress, anxiety sensitivity and Liebowitz social anxiety sores in psoriasis patients (p>0.05) (**Table 6**). However, a strong positive correlation was found between scores on the Perceived Stress Scale and Beck Anxiety and Beck Depression Inventories (r=0.735, p=0.001; r=0.773, p=0.001, respectively). In psoriasis patients, a moderate, statistically significant positive correlation was found between scores on the Perceived Stress Scale and avoidance and total scores on the Liebowitz Social Anxiety Scale (r=0.435, p=0.005; r=0.373, p=0.018, respectively); in contrast, there was no statistically significant correlation between the Perceived Stress Scale scores and Liebowitz Social Anxiety Scale anxiety scores (p>0.05). There was also no statistically significant correlation between the anxiety sensitivity scores and Beck anxiety, Beck depression, perceived stress, anxiety sensitivity and Liebowitz social anxiety scores (p>0.05) (**Table 7**).

Table 5. Comparison of PASI scores, scale scores, and other variables by sex in psoriasis patients

	Female (n=18)	Male (n=22)	P
Disease duration	12.97±9.05	11.2±9.55	0.381
Psoriasis area severity index	6.49±6.23	10.75±6.08	0.009*
Age at disease onset for psoriasis	20.11±11.65	26.91±13.03	0.112
Beck Depression Inventory	12.61±9.6	10.45±7.72	0.619
Beck Anxiety Inventory	9.44±9.19	6.09±7.41	0.286
Perceived Stress Scale	21.83±11.52	20.95±10.26	0.882
Liebowitz Social Anxiety Scale Anxiety	46.17±15.35	37.91±11.08	0.070
Liebowitz Social Anxiety Scale Avoidance	42.89±17.18	38.32±11.03	0.657
Liebowitz Social Anxiety Scale Total	89.06±31.46	76.23±20.76	0.251
Anxiety Sensitivity Index	35.94±10.62	30.73±13.34	0.219

*Significant at 0.05 level; Mann-Whitney U-test

Table 6. Correlation of age at disease onset, disease duration, and PASI scores with Beck Depression Inventory, Beck Anxiety Inventory, Liebowitz Social Anxiety Scale, perceived stress and anxiety sensitivity scores in psoriasis patients

		Age at disease onset for psoriasis	Disease duration	Psoriasis Area Severity Index
Beck Depression Inventory	r	-0.097	0.006	0.073
	P	0.550	0.972	0.655
Beck Anxiety Inventory	r	-0.145	-0.001	0.072
	p	0.372	0.995	0.660
Perceived Stress Scale	r	-0.120	-0.018	0.081
	p	0.462	0.911	0.621
Liebowitz Social Anxiety Scale Anxiety	r	-0.205	0.031	-0.276
	p	0.204	0.851	0.085
Liebowitz Social Anxiety Scale Avoidance	r	0.024	-0.166	-0.264
	p	0.883	0.305	0.100
Liebowitz Social Anxiety Scale Total	r	-0.088	-0.088	-0.250
	p	0.591	0.589	0.120
Anxiety Sensitivity Index	r	-0.072	0.096	-0.079
	p	0.660	0.557	0.626

*Significant at 0.05 level; r: Spearman correlation coefficient.

Table 7. Correlation of anxiety sensitivity and perceived stress scores with Beck Depression Inventory, Beck Anxiety Inventory, Liebowitz Social Anxiety Scale anxiety, avoidance and total scores in psoriasis patients

		Beck Anxiety Inventory	Beck Depression Inventory	Liebowitz Social Anxiety Scale Anxiety	Liebowitz Social Anxiety Scale Avoidance	Liebowitz Social Anxiety Scale Total
Anxiety Sensitivity Index	r	0.053	0.127	-0.185	-0.076	-0.190
	p	0.744	0.435	0.252	0.642	0.240
Perceived Stress Scale	r	0.735**	0.773**	0.281	0.435**	0.373*
	p	0.001	0.001	0.079	0.005	0.018

*Significant at 0.05 level; **Significant at 0.01 level; r: Spearman correlation coefficient.

DISCUSSION

The main findings of our study were, first, that levels of anxiety, depression, anxiety sensitivity, perceived stress, and social anxiety were significantly higher in psoriasis patients than in healthy controls. Second, there was no significant relationship between disease duration and PASI scores measuring disease severity and levels of anxiety, depression, anxiety sensitivity, perceived stress, and social anxiety. Third, although the relationship between anxiety and depression levels and disease severity in psoriasis patients has been frequently studied, there are few studies examining the relationship between social anxiety and perceived stress and disease severity. To the best of our knowledge, our study is the first to elucidate the relationship between anxiety sensitivity and disease severity in psoriasis patients.

Psychological symptoms play an important role in the development and exacerbation of psoriasis.[11] The fact that psoriasis is a disease with a chronic course, its impact on external appearance, and the associated social stigma may increase the stress associated with the disease and cause psychiatric symptoms.[22] The incidence of psychiatric disorders in psoriasis patients is four times higher than in other dermatological diseases.[37] At the same time, an accompanying psychiatric disorder of psoriasis may exacerbate the disease, delay recovery by impairing response to treatment and cause relapse.[38] Akay et al. investigated the depression levels of psoriasis patients and found that the severity of depression was significantly higher in psoriasis patients than in the control group.[39] In a study comparing 100 psoriasis patients with 100 healthy controls, depression and anxiety levels were higher in psoriasis patients than in controls.[40] In our study, anxiety and depression levels were significantly higher in psoriasis patients than in healthy controls.

Different results were reported in studies investigating the association between disease severity and duration and anxiety and depression in psoriasis patients. Köşger et al. found a positive correlation between PASI scores and anxiety scores in psoriasis patients, but no correlation of PASI scores with depression scores.[41] The study by Özgüven et al. showed a positive correlation of psoriasis severity with depression scores, but no correlation with anxiety scores. In the same study, a negative correlation was found between depression scores and disease duration, and it was reported that this fact could be due to learning to cope with the psychosocial impact of the disease or selecting patients with low PASI scores.[42] In their study, Kılıç et al. found no correlation between PASI scores and disease duration and anxiety and depression levels in psoriasis patients.[43] In the study of Taner et al., it was reported that there was no correlation between disease duration and depression and anxiety scores in psoriasis patients.[44]

Similarly, no correlation was found between PASI scores and disease duration and anxiety and depression scores in psoriasis patients in our study.

In general, patient-assessed subjective disease severity has been more strongly associated with anxiety and depression than PASI score.[45] Therefore, the patient's subjective perception of disease severity, quality of life, and functionality may be more useful in predicting the patient's psychiatric well-being than objective scale instruments related to disease severity.[46,47] Although our study excluded individuals with known psychiatric illnesses, high depression and anxiety severity in psoriasis patients may be related to chronic daily stress caused by chronic disease progression, relapse progression, the need for long-term treatment, failure to fully recover, the impact of the disease on external appearance, social stigma, increased anxiety sensitivity, perceived stress, and the impact of having to live with the disease.[15-17]

There are few studies examining social anxiety in psoriasis patients. For example, one study reported that social anxiety was high in psoriasis patients with visible lesions on the body and that there was an association between social anxiety and disease severity.[48] In a recent study in our country, social anxiety scores were significantly higher in psoriasis patients than in healthy controls, and social anxiety and avoidance behavior scores were reported to be associated with poor quality of life but not with PASI scores.[49] In our study, similar to studies in the literature, we found that psoriasis patients had significantly higher social anxiety levels than healthy controls and that there was no relationship between social anxiety and disease severity and duration, measured by PASI.

Psoriasis is associated with social stigma due to the visible skin lesions and the perception that the disease is contagious in society.[50] As a result, psoriasis patients experience psychosocial difficulties due to low self-esteem and feelings of shame about their external appearance.[51] Furthermore, they continue to suffer from stress even after the lesions have healed.[52-54] A previous study reported that social anxiety was related to disease severity, feelings of inadequacy, and perceived levels of social support in psoriasis patients.[23] It was also highlighted that the level of social anxiety was associated with the severity of the disease in patients whose disease onset was in adolescence.

In contrast, the level of social anxiety was not associated with the severity of the disease in patients with disease onset in adulthood.[55] It has also been reported that lesion location is more related to social anxiety than to disease severity and that social anxiety levels are higher in patients with visible lesions, as expected.[49] Therefore, our study is crucial as it is the second controlled study to assess the level of social anxiety in psoriasis patients in our country.

Another aim of our study was to assess the perceived level of stress in psoriasis patients. As far as we know, this is the second study to assess perceived stress in psoriasis patients. It is well known that stress is a predisposing, triggering, and maintaining factor for psoriasis. Many studies have reported that psychological stress plays a role in developing and exacerbating the disease and influences disease progression.[56-57] In conjunction with stress, increased hypothalamic-pituitary-adrenal axis activity likely triggers the inflammatory process.[58-59] In a recent study, perceived stress levels were higher in psoriasis patients than in healthy controls, and perceived stress was reported to be associated with life events in the past six months.[60] In our study, too, perceived stress levels were higher in psoriasis patients than in healthy controls, and no correlation was found between disease severity and duration and perceived stress. Thus, our results are consistent with the hypothesis that perceived stress is higher in psoriasis patients.[61] In addition, it is hypothesized that psoriasis affects patients' perception of stress.[60] Psychological stress is important because it has a negative impact on the treatment of the disease.[62]

The last parameter we evaluated in our study was anxiety sensitivity in psoriasis patients. Anxiety sensitivity is defined as an anxiety amplifier characterized by fear of experiencing anxiety due to the social, cognitive, and physical consequences of anxiety that the individual perceives as harmful.[26] Anxiety sensitivity stands out as a predisposing factor that contributes to the development, exacerbation, and maintenance of psychiatric disorders and chronic diseases, particularly anxiety disorders.[63,64] Moreover, high anxiety sensitivity may increase the severity of psychodermatological diseases and worsen their course.[65] In a study examining anxiety sensitivity in dermatology patients, patients were divided into two groups: those with and those without psychodermatological disorder; anxiety sensitivity scores were higher in patients with psychodermatological disease than in those without.[66] Anxiety sensitivity may also be increased in dermatology patients due to visible lesions. Another study that examined patients with psychodermatologic symptoms showed that anxiety sensitivity is associated with social anxiety symptoms.[67] In our study, anxiety sensitivity levels were higher in psoriasis patients than in healthy controls, and anxiety sensitivity was not associated with disease severity and duration. Stress produces physiological responses by affecting the skin, immune, and neuroendocrine systems. Anxiety sensitivity may trigger or exacerbate anxiety and dermatologic symptoms by increasing the stress response in psoriasis patients.[66] Prospective studies are needed to better understand the interaction of anxiety sensitivity with psoriasis and to evaluate the contributing mechanisms and effects on quality of life and disease prognosis.

Our study has several limitations. First, it was a cross-sectional study. Second, the sample was relatively small. Third, the psychiatric assessment in this study was conducted using self-report scales. Patients with an existing psychiatric illness who had not received a psychiatric diagnosis from a psychiatrist were excluded. Fourth, patient selection was not randomized; healthy subjects were composed of hospital staff. Therefore, we believe that prospective studies should support our study with larger samples and psychiatric diagnostic interviews.

To our knowledge, our study is the first to assess anxiety sensitivity in psoriasis patients and it is one of the few studies to assess social anxiety and perceived stress. In our study, the high levels of anxiety sensitivity, social anxiety and perceived stress were not associated with the duration and severity of the disease. Studies with larger samples are needed to elucidate the relationship of these parameters with disease duration and severity.

CONCLUSION

The high levels of anxiety, depression, social anxiety, perceived stress and anxiety sensitivity in our study demonstrate that psychiatric assessment is vital in psoriasis patients at every stage of the disease, regardless of disease severity and disease duration. Thus, in patients with psoriasis, defined as a psychodermatological disease, psychiatric assessment and identification of patients in need of psychiatric treatment lead to more successful treatment responses and contribute to the prevention of psychiatric comorbidity by supporting early diagnosis and treatment of psychiatric diseases.

ETHICAL DECLARATIONS

Ethics Committee Approval: Study permission was obtained by the Ethics Committee of Abant İzzet Baysal University Faculty of Medicine (2016/8).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

Evaluation of the Role of Whole Body Computed Tomography in the Management of Minor Trauma Patients

Minör Travma Hastalarının Yönetiminde Tüm Vücut Bilgisayarlı Tomografinin Rolünün Değerlendirilmesi

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Abstract

Aim: Whole body of computed tomography (WBCT) approach is increasingly being preferred by the clinicians over the traditional selected CT approach worldwide, not only for major trauma patients but even for minor trauma patients. Our aim was to determine the ratio of polytrauma patients in minor trauma patients imaged with WBCT and to determine demographical and clinical predictors of polytrauma.

Material and Method: This retrospective-descriptive-study was conducted at the emergency department with patients older than 16 but had an injury severity scores of less than 16 and those who underwent WBCT trauma patients between January 2015 and December 2018. The presence of polytrauma, which defined presence of injury with an abbreviated injury scale score ≥2 according to tomography results in at least two body regions, was considered as the primary outcome of the study.

Results: Total 3924 patients' data were enrolled in the study. Only in 278 of all patients (7.1%) polytrauma was detected. After the multi-logistic regression analysis, fall from height (>3 meters), pedestrian struck, altered mental status (GCS <14), and male sex were found as significant predictor factors for presence of polytrauma. When created a model with these parameters, it was found that it had low diagnostic accuracy value as 0.6 (95%CI: 0.59 to 0.72).

Conclusion: When considered only minor trauma patients with small polytrauma and mortality ratio, routine using of WBCT approach is not rational. The predictors found in our study can be used to develop a clinical decision rule in the future for minor trauma patients.

Keywords: Whole body computed tomography, pan-CT, tomography, X ray computed, multiple traumas, radiation exposure, polytrauma, emergency departments

Öz

Amaç: Tüm vücut bilgisayarlı tomografi (TVBT) yaklaşımı, klinisyenler tarafından sadece majör travma hastaları için değil, hatta minör travma hastaları için de dünya çapında geleneksel seçilmiş BT yaklaşımına göre giderek daha fazla tercih edilmektedir. Amacımız, TVBT ile görüntülenen minör travma hastalarında çoklu travma hastalarının oranını belirlemek ve çoklu travmanın demografik ve klinik belirleyicilerini belirlemekti.

Gereç ve Yöntem: Bu retrospektif-tanımlayıcı-çalışma, acil serviste 16 yaşından büyük ancak injury severty skoru <16 olan ve Ocak 2015 ile Aralık 2018 tarihleri arasında, WBCT çekilmiş olan travma hastalarının verileri incelenerek yapıldı. En az iki vücut bölgesinde tomografi sonuçlarına göre abbreviated injury scale skoru ≥2 olan yaralanma varlığı çalışmanın birincil sonlanımı olarak belirlendi.

Bulgular: Çalışmaya toplam 3924 hastanın verileri dahil edildi. Tüm hastaların sadece 278'inde (%7,1) çoklu travma tespit edildi. Çoklu lojistik regresyon analiz sonuçlarına göre, yüksekten düşme (>3 metre), yayaya araç çarpması, değişen mental durum (GCS <14) ve erkek cinsiyet, çoklu travma varlığı için anlamlı değişkenler olarak bulundu. Bu değişkenlerle bir model oluşturulduğunda, bu modelin 0,6 (%95 CI: 0,59 ila 0,72) gibi düşük tanısal doğruluk değerine sahip olduğu bulunmuştur.

Sonuç: Çoklu travma ve mortalite oranı küçük olan sadece minör travma hastaları düşünüldüğünde, TVBT yaklaşımının rutin kullanımı akılcı değildir. Çalışmamızda bulunan prediktörler, minör travma hastaları için gelecekte klinik bir karar kuralı geliştirmek için kullanılabilir.

Anahtar Kelimeler: Tüm vücut bilgisayarlı tomografi, pan-CT, çoklu travma, radyasyon maruziyeti, politravma, acil tıp

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INTRODUCTION

The whole-body computed tomography (WBCT) which consists of unenhanced head and cervical, and contrast-enhanced chest, abdomen, and pelvis computed tomography (CT), is an important imaging option in the management of multiple trauma patients. Contrary this approach, the traditional selected CT (SCT) approach of the ATLS is primarily to order conventional radiographs and focused abdominal sonography in trauma (FAST), and then to perform CT of the relevant body region within the indication.[1,2] However, superiority of WBCT to SCT approach is still controversial. The main concerns about WBCT approach can be summarized as unnecessary radiation exposure it may cause and inadequate data on its mortality and morbidity benefit.[3] Conflicting results regarding the effect of WBCT on mortality rates have been reported in the study results, which were mostly retrospective in the literature.[4-11] Although Sierink et al reported in their randomized controlled study (REACT-2 trial) that there was no significant difference on mortality between two approaches, the effect of WBCT approach on mortality and morbidity is still unclear.[12]

Despite this uncertainty in the literature, WBCT approach is increasingly being preferred by the clinicians over SCT approach worldwide. In fact, this preference is not only for major trauma patients but even for minor trauma patients. Among the possible reasons why WBCT is preferred even in minor trauma patients, some clinicians believe that WBCT may be advantageous in two issues; first, especially those such as crowded emergency departments in the US and Turkey,[13] as SCT is a time-consuming approach, the WBCT approach decreases the emergency crowd by decreasing the patients' length of stay in the emergency department. Second, again, especially in these crowded emergency departments, it is thought that physicians working under intensive patient burden reduce the risk of misdiagnosis and prevent medico-legal problems when WBCT approach was preferred.

We aimed to analyze the data of minor trauma patients (injury severity score (ISS) <16) underwent WBCT by questioning the necessity of WBCT in these patients. The primary outcome of this study is to identify patients with polytrauma among these minor traumas. We aimed to determine, if detected, what parameters were present in the patient group, in which the WBCT approach was beneficial, the WBCT approach could detect patients with polytrauma.

MATERIAL AND METHOD

Study design and setting

This study was conducted at the emergency department (ED) of a tertiary care teaching hospital having annually 580,000 emergency patient admissions between January 2015 and December 2018. We examined the electronic records of patients admitted to the ED following local ethical committee approval.

Selection of participants

The hospital's electronic patient record management system was used for screening the data of the adult patients admitted to ED with trauma. The patients older than 16 but had an ISS of less than 16 and those who underwent WBCT were included in the study. Pregnant patients, duplicate applications and those with a lack of data were excluded from the study.

Measurements

Trauma patients who underwent unenhanced head and cervical, and contrast-enhanced chest, abdomen, and pelvis CTs were considered to be managed by the WBCT approach. All these CTs were accepted as WBCT protocol only if they were all taken with the same protocol and none were missing.

Five researchers who were emergency physicians with at least 3 years of experience were trained to collect data from the hospital data-registration system and to calculate the ISS of the patients before the study period. They scanned all trauma patients who underwent WBCT during the study period and calculated the ISS according to patients'WBCT results reported by a radiologist and physical examination records. When the agreement of the researchers in the calculation of the ISS is calculated with 100 same patients, the intraclass correlation was found good (intraclass correlation=0.793).

Outcomes

We determined the presence of polytrauma as the primary outcome of the study, as the potential benefit of the WBCT approach is thought to diagnose injuries in other systems outside the body region where the primary injury is. We defined polytrauma as the presence of injury with an Abbreviated Injury Scale (AIS) ≥2 according to tomography results in at least two body regions.[14] Accordingly, patients were divided into two groups; those with and without polytrauma. By determining which variables can predict the presence of polytrauma, we aimed to determine which patients could benefit from WBCT.

Analysis

All data were analyzed by IBM SPSS Statistics for Mac, version 25.0 for Mac OS X (IBM Corp., Armonk, N.Y., USA). The normality of the data distribution was determined by the Shapiro-Wilk test, histogram, and Q-Q plots. The categorical values of the patients were expressed as a number and a percentage and were analyzed with a Chi-square test. Continued values were presented as a mean and standard deviation or median values and an inter quartile range of 25%–75%. The non-parametric values were analyzed using the Mann–Whitney U, and the parametric ones with T test. To determine the predictive value of several variables, a multivariate regression model was created using variables whose p value was <0.1 in univariate analyses. To assess the model's goodness of fit, the Hosmer-Lemeshow test was performed. A two-tailed p value <0.05 was considered statistically significant.

RESULTS

In study period, 3924 minor trauma patients (ISS<16) who admitted to our emergency department due to several trauma reasons and underwent WBCT were enrolled in the study. The median age of patients was 33 (IQR25-75%: 24 to 46) and 2979 (75.9%) of them were male. Although there were no significant injuries after evaluation of WBCT in 2618 of all patients (66.7%), several injuries were detected in 1306 patients (33.3%), and only in 278 of all patients (%7.1), injuries of multiple body parts were detected and accepted as polytrauma. Baseline characteristics of all patients were shown on **Table 1**.

When several demographical and clinical characteristics of patients were analyzed according to presence of polytrauma, significantly differences were found terms of several parameters between both groups and they were summarized in **Table 2**. To determine the potential variables for prediction of polytrauma, a multivariate logistic regression model was created. Fall from height (>3 meters), pedestrian struck, motor vehicle collision, altered mental status (GCS <14), male sex, and age over 65 years were included to initial model. In addition, even though significant difference was found terms of serum lactate level, pH, base excess, and vital signs between both groups in **Table 1**, these variables were not included to model, because these values were not examined in all patients, only in 574 patients for venous blood gases analysis, in 3085 patients for oxygen saturation, in 1467 patients for respiratory rate, and in 3298 patients for pulse rate. The data of these variables were presented as only univariate analysis in **Table 2**. Overall, according to final model, fall from height (>3 meters), pedestrian struck, altered mental status (GCS <14), and male sex were found as significant predictor factors for polytrauma (**Table 3**).

Table 1. Characteristics of the patients

Variables	N:3924	Variables	N:3924
Gender N (%)		**Injuries detected by WBCT** N (%)	
Male	2979 (75.9)	Totally normal	2618 (66.7)
Female	945 (24.1)	Intraparenchymal hemorrhage	8 (0.2)
Age median (IQR 25-75%)	33 (24 to 46)	Subdural hemorrhage	33 (0.8)
Presence of comorbidities N (%)	170 (4.3)	Epidural hemorrhage	23 (0.6)
Chronic hypertension	99 (2.5)	Subarachnoid hemorrhage	57 (1.5)
Diabetes mellitus	65 (1.7)	Cerebral contusion	29 (0.7)
Coronary artery disease	35 (0.9)	Compression fracture	9 (0.2)
Chronic kidney disease	10 (0.3)	Linear fracture	102 (2.6)
Stroke	8 (0.2)	Cervical spine fracture	29 (0.7)
Congestive heart failure	9 (0.2)	Cervical Spondylolisthesis	1 (0.0)
COPD	15 (0.4)	Thoracolumbar spine fracture	297 (7.6)
Mental retardation	5 (0.1)	Thoracolumbar spondylolisthesis	7 (0.2)
Use of anti-thrombotic agent N (%)		Cot fractures (less than 3)	108 (2.8)
Anticoagulant agent	10 (0.3)	Multiple cot fractures (3 or more)	74 (1.9)
Antiplatelet agent	19 (0.5)	Hemothorax	45 (1.1)
Trauma mechanism N (%)		Pneumothorax	76 (1.9)
Motor vehicle collision	1440 (36.7)	Pulmonary contusion	232 (5.9)
Pedestrian struck	532 (13.6)	Intra-abdominal solid organ injury	41 (1)
Fall from height (≥3 meters)	315 (8)	Gastrointestinal tract injury	2 (0.1)
Fall from height (<3 meters)	416 (10.6)	Renal injury	5 (0.1)
Fall from same level	203 (5.2)	Bladder injury	1 (0.0)
Motorcycle accident	617 (15.7)	Bone fractures of extremities	665 (17)
Bicycle accident	38 (1)	Maxillofacial fractures	97 (2.5)
Violence	238 (6.1)	**Patients outcomes** N (%)	
Other	125 (3.2)	Exitus in ED	2 (0.1)
Vital signs on admission median (IQR 25-75%)		Admission to ICU	51 (1.3)
Respiratory rate (for 1467 patients)	17 (15 to 18)	Admission to hospital bed	529 (13.5)
Pulse rate (for 3298 patients)	80 (76 to 88)	Transfer to another hospital	25 (0.6)
Oxygen saturation % (for 3085 patients)	98 (97 to 99)	Treatment refusal	188 (4.8)
Systolic blood pressure (for 3394 patients)	123 (119 to 132)	Discharged from ED	3129 (79.7)
Diastolic blood pressure (for 3394 patients)	76 (70 to 80)	**Polytrauma** N (%)	278 (7.1)
Glasgow coma scale median (min-max)	15 (3 to 15)	**Mortality** N (%)	
ISS median (IQR 25-75%)	2 (1 to 5)	Mortality within 30 day	11 (0.3)
Laboratory findings on admission median (IQR 25-75%)		Mortality within first 24 hours	3 (0.1)
pH (for 574 patients)	7.38 (7.35 to 7.42)	Mortality in hospital	8 (0.2)
Base excess (for 574 patients)	0.40 (-1.6 to 2.1)	**RBC Transfusion** mean/median (min-max)	0.9/ 0 (0-21)
Lactate (for 574 patients)	2.0 (1.5 to 2.9)	**Need for intubation N (%)**	33 (0.8)
Hemoglobin (for 3848 patients)	14.2 (13 to 15.1)	**Need for operation N (%)**	381 (9.7)
Hematocrit (for 3848 patients)	42.3 (39 to 44)		
INR (for 1427 patients)	1.09 (1.02 to 1.19)		

Table 2. Demographical and clinical characteristics of the patients according to the presence of polytrauma.

Variables	Non-Polytrauma (N: 3646)	Polytrauma (N: 278)	P value
Gender N (%)			0.006
Male	2749 (75.4)	230 (82.7)	
Female	897 (24.6)	48 (17.3)	
Age median (IQR 25-75%)	33 (24 to 46)	37 (28 to 51)	<0.001
Age (>65 year) N (%)	243 (6.7)	26 (9.4)	0.08
Presence of Comorbidities N (%)	151 (4.1)	19 (6.8)	0.03
Chronic hypertension	93 (2.6)	6 (2.2)	0.6
Diabetes mellitus	61 (1.7)	4 (1.4)	0.7
Coronary artery disease	32 (0.9)	3 (1.1)	0.7
Chronic kidney disease	9 (0.2)	1 (0.4)	0.7
Prevent stroke	7 (0.2)	1 (0.4)	0.5
Congestive heart failure	5 (0.1)	4 (1.4)	<0.001
COPD	8 (0.2)	7 (2.3)	<0.001
Mental retardation	10 (0.2)	0 (0.0)	N/A
Use of anti-thrombotic agent N (%)			
Anticoagulant agent	8 (0.2)	2 (0.7)	0.1
Antiplatelet agent	16 (0.4)	3 (1)	0.1
Trauma mechanism N (%)			
Motor vehicle collision	1385 (38)	55 (19.8)	<0.001
Pedestrian struck	483 (13.2)	49 (17.6)	0.04
Fall from height ≥3 meters)	257 (7)	58 (20.9)	<0.001
Fall from height (<3 meters)	385 (10.6)	31 (11.2)	0.7
Fall from same level	192 (5.3)	11 (4)	0.3
Motorcycle accident	581 (15.9)	36 (12.9)	0.2
Bicycle accident	36 (1)	2 (0.7)	0.6
Violence	219 (6)	19 (6.8)	0.5
Other	108 (3)	17 (6.1)	0.04
Vital signs on admission median (IQR25-75%)			
Respiratory rate (for 1467 patients)	17 (15 to 19)	16 (15 to 17)	<0.001
Pulse rate (for 3298 patients)	80 (76 to 88)	82 (76 to 90)	0.01
Oxygen saturation % (for 3085 patients)	98 (97 to 99)	98 (95 to 99)	<0.001
Systolic blood pressure (for 3384 patients)	123 (120 to 132)	124 (115 to 134)	0.5
Diastolic blood pressure (for 3384 patients)	76 (70 to 80)	76 (70 to 82)	0.5
Altered mental status (GCS <14)	41 (1.1)	19 (6.8)	<0.001
ISS median (IQR 25-75%)	2 (1 to 4)	9 (8 to 13)	<0.001
Laboratory findings on admission			
pH (for 574 patients; 489/85)	7.39 (7.36 to 7.42)	7.36 (7.33 to 7.41)	0.002
Base excess (for 574 patients; 489/85)	0.6 (-1.3 to 2.1)	-0.7 (-3.5 to 1.45)	<0.001
Lactate (for 574 patients; 489/85)	1.9 (1.4 to 2.8)	2.4 (1.9 to 3.6)	<0.001
Hemoglobin (for 3848 patients; 3575/273)	14.2 (13 to 15)	14.1 (13 to 15)	0.6
Hematocrit (for 3848 patients; 3575/273)	42.3 (39 to 44)	42 (39 to 44.6)	0.5
INR (for 1427 patients; 1264/163)	1.09 (1.02 to 1.16)	1.11 (1.05 to 1.1)	0.002
Patients outcomes N (%)			
Exitus in ED	0 (0)	2 (0.7)	N/A
Admission to ICU	26 (0.7)	25 (9)	N/A
Admission to hospital bed	402 (11)	127 (45.7)	N/A
Transfer to another hospital	17 (0.5)	8 (2.9)	N/A
Treatment refusal	178 (4.9)	10 (3.6)	N/A
Discharged from ED	3023 (82.9)	106 (38.1)	N/A
Mortality N (%)			
Mortality within 30 day	5 (0.1)	6 (2.2)	<0.001
Mortality within first 24 hours	0 (0)	3 (1.1)	N/A
Mortality in hospital	3 (0.1)	5 (1.8)	<0.001
RBC Transfusion mean/median (min-max)	0.6/ 0 (0-21)	0.57/ 0 (0-13)	<0.001
Need for intubation N (%)	14 (0.4)	19 (6.8)	<0.001
Need for operation N (%)	298 (8.2)	83 (29.9)	<0.001

Table 3. Multivariate logistic regression to predict polytrauma in minor trauma patients.

	Wald	P value	OR (95% CI)
Fall from height (>3 meters)	62.632	0.001	3.76 (2.7 to 5.2)
Pedestrian struck	10.323	<0.001	1.76 (1.2 to 2.4)
Altered mental status (GCS <14)	38.239	<0.001	6.07 (3.4 to 10)
Male sex	7.121	0.008	1.57 (1.18 to 2.1)
>65-year-old	2.645	0.1	1.44 (0.9 to 2.2)

When created a model with four parameters (presence of any parameters was accepted as prediction polytrauma and absence of all parameter was accepted as prediction non-polytrauma), it was found that it had low diagnostic accuracy value as 0.6 (95%CI: 0.59 to 0.72), other diagnostic values were as follows; sensitivity was 52% (95%CI: 46 to 58), specificity was 61%(95%CI: 59 to 62), negative likelihood ratio was 0.77 (95%CI: 0.68 to 87) and positive likelihood ratio was 1.37 (95%CI: 1.22 to 1.54).

DISCUSSION

Although indications of WBCT criteria is not well defined and controversies are continued, routine use of WBCT approach is spreading in moderate and severe trauma patients. As a matter of fact, we - as the authors of this study – support this WBCT approaching in management of moderate and severe trauma patients. However, we notice with concern the situation is that this trend is spreading even in minor trauma patients to reduce the likelihood of misdiagnosis and to decrease delay, especially in overcrowded emergency services. Therefore, we decided to focus on minor trauma patients and query whether there is necessity of WBCT in management of minor trauma patients. Obviously, our study showed that the rate of negative or unnecessary WBCT was high as 66.7%, rate of polytrauma was %7.1, and mortality rate was only 0.3% in minor trauma patients. The unnecessary or negative WBCT rate of the previously studies, which conducted with generally major trauma patients, was reported as lower than our results, ranging from 14 to 30%.[1,8,15,16] Similarly, reported mortality rate in previously studies is too higher than our results, as ranged from 4.7 to 22%.[1,4,17] When considered these data, it seems that contribution of routine WBCT using is too limited in management of minor trauma patients. Therefore, we believe that routine using of WBCT approach is not rational and when considered unnecessary radiation exposure, it may be harmful.

On the other hand, some authors in their well written review pointed out that diagnosing occult injuries with routine WBCT allows of safe and fast disposition from ED and obviates requiring of subsequent imaging and medical evaluation when patients present for follow-up with nonspecific pain or other complaints.[18] And, rightly again, they concluded that even some minor injuries, that may be misdiagnosed when WBCT wasn't used, can be fatal in the special population. Similarly, in our study, though number is few, there were also polytrauma subjects (7.1%) in minor trauma patients. Through our regression analysis, we have found four parameters (fall from height (>3 meters), pedestrian struck, altered mental status (GCS <14), and male sex) that can predict which WBCT scanning have polytrauma. To our knowledge, there is no study focused only minor traumas investigating the effectiveness of WBCT. Previously studies aimed to develop a criterion for WBCT have generally focused on all trauma patients. In a prospective study, conducted by J. Babaud et al., the Vittel criteria, which consist of several preadmission physiological variables, trauma mechanism, anatomic location of injuries, and comorbidities, was evaluated to whether could be used to determine the need for WBCT.[19] Finally, Glasgow Coma Scale (GCS) score less than 13, penetrating trauma, and resuscitation with greater than 1000 mL of colloids were found as independent predictor for needing WBCT. Another retrospective study was conducted by Davies et al., a model created and evaluated to detect significant injuries as a decision rule for WBCT in major trauma patients.[14] After final regression model, five independent predictors of polytrauma clinical signs in more than one body region, GCS score < 14, presence of hemodynamic abnormality (SBP <100 mmHg, or heart rate >100 bpm), presence of respiratory abnormality (respiratory rate >24 breaths/min, or pSO_2 <93%), and mechanism of the injury. However, when evaluated diagnostic accuracy of this model, the accuracy or the area under the curve (AUC) of the receiver operating characteristic (ROC) was reported as 0.82, with the sensitivity and specificity values of 79% and 71%, respectively. Finally, in another retrospective study which was conducted by Hsiao et al. with 660 trauma patients, it was aimed to identify the independent predictors and create a diagnostic decision rule to detect needing WBCT.[11] After regression analysis, independent predictors were defined as; male sex, GCS score < 9, mechanism of the injury (fall > 5 m and being a cyclist). The accuracy of this model was reported as 0.74 (95% CI: 0.67–0.80). In addition, the authors reported the accuracy of only clinical decision trauma leader without any formal protocol as 0.70 (95% CI 0.63–0.76) and they concluded that there was not any clinically significant contribution of their decision rule. Similarly, in our study, though we found four significant independent predictors, the accuracy of the model that created with them is found so low as 0.6.

Due to retrospective nature of this present study, several potential predictor factors could not be considered such as; detail of trauma mechanism (vehicle estimated speed, presence helmet/seat belt), detail of resuscitation in prehospital period, etc. When considered our predictors inadequate to explain variance on outcome variable (polytrauma) in our model, these potential predictors might have been explained to important part of variance on outcome variable. Similarly, though vital signs and several laboratory results on admission were evaluated in this study, these potential predictors could not be included to model since there is no record for every patient. Finally, another potential limitation is that ISS values were calculated retrospectively based on CT findings and medical records.

CONCLUSION

As a conclusion, when considered the results of previous and present studies, though it seems that several predictors including trauma mechanism, clinical findings on admission, laboratory examining in the early period of resuscitation are related to needing WBCT, models created with these predictors seem to be far from being sufficient for determine indication WBCT. When considered only minor trauma patients with small polytrauma and mortality ratio, routine using of WBCT approach is not rational and when considered unnecessary radiation exposure, it may be harmful. Though our data is not enough to suggest a decision model to determine needing of WBCT, we believe that predictors found in our study (fall from height (>3 meters), pedestrian struck, altered mental status (GCS score <14), and male sex), along with other possible predictors, can be used to develop a clinical decision rule in the future for minor trauma patients..

ETHICAL DECLARATIONS

Ethics Committee Approval: University of Health Sciences, Umraniye Training and Research Hospital, Clinical Research Ethics Committee, Approval date: 23.01.2019, Decision No: B.10.1.THK.4.34.H.GP.0.001/12.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

Our Experiences on Kyphosis and Scoliosis Surgery in Juvenile and Adolescent Patients During Pandemic Period

Pandemi Sürecinde Juvenil ve Adolesanlarda Kifoz ve Skolyoz Cerrahisi Deneyimlerimiz

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Abstract

Aim: In this study, we aimed to contribute to the literature by sharing our experiences regarding the major spine surgeries we have applied to juvenile and adolescent patients during the Covid-19 pandemic process.

Material and Method: We retrospectively evaluated a total of 26 juvenile and adolescent idiopathic scoliosis and kyphosis patients we operated within a year from April 2020, when pandemic measures were implemented in our country up to April 2021.

Results: Any respiratory complications or symptoms and signs of Covid-19 were not observed in our patients in the preoperative and / or postoperative period.

Conclusion: During this pandemic period, it was ensured that major spine deformity surgeries in juvenile and adolescent patients were successfully managed for both our patients and our healthcare personnel.

Keywords: Adolescent, Covid-19, pandemic, scoliosis

Öz

Amaç: Biz bu çalışmada, Covid-19 pandemi sürecinde juvenil ve adolesanlara uyguladığımız major omurga cerrahileri ile ilgili tecrübelerimizi paylaşarak literatüre katkıda bulunmayı amaçladık.

Gereç ve Yöntem: Ülkemizde pandemi önlemlerinin uygulamaya başlandığı Nisan 2020'den Nisan 2021'e kadar geçen bir yıllık süreçte ameliyat ettiğimiz toplam 26 juvenil ve adelosan idiopatik skolyoz ve kifoz hastasını retrospektif olarak değerlendirdik.

Bulgular: Hastalarımızda preoperatif ve/veya postoperatif dönemde solunumsal bir komplikasyon ya da Covid-19 semptom ve bulguları görülmedi.

Sonuç: Bu pandemi döneminde, juvenil ve adolesanlarda major omurga deformitesi ameliyatlarının hem hastalarımız hem de sağlık personelimiz açısından başarılı bir şekilde yönetilmesi sağlanmıştır.

Anahtar Kelimeler: Adolesan, Covid-19, pandemi, skolyoz

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INTRODUCTION

The coronavirus (Covid-19) pandemic has affected patients all over the world and doctors, nurses and other auxillary health professionals involved in the delivery of health services.[1] Elective surgical interventions of many patients in all surgical branches worldwide have been postponed because of the increased burden of hospitals due to Covid-19 and the increased risk of complications caused by Covid-19. Operation time is an important factor for disease prognosis in juvenile and adolescent idiopathic scoliosis surgery. Studies have shown that waiting more than 6 months for surgery in juvenile and adolescent idiopathic scoliosis patients is a risk for progression of deformity.[2] Delayed surgical treatment of deformity may lead to additional surgical procedures, prolonged operation time and greater amount of blood loss, and also may adversely affect the patient's psychology.[1,3,4] Spine surgery during the Covid-19 epidemic involves a complex decision-making process that includes sociological, clinical and economic factors.[5]

Although some algorithms and scoring systems have been published that determine surgical priorities in spinal surgeries, there is no publication in the literature that shares authors'experience on spinal deformities such as scoliosis and kyphosis surgery during the pandemic period. In our study, we aimed to contribute to the literature by sharing our experiences with major spine surgeries such as scoliosis and kyphosis surgery in juvenile and adolescent patients in one year period of the Covid-19 pandemic.

MATERIAL AND METHOD

We retrospectively evaluated a total of 26 juvenile and adolescent idiopathic scoliosis and kyphosis patients we operated in a year starting from April 2020, when pandemic measures were implemented in our country, up to April 2021. The demographic characteristics and diagnoses of the patients are presented in **Table 1.** In line with the current guidelines published by the Ministry of Health, all patients before surgery were questioned in terms of viral symptoms such as fever, sore throat, cough, myalgia, shortness of breath or anosmia, and were evaluated by performing Covid-19 PCR test and blood tests 24 hours in advance, regardless of clinical symptoms. Written informed consent was obtained from the relatives of the patients by explaining the complications that may develop due to Covid-19 infection during the pandemic. After the Covid-19 diagnosis was excluded, they were operated on. Postoperative length of stay and early and late complications of the patients were recorded. The patients were intubated in line with the current guidelines of the Ministry of Health. Neuromonitoring was used routinely during the operations, and no pathological finding was found in the neuromonitor parameters during the operation. Patients who were kept in the recovery room for sufficient time after being extubated were then admitted to single rooms in the service. Paracetamol and morphine were given for pain control. The patients who were mobilized with a corset on the second day were discharged on the fifth day (**Figure 1.a,b**). All protocols were approved by Ethics Committee of Bursa Hospital (05.05.2021-2020-8/3).

RESULTS

Average amount of blood loss per case was 600 ml. and the average operative time was 4 hours and 23 minutes. No major respiratory complications were observed in the patients during the intraoperative and / or postoperative period. One patient was found to have Horner syndrome 10 days after discharge, and the right-sided T1 screw was removed by revision surgery. In another patient, the L1 screw was revised as it touched the spinal root from the medial of the pedicle. No patients had symptoms and signs of Covid-19 during the one-month follow-up after discharge, including revision surgeries performed on these two patients (**Table 1**).

DISCUSSION

In the coronavirus pandemic, as the healthcare system and hospitals primarily use their resources to combat the epidemic, it has led to an accumulation of patients awaiting major surgeries such as spinal deformities.[6] In such a pandemic environment, daily medical practices have been rediscovered for every medical field.[7] Due to the suspension of most elective surgeries worldwide, many surgeons had to work in Covid outpatient clinics and wards. This situation had negative effects on surgeons.[8]

During the pandemic, in accordance with the guidelines formulated by the French Spine Surgery Society, it was recommended that the operations be postponed to a later date for spinal deformities (scoliosis and kyphosis).[7] Similarly Sciubba DM et al.[9] determined surgical priorities with the scoring system designed by them but left the decision to the surgeon who performed the surgery. Neurosurgical operations were divided into five categories during the pandemic by the American College of Surgeons, and an algorithm was created accordingly.[10] According to these publications by spine surgeons, some have defined algorithms for the recovery of neurological functions and pain reduction, while others have published algorithms for preserving lung function, managing infection and preventing neurological damage.[1]

The existence of asymptomatic carriers and evidence that they have viral loads similar to symptomatic patients and that PCR-negative patients may have been infected with Covid-19, shows that surgeries pose a high risk for both healthcare professionals and patients.[11] Various measures have been proposed to limit the spread of Covid-19 infections during surgery.[12] In addition, it is important to protect patients from Covid-19 infection in the postoperative period. New guidelines have been developed in addition to existing standard precautions to protect healthcare workers against the high contagiousness of this viral disease.[10]

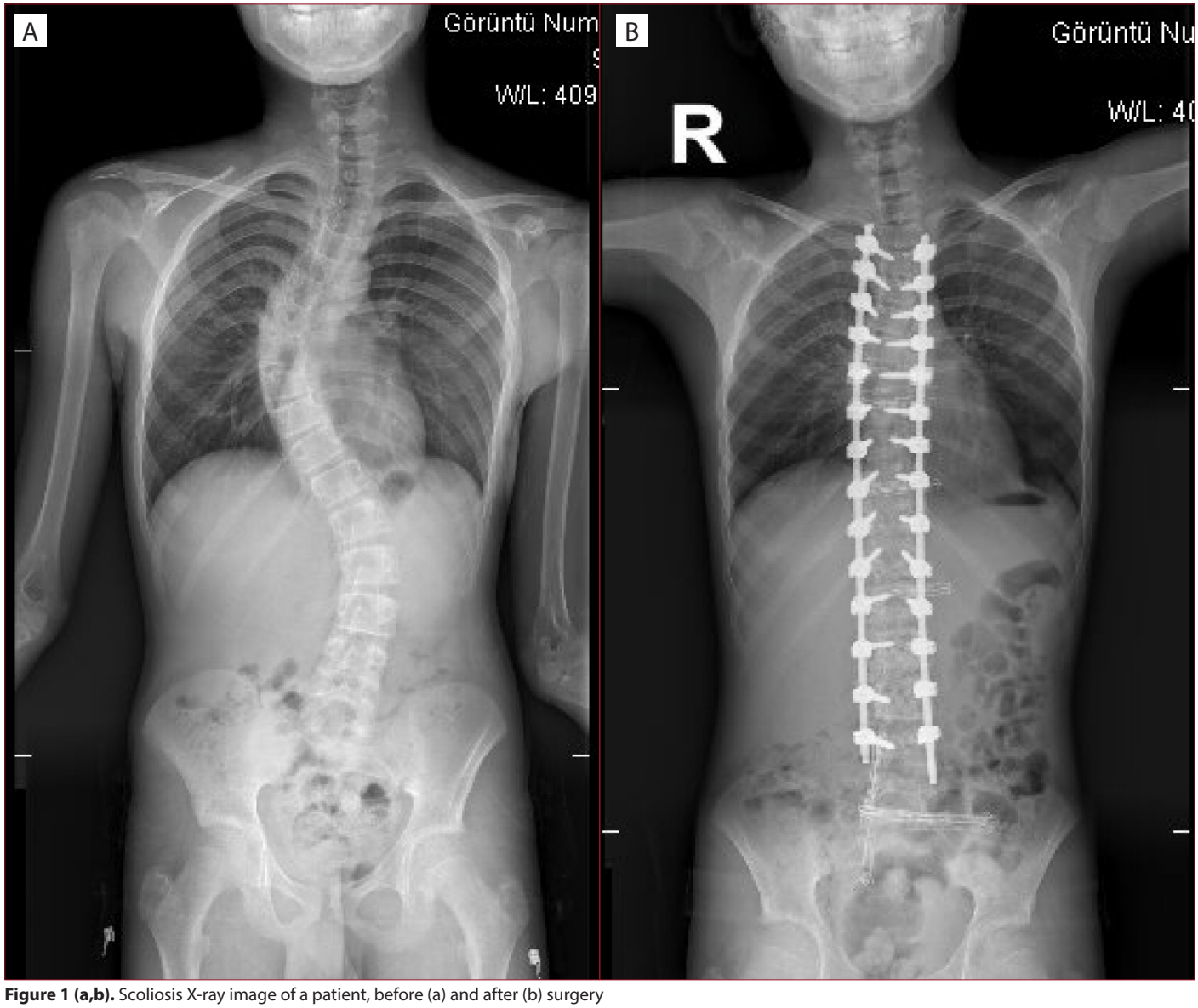

Figure 1 (a,b). Scoliosis X-ray image of a patient, before (a) and after (b) surgery

Although neurosurgical patients are generally middle-aged or older and the mortality rate for Covid-19 is significantly higher in older adults, those with various cardiopulmonary comorbidities, brain or spine tumors and/or receiving chemotherapy,[13,14] patients we operated with the diagnosis of spinal deformity were juvenile and adolescent patients Covid-19 infection is essentially asymptomatic or mild in juvenile and adolescent individuals.[15,16] Especially parents should be aware that the delayed risks of diseases such as spinal deformity may be higher than the risks that Covid-19 may cause.[17]

While the burden of emergency neurosurgical procedures remained unchanged throughout the pandemic, the burden of non-emergency elective cases was significantly reduced. These surgeries have shown that, especially with strict screening for Covid-19 infections, neurosurgical procedures can be performed safely in the pandemic phase.[18]

In the beginning, it was understood that the pandemic was difficult to overcome in a short time due to reasons such as failure to discover the vaccine within a short time, the fact that the whole world could not be vaccinated in a short time after the vaccine was found, an infected person could be re-infected, so we arrived at a conclusion that the surgical treatment of progressive and important spinal diseases such as scoliosis and kyphosis will not be delayed for a long time. We contacted with the families of the patients and reached a consensus that treatment should not be refused due to the fear of infection, and we performed these operations by taking the necessary precautions. According to our knowledge, there is no risk specific to Covid-19 for elective spine surgeries.[19] Our study supports this fact.

This study has certain limitations. Patients with adult degenerative kyphosis or scoliosis were not included in our study. This prevented the generalizability of the results.

Table 1. The demographic characteristics, diagnoses, operation time, fusion levels, complications etc. of the patients

Patient No	Age	Gender	Date of Surgery	Diagnosis	Fusion Level	Operation Time	Blood Loss	Erythrocyte Suspension	Complications	Covid PCR
1	5	F	June 2020	Congenital scoliosis	Costal distractiton system	200 min	300 ml	160 ml	ø	Negatif
2	11	M	June 2020	Congenital scoliosis	Costal distractiton system	240 min	200 ml	ø	ø	Negatif
3	9	F	June 2020	Congenital scoliosis	Costal distractiton system	160 min	200 ml	ø	ø	Negatif
4	14	F	July 2020	Adolescent idiopathic scoliosis	T3-L1 post.inst. fusion	285 min	400 ml	ø	ø	Negatif
5	16	M	July 2020	Scheuermann kyphosis	T4-L3 post.inst. fusion	250 min	500 ml	ø	Screw Malposition	Negatif
6	13	F	August 2020	Adolescent idiopathic scoliosis	T1-L4 post.inst. fusion	360 min	1000 ml	480 ml	ø	Negatif
7	16	F	August 2020	Adolescent idiopathic scoliosis	T5-S1-iliac post.inst. fusion	360 min	1100 ml	480 ml	ø	Negatif
8	15	F	September 2020	Congenital scoliosis	T1-L5 post.inst. fusion	330 min	1400 ml	720 ml	ø	Negatif
9	16	F	September 2020	Adolescent idiopathic scoliosis	T6-L5 post.inst. fusion	345 min	900 ml	480 ml	ø	Negatif
10	17	F	September 2020	Adolescent idiopathic scoliosis	T5-L5 post.inst. fusion	360 min	800 ml	480 ml	ø	Negatif
11	8	M	September 2020	Congenital scoliosis	Growing rod	135 min	150 ml	ø	ø	Negatif
12	12	F	October 2020	Adolescent idiopathic scoliosis	T4-L3 post.inst. fusion	240 min	450 ml	240 ml	ø	Negatif
13	16	F	October 2020	Congenital scoliosis	T2-L5 post.inst. fusion	300 min	400 ml	240 ml	ø	Negatif
14	15	F	November 2020	Adolescent idiopathic scoliosis	T3-L4 post.inst. fusion	240 min	1000 ml	720 ml	ø	Negatif
15	13	M	November 2020	Adolescent idiopathic scoliosis	T3-L5 post.inst. fusion	300 min	700 ml	480 ml	ø	Negatif
16	11	M	December 2020	Congenital scoliosis	Costal distractiton system	180 min	150 ml	ø	ø	Negatif
17	12	F	December 2020	Adolescent idiopathic scoliosis	T4-L5 post.inst. fusion	285 min	600 ml	240 ml	ø	Negatif
18	12	F	January 2021	Adolescent idiopathic scoliosis	T3-L5 post.inst. fusion	275 min	700 ml	240 ml	ø	Negatif
19	13	M	January 2021	Adolescent idiopathic scoliosis	T3-L4 post.inst. fusion	280 min	900 ml	240 ml	ø	Negatif
20	18	M	February 2021	Adolescent idiopathic scoliosis	T3-L4 post.inst. fusion	300 min	700 ml	240 ml	ø	Negatif
21	17	F	February 2021	Scheuermann kyphosis	T4-L3 post.inst. fusion	270 min	700 ml	240 ml	ø	Negatif
22	9	F	February 2021	Congenital scoliosis	Costal distractiton system	200 min	200 ml	ø	ø	Negatif
23	14	F	March 2021	Adolescent idiopathic scoliosis	T6-L4 post.inst. fusion	240 min	500 ml	240 ml	ø	Negatif
24	14	F	March 2021	Congenital scoliosis	T1-L4 post.inst. fusion	280 min	750 ml	240 ml	Horner Syndrome	Negatif
25	14	M	March 2021	Scheuermann kyphosis	T4-L3 post.inst. fusion	220 min	400 ml	ø	ø	Negatif
26	12	M	April 2021	Scheuermann kyphosis	T3-L2 post.inst. fusion	200 min	450 ml	ø	ø	Negatif

F: Female, M: Male,

CONCLUSION

In spite of all these disadvantages, we performed these surgeries by taking the necessary precautions in order to prevent development of overwhelming problems caused by not being operated on spinal deformities during the pandemic, and as a result, we found that these surgeries did not cause serious problems. During this pandemic crisis, successful surgical management of spinal deformities without infecting healthcare personnel was achieved. At the same time, Covid-19 infection or any complications were not observed in patients we operated during the perioperative and postoperative follow-up period.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for the study was obtained from the Ethics Committee of Bursa City Hospital (05.05.2021-2020-8/3).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

The Effectiveness of California Tri-Pull Kinesiotaping in Reducing Glenohumeral Shoulder Subluxation After Stroke: AB design

California Tri-Pull Kinezyo bantlamanın İnme Sonrası Glenohumeral Omuz Subluksasyonunu Azaltmadaki Etkinliği: AB tasarımı

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Abstract

Aim: Glenohumeral subluxation (GHS) is a common complication of hemiplegia after stroke. The inferior dislocation is the most frequently encountered GHS in stroke patients, and it is important to choose the proper treatment to promote better stability after repositioning the humerus. To evaluate the short-term effect of the California tri-pull taping method with elastic kinesiotape (CTPK) on pain, recovery of movement and daily life activities in Turkish hemiplegic patients.

Material and Method: Fourteen hemiplegic participants with GHS involved in this study All patients had at least three weeks of conventional inpatient neurorehabilitation. During the rehabilitation program, all patients with GHS had kinesiotaping four times with five-day interval for three weeks. Outcome measures were a verbal descriptive pain scale (VPDS), the Katz index of independence in activities of daily living, and a radiologic and physical examination.

Results: No significant difference was found between the participants regarding sex, age, duration of stroke, and VPDS scores (p>0.05). Motor recovery stages were improved after CTPK, pain scores decreased, and Katz index increased with the treatment. Passive ROMs of the shoulder were significantly increased. Subluxation was found by palpation to be improved but did not show any radiographic changes.

Conclusion: CTPK can reduce pain and improve quality of life, passive ROM and subluxation. Our findings suggest that radiological grading of subluxation is not sensitive enough and should not be used to evaluate improvement of inferior subluxation in stroke patients.

Keywords: stroke, shoulder, subluxation, kinesiotaping

Öz

Amaç: Glenohumeral subluksasyon (GHS), inme sonrası hemiplejinin sık görülen bir komplikasyonudur. İnme hastalarında omuzun inferiora sublukse olması en sık karşılaşılan GHS'dir ve humerusu yeniden konumlandırdıktan sonra daha iyi stabiliteyi sağlamak için uygun tedaviyi seçmek önemlidir. Amacımız, hemiplejik GHS hastalarında, California tri-pull bantlama yöntemi ile uygulanan elastik kinezyo bantlama (CTPK) ile hastalardaki ağrı, hareket geri kazanımı ve günlük yaşam aktiviteleri üzerine kısa süreli etkisini değerlendirmektir.

Gereç ve Yöntem: Bu çalışmaya katılan GHS'li on dört hemiplejik hastaya haftada en az üç kez geleneksel yatarak nörorehabilitasyon uygulandı. Rehabilitasyon programı sırasında GHS'li tüm hastalara üç hafta boyunca beş gün arayla dört kez kinezyo bantlama yapıldı. Hastalar, sözel tanımlayıcı ağrı skalası (VPDS), günlük yaşam aktivitelerinde Katz bağımsızlık indeksi ve radyolojik görüntüleme ve fizik muayene ile değerlendirildi.

Bulgular: Katılımcılar arasında cinsiyet, yaş, inme süresi ve VPDS puanları açısından anlamlı fark bulunamadı (p>0,05). Tedavi ile CTPK sonrası motor iyileşme evreleri düzeldi, ağrı skorları azaldı ve Katz indeksi arttı. Omuzun pasif ROM'ları önemli ölçüde arttı. Subluksasyonun palpasyonla düzeldiği bulundu, ancak herhangi bir radyografik değişiklik gözlenmedi.

Sonuç: CTPK ağrıyı azaltabilir ve yaşam kalitesini, pasif ROM'u ve subluksasyonu iyileştirebilir. Bulgularımız subluksasyonun radyolojik derecelendirmesinin yeterince hassas olmadığını ve inme hastalarında inferior subluksasyonun iyileşmesini değerlendirmek için kullanılmaması gerektiğini göstermektedir.

Anahtar Kelimeler: inme, omuz, subluksasyon, kinezyo bantlama

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INTRODUCTION

Glenohumeral subluxation (GHS) is a common complication of hemiplegia after stroke with a high prevalence of 46-81%.[1-3] Complex regional pain syndrome and rotator cuff injuries can occur as a result of GHS, and the associated severe pain restricts upper limb movement and slows the rehabilitation process.[4,5] Thus, the management of GHS is a key element for rehabilitating the stroke patient.

Slings, strapping, positioning and electrical stimulation are widely used for the prevention and treatment of GHS.[6 7] The inferior dislocation is the most frequently encountered GHS in stroke patients, and it is important to choose the proper treatment to promote better stability by focusing on correct positioning of the humerus.[8] Studies evaluating the effect of taping on GHS reported contradictory results from improvement in shoulder range of motion (ROM), and reduction in pain and disability,[9-11] to no effect on pain and disability.[12] This appeared to result from the use of different taping techniques.[9-12] Hayner developed the California tri-pull taping (CTPT) method to specifically treat subluxation in stroke patients, and showed its effectiveness in reducing subluxation, and improving activities of daily life and active ROM, but without changing the severity of shoulder pain.[13] In a randomized controlled clinical trial, CTPT was shown to reduce pain and improve flexion and upper extremity function.[14] Since there had been no study of the CTPT method with kinesiotaping in one-year onset hemiplegic patients with radiographic follow-up, we aimed to evaluate its effectiveness in reducing pain and improving ROM and daily life activities in Turkish hemiplegic patients.

MATERIAL AND METHOD

Research Type

The study reported here is a modification of a previously described quasi-experimental, single-subject AB design.[13] with fourteen participants. In the AB design, the patients act as their own controls because of the inability to exclude the placebo effect of kinesiotaping over conventional neurorehabilitation treatment.

Participants

Twenty-five hemiplegic patients with GHS admitted to Physical Medicine and Rehabilitation Clinics at the University of Health Sciences, Ankara Physical Medicine and Rehabilitation Training and Research Hospital and Sultan Abdulhamid Han Training and Research Hospital were screened for the study. Six were excluded, and 2 refused to participate; thus, 18 patients diagnosed with shoulder subluxation participated in this study. Four patients dropped out from study. Only one patient ceased the treatment due to personal reasons. One patient received intraarticular injection on day 2 and two of the patients removed their kinesiotape after having shower. Therefore only 14 patients included in statistical analysis (**Figure 1**). Inclusion criteria were (1) 18 to 90 years of age, (2) stroke onset within one year, (3) shoulder subluxation in the involved upper extremity and (4) being oriented and cooperative. Exclusion criteria of the study were (1) global aphasia, (2) malignancy, (3) previous shoulder pain or surgery, (4) other neuromuscular disorders and (5) severe cardiopulmonary disease that affects daily life activities. The treatment was ceased if a surgery or intervention was planned to effected shoulder or extremity or if the patient did not want to continue to the study (**Figure 2**).

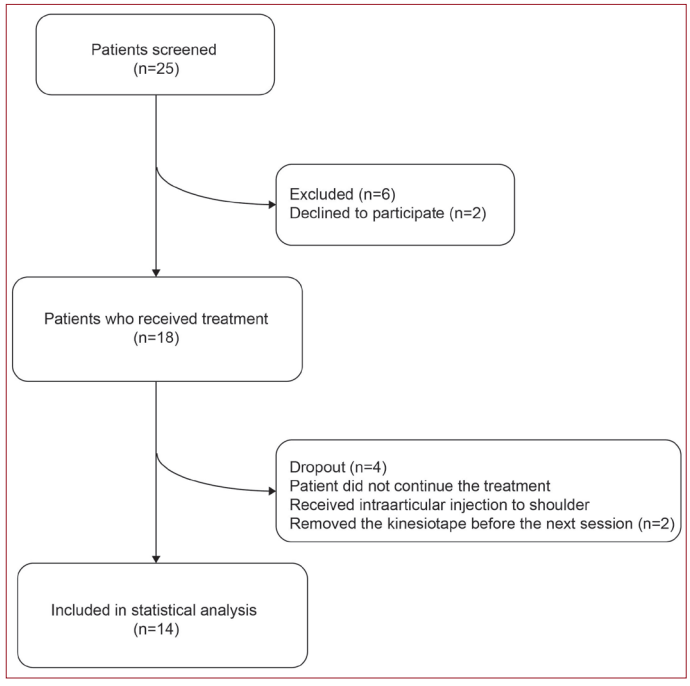

Figure 1. Flow chart for study

Inclusion criteria	Exclusion criteria	Ending criteria
• 18 to 90 years of age • Stroke onset within one year • Shoulder subluxation in the involved upper extremity • Being oriented and cooperative	• Global aphasia • Malignancy • Previous shoulder pain or surgery • Other neuromuscular disorders • Severe cardiopulmonary disease that affects daily life activities	• Person does not want to continue treatment any longer • Misuse of kinesiotaping such as removing the tape before the next session • Increase in pain • Adverse effects of kinesoitaping • Recieving any other treatment to effected shoulder or extremity

Figure 2. Eligibility criteria for the study

All procedures performed in studies involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by local ethic committee of Ankara Physical Therapy and Rehabilitation Training and Research Hospital. An informed consent was taken from all participants who wish to participate the study. This study is registered to clinicaltrials.org (ID: NCT04468750).

Intervention

All patients had at least three weeks of inpatient conventional neurorehabilitation. During the rehabilitation program, all patients with GHS had kinesiotaping four times with five day interval for three weeks. Kinesiotape (Nasara, Korea) was applied using the California tri-pull taping (CTPT) method with a 100% stretch. Three strips (5.0 cm width) were prepared, and all strips were applied starting from 3.5 cm below the deltoid tuberosity to the middle of the scapular spine, and 5 cm above to the top of the glenoid fossa between the clavicle and the spine of the scapula; and, also on the front of the humeral head, over the coracoid process to 3.5 cm above the clavicle as described in the Hayner study.[13]

In the conventional neurorehabilitation program, all patients received one hour of inpatient treatment five days per week for three weeks. Each day's 60-minute therapy session consisted of active and passive range of motions (ROM), neuromuscular re-education, upper extremity functional activities, balancing, sitting, standing, and transferring and ambulation education.

All patients were evaluated before and after the treatment. Pain, ROM, subluxation, Brunnstrom motor recovery stage and daily life activities were evaluated.

Primary Outcome Measures

Subluxation: Subluxation was measured by physical examination and radiography. For the physical exam, a clinician measured the gap between the acromion and the humeral head with the fingerbreadth at the distal interphalangeal joint of the right index and middle fingers. The anterio-posterior shoulder X-ray was taken in an erect position, and subluxation was evaluated by Van Langenberghe's five point classification.[3,15] Higher point indicates higher subluxation gap.

Pain: Pain with motion was measured by a verbal descriptive pain scale (VDPS). The VDPS was developed by Melzack and Katz and is composed of words such as "mild" (level 1) to "very severe pain" (level 5).[16] The scale has been used with Turkish people.[17] and is preferred for patients who cannot rate their pain by numbers because of cognitive issues.[18]

Secondary Outcome Measures

Range of motion: Passive shoulder ROM (flexion and abduction) was measured with a goniometer. Passive shoulder ROM was used in order to exclude patient`s neurological status (motor recovery status).

Motor recovery stage: The motor recovery stage of the subjects was assessed with the Brunnstrom (BRS) index for hand and arm. BRS was a staging system aim to describe the sequence of motor recovery after stroke based on synergy patterns. The BRS scored on a 6-level Likert-type scale (level I to VI), can be assessed in three regions; arm, hand and lower extremity.3 items. Higher levels indicates better motor function.[19,20]

Daily life activities: Daily life activities were evaluated using the Katz index of independence in activities of daily living, which evaluates the patients in bathing, dressing, toileting, transferring, continence, and eating. Activities were scored as zero or one with the total score ranging from zero to six.[21]

Statistics

Statistical Package for the Social Sciences 20.0 was used for performing the statistical analysis. Descriptive statistics (frequency, mean, percentage and standard deviation) were used for analyzing the sociodemographic and clinical features. Categorical parameters were assessed through Fisher's exact test. For two independent groups, the Mann–Whitney U test was used, whereas the Marginal Homogenity test was used for more than two independent categorical groups. A post-hoc Bonferroni analysis was performed to assess the statistical significance. The Spearman correlation was used to analyze the relationship of quantitative data to each other. The results were analyzed using a 95% confidence interval and a significance level of $p<0.05$.

RESULTS

The patients' demographics are summarized in **Table 1**, and no significant differences were found with regard to sex, age, duration of stroke, and VPDS ($p>0.05$). Each stroke patient had an inferior subluxation of the shoulder diagnosed by radiography, but only four (28.6%) were on analgesics. Most did not receive any treatment that was not indicated in the methods section, and no patient reported discomfort from the CTPK treatment.

Table 1. Demographics of patients

	n
Sex	
Female	5 (35.7%)
Male	9 (64.3%)
Coexistance of disease	
Diabetes mellitus	8 (57.14%)
Hypertension	11 (78.57%)
Hyperlipidemia	3 (21.43%)
Coronary artery disease	6 (42.86%)
Age (mean±SD)	55.9±14.3 y (26-76 y)
Duration of stroke (mean±SD)	7.7±4.5 mo. (1-12 mo.)

mo: months, n: number, SD: standard deviation, y: year

The average reduction in the amount of subluxation measured by palpation was 0.54 fingerbreadth on day 21 ($p=0.003$). The reduction from baseline was 0.5 in four patients, 1 in two patients and 1.5 fingerbreadths in two patients. Four patients did not reveal any change in subluxation with treatment (**Figure 3**). However, there was no change in radiographic Van Langenberghe classification between the baseline and posttreatment phase ($p=1$). Most of the patients had either grade 1, V shaped widening (35.7%), or grade 2, moderate subluxation (50%), which remain unchanged after the treatment (**Table 2**).

The pain experienced at posttreatment was mostly during motion and indicated a decreasing trend ($p<0.001$). Most patients who reported "moderate" pain said that it was now "mild" and "severe" pain had become "moderate" (**Table 2**).

Table 2.

	Time	Levels/ Classification						P
Brunstrumm Levels		I	II	III	IV	V	VI	
Hand	Baseline	0	9	3	0	1	1	0.014*
	Day 21	0	5	5	2	1	1	
Arm	Baseline	2	8	1	1	1	1	0.025*
	Day 21	1	6	3	2	1	1	
Verbal Pain Descriptive Scale		I	II	III	IV	V		
	Baseline	0	8	6	0	0		0.001*
	Day 21	8	5	1	0	0		
Van Langenberghe's Classification		0	I	II	III	IV		
	Baseline	0	6	7	1	0		1*
	Day 21	0	6	7	1	0		

n, number; VPDS, Verbal Pain Descriptive Scale; VLC, Van Langenberghe's Classification. *Difference between baseline and day 21. Marginal homogeneity test is used.

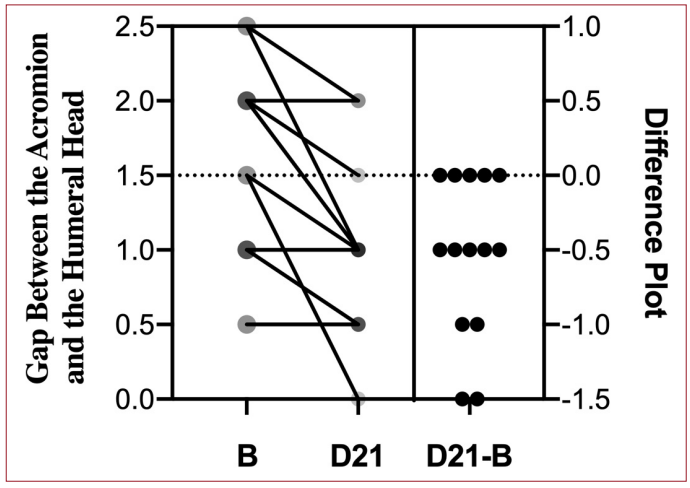

Figure 3. Estimation and difference plot of subluxation gap. B: Baseline D: Day

The motor recovery stage of the subjects was assessed with the Brunnstrom index for hand and arm. The median values of the Brunnstrom recovery stage of the hand and arm were significantly increased between the baseline and day 21 (**Table 2**). The median value of the Brunnstrom of the hand at baseline was 2 and at posttreatment, 3 (p=0.014). The median value of the Brunnstrom of the arm at baseline was 2 and at posttreatment, 2.5 (p=0.025). Even though the change of the Brunnstrom of the arm did not reach significant, the decreasing trend was observed.

The median ADL function score (Katz index) was 2 at baseline and 3 at posttreatment and the difference was statistically significant (p=0.028) (**Figure 4A**).

Goniometric measurement of passive ROM indicated a statistically significant increase in ROM angle of both shoulder abduction and flexion after three weeks (p=0.008 and p=0.004, respectively) (**Figure 4B**). Initial baseline of shoulder abduction ROM (mean±SD) was 96.5±4.25 degrees (ranging from 60 to 120 degrees) while shoulder flexion (mean±SD) was 91.5±6.28 degrees (ranging from 45 to 120 degrees). After treatment, both abduction and flexion ROM (median) were 120 degrees, ranging from 80 to 135 degrees and 70 to 120 degrees respectively.

DISCUSSION

Our results showed that CTPT treatment of this group of post-stroke GHS patients, improved subluxation, functional motor recovery and shoulder ROM, and reduced pain. Hayner.[13] and Chatterjee et al.[14] used the CTPT method with two types of tape: cotton undercover tape and rigid strapping tape. Hayner found no significant difference in pain, but Chatterjee et al. reported significant pain reduction. In our study, CTPT method executed with elastic kinesiotape. Even though, the results of kinesiotaping with different methods on shoulder pain are conflicting for both hemiplegic and non-hemiplegic patients,[9,11,12,22-25] the patients in our study had significant

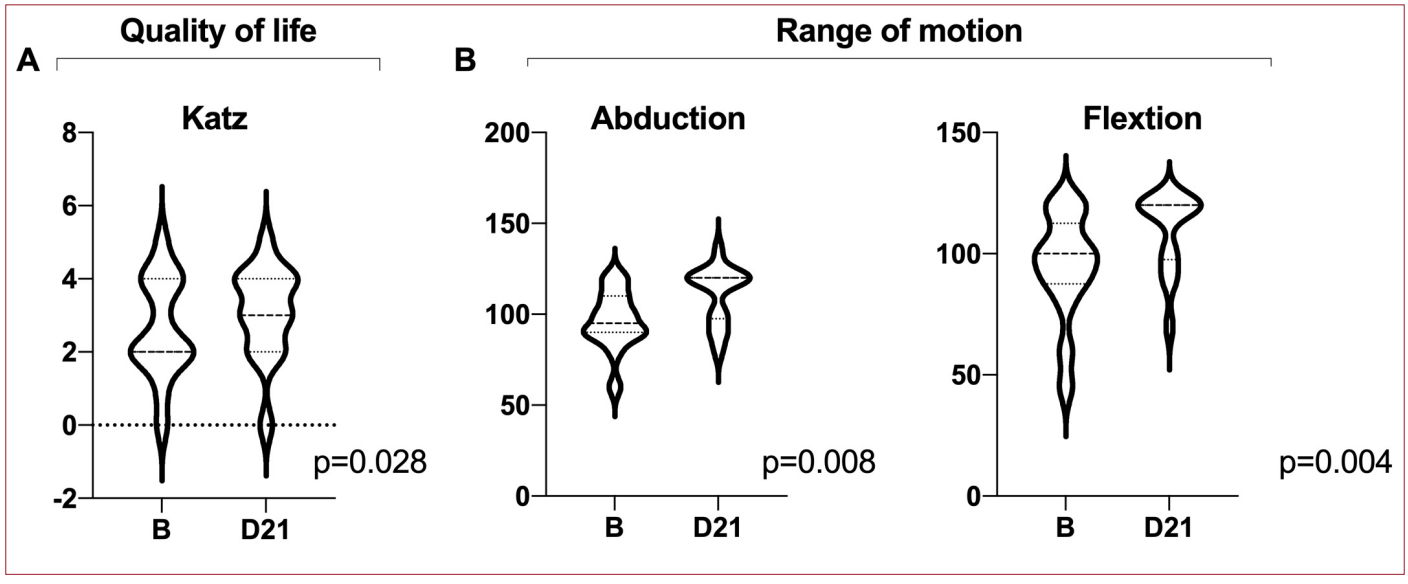

Figure 4. Violin plot of Katz and range of motion. B: Baseline D: Day

reductions in pain scores and significant improvement in pain-free ROM. Although the mechanism of action of kinesiotape is not clear, it is superior to non-stretchable tape in being inexpensive, flexible, easily stretched and applied, and it has been found effective for hemiplegic shoulder pain.[24]

In this study, we evaluated the effects of kinesiotaping on subluxation by physical examination (palpation) and radiography and only found significant improvement by palpation. Since CTPT helps to pull the humeral head upwards and improves stabilization and pain-free ROM, subluxation detected by palpation was expected to be improved. Studies using this method showed palpable reduction in acromiohumeral distance but none of them used radiography to grade the degree of subluxation.[8,13,14] One of our aim in this study was to determine whether radiography would provide the same results as palpation. Other tests of kinesiotaping designed to alleviate hemiplegic shoulder pain used different taping methods that did not pull the humerus upwards and they did not show significant reduction in subluxation using ultrasonography imaging.[9,11]

Chatterjee at al. evaluated active flexion only, while Hayner evaluated active flexion and abduction. They both found significant improvement in shoulder ROM.[13,14] Peters et al. used a similar taping method on a single case and also showed significant improvement in passive abduction and flexion; however, his subject's upper extremity was nonfunctional before and after treatment so active ROM could not be evaluated.[8] To reduce the effect of motor recovery, we chose to evaluate passive abduction and flexion in our study, and significant improvement was seen in passive ROM as well. Kalichman et al. did not measure a positive effect of kinesiotape on active and passive shoulder abduction, but other studies reported benefits from kinesiotaping on passive shoulder ROM.[9,11,12] Investigations of the effect of kinesiotape on shoulder pain in non-hemiplegic patients also showed significant improvement in pain-free shoulder abduction.[22] Our data confirmed that CTPK could improve upper extremity function as evaluated by Brunnstrom motor recovery stage and the Katz index of independence in activities of daily living. Hayner, who developed the CTPT method, assessed daily life activities using the Katz index and found significant improvement as well.[13] Other researchers using different taping methods and different scales such as the Barthel index, the modified Barthel index, the Fugl-Meyer upper extremity motor assessment (FMA) and the shoulder pain and disability index, showed similar results.[8,9,11,14] Kalichman et al. evaluated patients' upper extremity functions with FMA and 'box & blocks', and found no improvement and no change in pain and ROM.[12] In our study, all patients had inpatient neurorehabilitation sessions in addition to kinesiotaping and the improvement in Brunnstrom motor recovery stage and the Katz index of activities may have been positively affected by the physical therapy. However, reduction in hand pain and improvement of passive ROM can lead to improvement in upper extremity function. Because the patients were one-year onset hemiplegic patients, it was deemed unethical to test the effect of kinesiotaping without neurorehabilitation.

One limitation in the design of our study is the lack of a control group; but the quasi-experimental AB method with inclusion of a baseline measurement followed by the intervention for each patient should reduce the statistical unevenness.

CONCLUSIONS

Our application of the CTPK method for hemiplegic patients who have inferior shoulder dislocation had positive effects on pain, shoulder ROM and function. X-ray evaluation of the effects on subluxation was unsuitable compared to the simple physical method of palpation. The CTPK technique is easy to apply, time- and cost-effective, and can be used as a supplementary treatment to a conventional neurorehabilitation program by occupational therapist without radiological evaluation. Further investigations with randomized, placebo-controlled designs are needed to confirm efficacy of the kinesiotaping method..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by local ethic committee of Ankara Physical Therapy and Rehabilitation Training and Research Hospital. This study is registered to clinicaltrials.org (ID: NCT04468750).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Note: This study was presented as poster in INEREM 2015 and National Physical Medicine and Rehabilitation Congress 2015.

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Orjinal Araştırma / Original Article

Differential Diagnosis of Stroke by Platelet Large Cell Ratio (P-LCR) Levels

Trombosit Büyük Hücre Oranı (P-LCR) Düzeylerine Göre İnmenin Ayırıcı Tanısı

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Abstract

Aim: Platelets play an important role in the pathogenesis of thrombosis and atherosclerosis. Platelet Large Cell Ratio (P-LCR), a routine hemogram parameter, is the largest fraction of platelets that are more closely related to thrombotic events. In this study, for the first time in the literature, P-LCR levels in ischemic and hemorrhagic stroke patients were compared with the levels in transient ischemic attack (TIA) group.

Material and Method: Retrospectively, hospital records between January 2016 and 2019, were searched by ICD-10 codes, and patients aged between 18-70 years who were diagnosed as ischemic stroke, hemorrhagic stroke and transient ischemic attack were included. The P-LCR test results in the first hemogram test of the patients taken at the time of admission to the hospital were included and compared.

Results: Of the 4511 patients, 92.6% (n=4177) were diagnosed with ischemic stroke, 6% (n=271) with hemorrhagic stroke, and 1.4% (n=63) of patients with TIA. The P-LCR levels of the ischemic and hemorrhagic stroke patients were found to be significantly higher than the TIA group (p=0.027; p=0.044, respectively). The Area Under the Curve (AUC) values for ischemic, hemorrhagic and total stroke versus TIA patients were 0.581, 0.568, and 0.580; respectively. The cut-off value of P-LCR was 26.65 ng/L between the ischemic stroke and TIA.

Conclusion: The increase in P-LCR levels can be used to distinguish ischemic and hemorrhagic stroke from TIA.

Keywords: Platelet Large Cell Ratio, stroke, ischemic, hemorrhagic, transient ischemic attack

Öz

Amaç: Trombositlerin tromboz ve ateroskleroz patogenezinde önemli rolleri bulunmaktadır. Rutin hemogramda bakılan bir parametre olan trombosit büyük hücre oranı (P-LCR), trombotik olaylarla daha yakından ilişkili olan trombositlerin, en büyük fraksiyonunun ölçümüdür. Bu çalışmada, literatürde ilk kez, iskemik ve hemorajik inme hastalarının P-LCR seviyeleri, geçici iskemik atak (TIA) hastalarının P-LCR seviyeleri ile karşılaştırılmıştır.

Gereç ve Yöntem: Ocak 2016-2019 tarihleri arasındaki hastane kayıtları retrospektif olarak ICD-10 kodlarına göre taranarak, iskemik inme, hemorajik inme ve geçici iskemik atak tanısı konmuş 18-70 yaş arası hastalar çalışmaya dâhil edilmiştir. Bu hastaların hastaneye başvuru anında yapılan ilk hemogram testlerindeki P-LCR sonuçları alınıp karşılaştırılmıştır.

Bulgular: Çalışmaya dâhil edilen 4511 hastanın %92,6'sının (n=4177) iskemik inme, %6'sının (n=271) hemorajik inme ve %1,4'ünün (n=63) TIA tanılı oldukları belirlenmiştir. İskemik ve hemorajik inme hastalarının P-LCR düzeylerinin, TIA grubuna göre istatistiksel olarak anlamlı yüksek oldukları saptanmıştır (sırasıyla p=0,027; p=0,044). İskemik, hemorajik ve total inme hastaları ile TIA hastaları karşılaştırıldığında, eğri altındaki alan (AUC) değerleri sırasıyla 0,581; 0,568 ve 0,580 olarak tespit edilmiştir. İskemik inme ve TIA arasında P-LCR kesme değeri 26,65 ng/L olarak saptanmıştır.

Sonuç: P-LCR seviyelerindeki artış, iskemik ve hemorajik inmeyi TIA'dan ayırt etmek için kullanılabilir.

Anahtar Kelimeler: trombosit büyük hücre oranı, inme, iskemik, hemorajik, geçici iskemik atak

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INTRODUCTION

Stroke is a neurological dysfunction caused by occlusion or rupture of the vascular structure of the central nervous system. As a pathophysiological basis, stroke is divided into two as ischemic and hemorrhagic. Both types of strokes have common risk factors. These risk factors are: hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, asymptomatic carotid stenosis, physical inactivation, smoking and alcohol consumption. Many of the risk factors that can be modifiable are based on atherosclerosis pathogenesis. Early detection or prevention of atherosclerosis risk is important in predicting the predisposing factors of stroke and in monitoring the prognosis.[1]

Platelets play an important role in the pathogenesis of thrombosis and atherosclerosis. Larger platelets have been associated with increased reactivity, increased cardiovascular risk, and higher complication rates after coronary stenting. The elevation of mean platelet volume (MPV) test, which indicates platelet volume increase, was evaluated as an independent risk factor for cardiovascular ischemic events.[2] Although increased platelet volume (MPV) has been found to be associated with platelet activation, and myocardial infarction and stroke[3,4] MPV testing has limitations due to many factors, such as age, sex, blood storage duration and ambient temperature[5] which hampers the routine use of MPV.

The Platelet Large Cell Ratio (P-LCR) test, which is another test in routine hemogram test, is defined as the largest fraction of platelets that are more closely related to thrombotic events. P-LCR levels were found to be significantly higher in patients with dyslipidemia, prone to thromboembolic ischemic events. [6] There are studies in the literature investigating the role of P-LCR in cardiovascular events. In a study investigating the availability of P-LCR testing as a prognostic factor in acute myocardial infarction, it was found to be significantly associated with P-LCR increase and mortality at the time of application.[7,8]

There are no studies in the literature that investigate the role of P-LCR levels in cerebrovascular events. Hemogram test is the most easily accessible test in all health care institutions, including primary care, as it is easy, cheap and quick to produce results. If the hemogram test determines the availability of stroke diagnosis, a fairly easy and fast test will reduce the time required to start treatment of stroke. In this study, for the first time in the literature, the relationship of the P-LCR test with stroke was studied, and its use in the diagnosis and distinction of hemorrhagic-ischemic stroke versus TIA was investigated.

MATERIAL AND METHOD

Ethical approval was taken from Atatürk University, Faculty of Medicine, Clinical Researches of Ethical Committee (Date: 07.11.2019, Decision No: 07/08). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Within the scope of our study, hospital records between January 1, 2016 and January 1, 2019 were searched by ICD-10 codes and patients aged between 18-70 years who were diagnosed as stroke were included in our study. ICD-10 codes of ischemic stroke, hemorrhagic stroke and transient ischemic attack were G45, G46, I60, I61, I62, I64, I65, I66, I67, I68, I69 and their subgroups. Since our study was planned retrospectively, no informed consent was obtained. Patients over 70 years of age were excluded from the study in order not to be affected by hematological abnormalities or problems that increase with age and the patients below 18 years of age or missing P-LCR test results were also excluded from the study in accordance with the exclusion criteria. Flow chart of the study was given in **Figure 1**. Ischemic or hemorrhagic stroke diagnoses were mandatory to be given as the definite diagnosis, since the preliminary diagnoses were neglected.

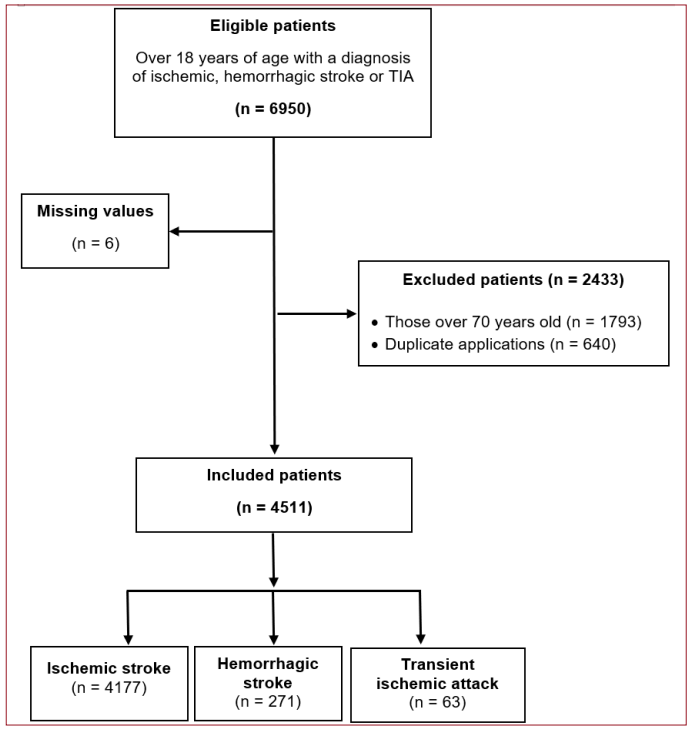

Figure 1. Flow chart of the study

In the study, statistical analyses were performed with SPSS 23.0 (IBM, USA) program. Kolmogorov-Smirnov test was used for the normal distribution assessment. If the groups were normally distributed, the Student–t test and one–way ANOVA test were taken for the analysis of two or more groups respectively. If the normal distribution was not determined, the Mann Whitney U test, and the Kruskal Wallis variance test was taken depend on the number of groups. The correlation analysis uses Pearson's correlation if there is a normal distribution, and Spearman's correlation test if there is no normal distribution. ROC curve analysis was performed to determine the cut-off value of the P-LCR test for stroke. Statistical significance was taken as $p<0.05$ in the whole study.

RESULTS

Of the 4511 stroke patients, 4177 (92.6%) patients with ischemic stroke, 271 (6%) patients with hemorrhagic strokes and 63 (1.4%) patients with TIA were identified. General characteristics of the patients were given in **Table 1**.

The mean age of 4177 patients with ischemic stroke was 45.29±14.62 years; 60.2% were female; and they were hospitalized for 6.8±8.94 days. The mean P-LCR test result of the patients with ischemic stroke was 28.15±7.43 ng/L. Female patients had significantly higher P-LCR test results than men (p<0.001). The Kruskal Wallis test of the P-LCR test according to age was not significant (p=0.088).

The mean age of 271 patients with hemorrhagic stroke was 47.96±15.25 years; the rate of male patients was higher (63.5%) and mean hospital stay was 10.38±12.16 days. The mean P-LCR test result of the patients with hemorrhagic stroke was 27.88±7.82 ng/L. In the analysis of P-LCR according to gender, t–test analysis of female patients showed a statistically significant higher P-LCR value (p =0.04). However, there was no significant difference in age–based analysis (p=0.276).

The mean age of 63 patients with transient ischemic attack (TIA) was 49.78±13.77 years; with the rate of male patients 57.1% and the mean hospital stay was 5.46±7.75 days. The mean P-LCR test result of the patients with TIA was 25.74±6.37 ng/L. In the analysis of P-LCR test by gender, it was higher in female patients, but not statistically significant (p=0.12). Similarly, no statistical difference was found in the analysis by age (p=0.198).

Comparisons of patients with ischemic, hemorrhagic stroke and TIA are given in **Table 2**. Accordingly, when the P-LCR test results of the ischemic stroke patients and the results of the TIA patients were compared, the P-LCR level of the ischemic stroke patients was found to be significantly higher (p=0.027). Spearman's correlation analysis showed a positive correlation between P-LCR and ischemic stroke (r=0.034). A statistically significant difference was found between the ages of patients with ischemic stroke and TIA (p=0.019). Ischemic stroke patients were mostly female, whereas TIA patients were mostly male (r=0.005). The duration of hospitalization in both groups was not significant (p=0.578).

When the P-LCR values of the patients with hemorrhagic stroke and TIA were compared, the P-LCR levels of the hemorrhagic stroke patients were statistically significantly higher (p=0.044). In Pearson correlation analysis, a positive correlation was found (r=0.110). The age and sex distribution of the two groups were not statistically different (p=0.385; p=0.352, respectively). However, the duration of hospitalization was significantly higher in the group with hemorrhagic stroke (p=0.002).

There was no statistically significant difference in the comparison of P-LCR test in patients with ischemic and hemorrhagic stroke (p=0.549). A statistically significant difference was observed between the average ages of two groups (p=0.002). Similarly, a significant difference was found in the duration of hospitalization (p<0.001). Ischemic stroke was more common in females and hemorrhagic stroke was more frequent in males and was statistically significant (p<0.001).

When all patients with ischemic and hemorrhagic strokes were taken as total stroke and P-LCR results of stroke group were compared with TIA, P-LCR values of stroke patients were significantly higher (p=0.029). In Spearman's correlation analysis, P-LCR height and stroke were positively correlated (r=0.033). A statistically significant difference was found between the age and sex of stroke patients and TIA patients (p=0.024 and p=0.011, respectively). There was no significant difference between the duration of hospitalization (p=0.372).

When the Receiver Operating Characteristic (ROC) curve analysis of the P-LCR test was performed, the Area Under the Curve (AUC) values for ischemic stroke vs TIA; hemorrhagic stroke vs TIA; ischemic vs hemorrhagic Stroke; and total stroke vs. TIA were 0,581; 0,568; 0,511 and 0,580; respectively (**Table 3**). The cut-off value between the ischemic stroke and TIA was 26.65 ng/L (p=0.027), and the cut-off value between the total stroke group and TIA was also 26.65 ng/L (p=0.029). Besides, the sensitivity and specificity of the cut-off values were relatively low (54.9 and 54% relatively) However, P-LCR cut-off value between hemorrhagic stroke and TIA and ischemic stroke and hemorrhagic stroke was not statistically significant (p>0.05). The ROC curve analyses are given in **Figure 2**.

Table 1. General features of patients.

	Ischemic Stroke	Hemoragic Stroke	TIA
Patients (n. %)	4177 (92.6%)	271 (6%)	63 (1.4%)
Age (Mean. Std. Dev.)	45.29±14.62	47.96±15.25	49.78±13.77
Sex	60.2% Women	63.5% Men	57.1% Men
Hospital staying (days)	6.8±8.94	10.38±12.16	5.46±7.75
P-LCR (ng/L) (Mean. Std.Dev.)	28.15±7.43	27.88±7.82	25.74±6.38

Table 2. Statistical differences between groups

	Age (p)	Sex (p)	Hospital staying (p)	P-LCR (p)	Correlation
Ischemic Stroke vs. TIA	0.019	0.005	0.578	0.027	r=0.034
Hemorrhagic stroke vs. TIA	0.385	0.352	0.002	0.044	r=0.110
Ischemic vs. Hemorrhagic Stroke	0.002	<0.001	<0.001	0.549	-
Ischemic + Hemorrhagic stroke vs. TIA	0.024	0.011	0.372	0.029	r=0.033

Table 3. ROC analysis and cut off values of P-LCR.

	p	AUC	95% CI	Cut-off (ng/L)	Sens.%	Spec.%
Ischemic Stroke vs. TIA	0.027	0.581	0.513-0.648	26.65	54.9	54
Hemorrhagic stroke vs. TIA	0.090	0.568	0.495-0.642	26.65	54.2	54
Ischemic vs. Hemorrhagic Stroke	0.549	0.511	0.474-0.548	27.55	49.9	49.4
Ischemic + Hemorrhagic stroke vs. TIA	0.029	0.580	0.513-0.647	26.65	54.9	54

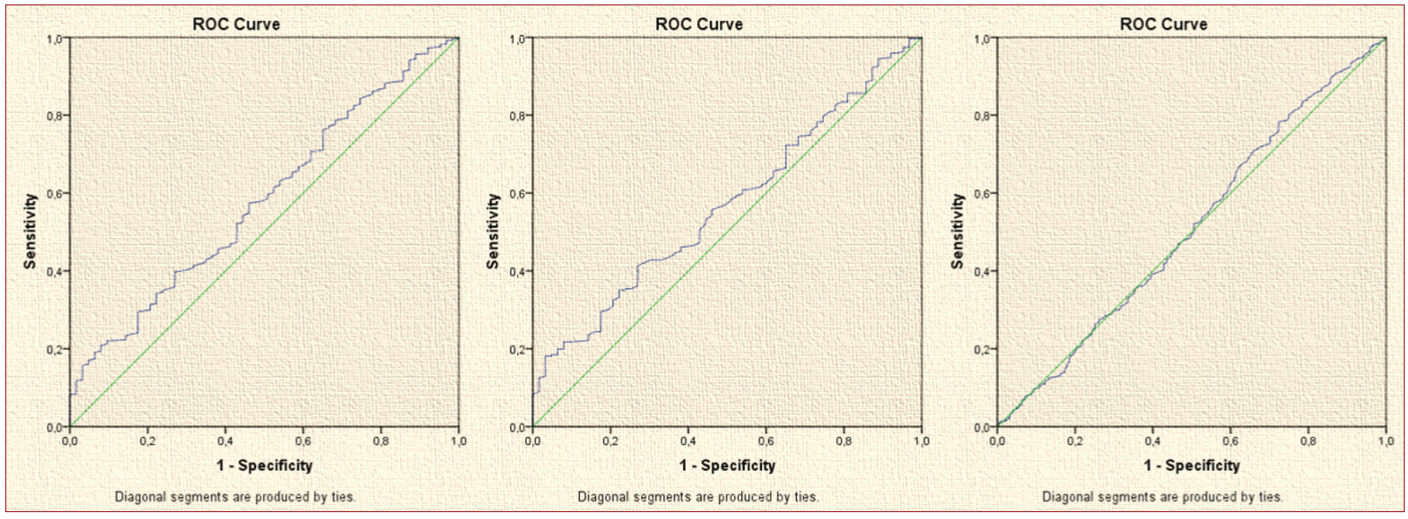

Figure 2. ROC curve graphics of (1) Ischemic stroke versus TIA; (2) Hemorrhagic stroke versus TIA; (3) Ischemic versus hemorrhagic stroke, respectively

DISCUSSION

In this study, for the first time in the literature, P-LCR test results of ischemic and hemorrhagic stroke patients and P-LCR test results of TIA patients were statistically compared. In our study, the effectiveness of P-LCR test in the diagnosis of ischemic and hemorrhagic stroke and differential diagnosis of ischemic-hemorrhagic stroke was investigated. As one of the parameters of the P-LCR test on the hemogram, easy, inexpensive, fast and feasibility can be an important advantage.

As a result of our study, it was found that P-LCR values of both ischemic and hemorrhagic stroke patients were statistically higher than TIA patients. It was determined that P-LCR test correlated positively but weakly with stroke. According to ROC analysis, P-LCR had a cut-off value of 26.65 ng/L. Thus, it was concluded that the height of the P-LCR test is an indicator that can support the diagnosis of stroke. This is the case with stroke patients who have to make quick diagnosis and referral, with only a simple hemogram test, easy and fast diagnosis will be obtained.

In the study, the P-LCR test in the differentiation of ischemic-hemorrhagic stroke was not found to be statistically significant. This suggests that the P-LCR value cannot be used as an indicator for the differential diagnosis of ischemic-hemorrhagic stroke.

Male gender and advanced age in stroke are considered as unmodifiable risk factors.[1] Due to the protective effect of estrogen, stroke is less common in premanopausal women, whereas, this ratio increases in postmenopausal and older ages, and the rate of stroke increases in females since they live longer.[9,10] However, studies show that female stroke rates are higher than men at all ages.[11] In our study, although the stroke patients older than 70 years were excluded, 58.8% of the ischemic and hemorrhagic stroke patients were female, which is similar to the literature. The mean age of stroke patients was 45.5 years in the study, which is a non-reflective result due to the absence of stroke patients over 70 years of age. Likewise, the reason for the higher incidence of ischemic stroke in our study (92.6%) than in the literature is that stroke patients older than 70 years of age were not included in the study.

In the literature, the relationship between P-LCR elevation and atherosclerotic vascular diseases has been mostly investigated in coronary artery diseases, and different opposite results were obtained in these studies. In a study performed by Khandekar et al. in acute myocardial infarction, unstable angina and stable angina groups, they found that P-LCR value was significantly higher in these patients.[12] Cerit et al. compared the platelet parameters with the coronary tortuosity associated myocardial ischemia and found that the P-LCR test of these patients was significantly higher than the control group.[13]

In another study investigating the relationship between coronary artery disease and P-LCR levels, it was found that there was no association between P-LCR levels, and P-LCR elevation could not be used as a marker for coronary events.[14] Yet again, in a study investigating the relationship between periprocedural myocardial infarction and P-LCR, no association with elevated P-LCR levels was found.[15] The remarkable point of this study was that, P-LCR elevation was found to be associated with a previous cerebrovascular event. However, according to our research, there are no studies investigating the relationship between P-LCR and stroke in the literature. In our study, for the first time in the literature, patients with the diagnosis of acute ischemic and hemorrhagic strokes were found to have elevated P-LCR at the time of first admission, and a conclusion that the P-LCR test was a diagnostic indicator in stroke.

Limitations: As a limitation of our study, due to the fact that it was a retrospective study, no history of drug use affecting platelet parameters of patients could be questioned. Also, in our study, patients aged between 18-70 years were screened and it was aimed to ignore the false results of P-LCR test due to the more frequent occurrence of hematological diseases

over 70 years of age. However, as a retrospective study, it is not known and could not be questioned whether patients included in the study have any hematological diseases or using any drugs affecting P-LCR test, which is as another limitation of our study.

CONCLUSION

The P-LCR test, which is one of the parameters measured in the hemogram test, was significantly higher in patients with ischemic and hemorrhagic stroke compared to TIA patients and the cut-off value of P-LCR was found to be 26.65 ng/L. This shows that the P-LCR test can be used as an indicator for stroke diagnosis. P-LCR test is fast, easy, inexpensive and accessible, and further studies are needed to prove its diagnostic effectiveness in stroke and even evaluate it among stroke risk factors.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval was taken from Atatürk University, Faculty of Medicine, Clinical Researches of Ethical Committee (Date: 07.11.2019, Decision No: 07/08).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

Evaluation of The Frequency and Types of Structural Heart Disease in Fetuses of Pregnant Women According to Risk Groups by Fetal Echocardiography

Gebelerin Risk Gruplarına Göre Fetüslerindeki Yapısal Kalp Hastalığı Sıklığı ve Tiplerinin Fetal Ekokardiyografi Tetkiki ile Değerlendirilmesi

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Abstract

Aim: The aim of this study is to evaluate the frequency of congenital heart diseases (CHD) encountered in low-risk and high-risk pregnant women by fetal echocardiographic (FE) examination.

Material and Method: The records of 855 pregnant women with a gestational week greater than 16 who applied to the pediatric cardiology outpatient clinic of our hospital between July 2019-October 2021 and underwent FE were analyzed retrospectively.

Results: CHD was detected in 109 (12.7%) of 855 pregnant women who were referred to our center and underwent FE examination. Frequency of CHD was given according to risk groups. The rate of CHD in patients in the high-risk group was 15.2%, while it was 9% in patients in the low-risk group (p=0.008). Significant CHD was 6.2% in the high-risk group versus 2.7% in the low-risk group (p=0.016). The most common structural cardiac anomaly in FE examination was ventricular septal defect (38.5% in 42 fetuses), and the second most common cardiac anomaly was atriyoventricular septal defect (18.3% in 20 fetuses).

Conclusion: We found a higher rate of CHD in pregnant women in the high-risk group than in the low-risk group and especially significant CHD was more common in pregnant women in the high-risk group. Therefore, we strongly recommend performing FE examination, especially in high-risk pregnant women.

Keywords: Fetal echocardiography, congenital heart defect, fetuses

Öz

Amaç: Bu çalışmanın amacı düşük riskli ve yüksek riskli gebelerde karşılaşılan konjenital kalp hastalıkları (KKH) sıklığının fetal ekokardiyografi (FE) tetkiki ile araştırılmasıdır.

Gereç ve Yöntem: Temmuz 2019-Ekim 2021 tarihleri arasında hastanemiz çocuk kardiyoloji polikliniğine başvuran ve FE uygulanan gestasyonel haftası 16 dan büyük 855 gebenin kayıtları geriye dönük olarak incelendi.

Bulgular: Çalışma yaptığımız merkezimize yönlendirilerek FE incelemesi yapılan 855 gebenin 109'unda (%12,7) KKH saptandı. KKH sıklığı risk gruplarına göre verildi. Başvuru nedenlerine göre yüksek riskli grupta yer alan hastalarda DKH nın oranı %15,2 iken düşük riskli gruptaki hastalarda %9 olarak tespit edildi (p=0,008). Önemli DKH yüksek riskli grupta %6,2 iken düşük riskli grupta %2,7 idi (p=0,016). Fetal ekokardiyografi incelemesinde en sık rastlanan kardiyak anomali ventriküler septal defekt (42 fetusta %38,5) ve ikinci sıklıkta tespit ettiğimiz kardiyak anomali ise atriyoventriküler septal defekt idi (20 fetusta %18,3).

Sonuç: Yüksek risk grubundaki gebelerde düşük risk grubundakilere göre daha yüksek oranda KKH saptadık ve özellikle önemli düzeydeki KKH yüksek risk grubundaki gebelerde daha sık oranda mevcuttu. Bu nedenle özellikle yüksek riskli gebelerde FE incelemesi yapılmasını şiddetle tavsiye ediyoruz.

Anahtar Kelimeler: Fetal ekokardiyografi, konjenital kalp defekti, fetüs

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INTRODUCTION

Examination of the fetal heart and cardiovascular system has improved significantly in the last 25-30 years as a result of technological development in imaging systems.[1] Thanks to fetal echocardiography (FE), congenital heart diseases (CHD) can be detected in the prenatal period and possible mortality and morbidity can be prevented by giving birth in an appopriate medical center where it can be intervened. In addition fetal arrhythmias can be diagnosed in FE and medical treatment can be performed in the antenatal period.

The incidence of congenital heart diseases (CHD) has been reported to be 6-12 per 1000 live births.[2,3] It is known that the incidence of CHD increases due to various maternal, hereditary and fetal reasons. Pregnancies can be divided into high-risk and low-risk in terms of CHD risk, according to the application indications for FE. Accordingly, those with an indication for absolute FE (estimated CHD risk >2%) are classified as high risk and those with an estimated CHD rate <2% are classified as low risk (**Table 1**).[1]

Table 1. Common Indications for Referral for Fetal Echocardiogram[1]

Indications with higher risk profile (estimated >2% absolute risk)
Maternal pregestational diabetes mellitus
Diabetes mellitus diagnosed in the first trimester
Maternal phenylketonuria (uncontrolled)
Maternal autoantibodies (SSA/SSB+)
Maternal medications
ACE inhibitors, Retinoic acid, NSAIDs in third trimester
Maternal first trimester rubella infection
Maternal infection with suspicion of fetal myocarditis
Assisted reproduction technology
CHD in first degree relative of fetus (maternal, paternal or sibling with CHD)
First or second degree relative with disorder with Mendelian inheritance with CHD association
Fetal cardiac abnormality suspected on obstetrical ultrasound
Fetal extracardiac abnormality suspected on obstetrical ultrasound
Fetal karyotype abnormality
Fetal tachycardia or bradycardia, or frequent or persistent irregular heart rhythm
Fetal increased NT >95% (≥3 mm)
Monochorionic twinning
Fetal hydrops or effusions
Indications with lower risk profile (estimated >1% but <2% absolute risk)
Maternal medications
Anticonvulsants, Lithium, Vitamin A, SSRIs (only paroxetine), NSAIDs in first/second trimester
CHD in second degree relative of fetus
Fetal abnormality of the umbilical cord or placenta
Fetal intra-abdominal venous anomaly
Not indicated (≤1% risk)
Maternal gestational diabetes mellitus with HbA1c <6%
Maternal medications
SSRIs (other than paroxetine), Vitamin K agonists (Coumadin), although fetal survey is recommended
Maternal infection other than rubella with seroconversion only
Isolated CHD in a relative other than first or second degree

ACE, angiotensin-converting enzyme; CHD, congenital heart disease; HbA1c, hemoglobin A1c; NSAID, nonsteroidal anti-inflammatory drug; NT, nuchal translucency; SSRI, selective serotonin reuptake inhibitor.

In our study, we aimed to investigation of the frequency of congenital heart diseases (CHD) encountered in low-risk and high-risk pregnant women by fetal echocardiography (FE) examination.

MATERIAL METHOD

Ethics committee approval was obtained from Ministry of Health and the local Ethics Committee (Decision No: 2021-10/13). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The records of 855 pregnant women with a gestational week greater than 16 who applied to the pediatric cardiology outpatient clinic of our hospital between July 2019 and October 2021 and underwent FE were analyzed retrospectively. Pregnant women were referred by the obstetricians and radiology specialists in our hospital and surrounding hospitals for FE examination for various reasons, such as suspicion of CHD in obstetric ultrasonography or inability to clearly see the fetal heart. Echocardiography measurements of the patients were performed by the same pediatric cardiologist using Vivid S60N (GE Gingmed Ultrasound AS Strandpromenaden 45, 3191 Horten, NORWAY) device and 1.5-6 MHz C 1-6 D Convex probe. Two-dimensional imaging was performed for four-chamber, five-chamber, three vessels, ductal arch, aortic arch positions, short and long axis views of great vessels. In accordance with the segmental approach; systemic and pulmonary venous connections; atrium and ventricular morphology (including the ratio of both atrium and ventricular cavities, wall thicknesses of the ventricles, anatomy of the atrial and ventricular septum); atrioventricular and semilunar valve morphology and size; The origin, size and positional relationships of the aorta and pulmonary artery; and the aortic and ductal arches were examined. AV valves, aortic and pulmonary valves, ductal and aortic arch velocities were recorded by pulsed Doppler examination. Cardiac rhythm was examined using two-dimensional, M-mode and pulsed Doppler methods. All echocardiographic examinations were performed according to the 2014 American Heart Association guidelines.[1]

Pregnant women with a CHD risk above 2% in the AHA guideline were in the high-risk group, while pregnant women with a CHD risk below 2% were classified as low-risk (**Table 1**).[1]

Structural cardiac anomalies detected in FE were divided into three groups according to the classification created by Wren et al and Hunter et al. (**Table 2**).[2,4]

In our study, the results of pregnant women in whom we detected fetal arrhythmia or who had covid 19 infection were also included.

Table 2. Current classification system in pediatric cardiology for structural heart diseases.[2,4]

Complex (absent or hypoplastic chamber or valve, or common valve)	includes complete atrioventricular septal defect, hypoplastic left heart syndrome, pulmonary atresia, tricuspid atresia, truncus arteriosus, double inlet left ventricle, mitral atresia, aortic atresia, congenital corrected transposition of the great arteries
Significant (congenital heart disease requiring operation or intervention, but not included in the complex group)	includes aorto-pulmonary window, critical aortic stenosis, partial atrioventricular septal defect, coarctation, ventricular septal defect (requiring operation), transposition of the great arteries, tetralogy of Fallot, total anomalous pulmonary venous connection (excludes persistent arterial duct and atrial septal defect)
Minor (no intervention- four chambers and four valves)	includes mainly small ventricular septal defect, less severe aortic stenosis, and pulmonary stenosis

Statistical Analysis

Statistical analysis of the study was performed using the Statistical Package for the Social Sciences (SPSS) for Windows version 20.0 package program. The expression n (%) was used for categorical variables, and for continuous variables, the mean±SD (standard deviation) values were used if they were compatible with the normal distribution. If they do not, the median (lower-upper limit) was used. Descriptive analysis was used in the analysis of the distribution and frequency of the data, and Chi-Square test was used in comparing two independent groups in frequency data. Mann-Whitney U test was used to compare two independent groups that were not normally distributed. Staticial signifance was inferred at $p<0.05$.

RESULTS

The mean age of the pregnant women was 29.1±4.8 years and the mean week of gestation was 25.2±5.7 weeks. FE examination was performed 1090 times in 855 pregnant women who applied to our outpatient clinic (620 pregnant women once and 235 pregnant women twice). While 137 of the pregnants applied to our polyclinic voluntarily, 718 pregnants were consulted by obstetricians and radiology specialists (**Table 3**).

Table 3. Demographic findings of pregnant women

Age (Year) Mean±SD	29.1±4.8
Pregnancy week (Week) Mean±SD	25.2±5.7
Number of pregnant women who applied voluntarily (n/N; %)	137/855; 16%
Number of pregnant women consulted by obstetricians and radiology specialists (n/N; %)	718/855; 84%
Number of high-risk pregnancies (n/N; %)	520/855; 61%
Number of low-risk pregnancies (n/N; %)	335/855; 39%

Fetal echocardiography examination was repeated in 235 pregnant women with unclear images (due to maternal obesity or fetal position mismatch), complex and significant heart disease or arrhythmia.

Four patients with hypoplastic left heart syndrome (HLHS) and one tricuspid atresia underwent medical abortion; Except for the aborted fetuses, the findings in other infants with CHD detected in FE were confirmed by postnatal transthoracic echocardiography. In the postnatal transthoracic echocardiography examination of three fetuses with small ventricular septal defect (VSD) in FE examination, it was observed that VSD disappeared. All other CHD detected in FE examination were also present in postnatal transthoracic echocardiography examination. Postnatal transthoracic echovardiography was performed in many babies who did not have CHD in FE examination, and CHD was not detected in any of them.

According to FE indications,[1] in high-risk pregnant women; Pregestational diabetes (4.1%) was the most common maternal indication, CHD in parents and siblings (13.9%) was the most common hereditary reason, and fetal cardiac anomaly suspected in obstetric ultrasonography (24%) was the most common fetal reason. In the low-risk group, advanced maternal age (15.4%) and inability to clearly evaluate the fetal heart in obstetric ultrasonography (11.5%) were the most common reasons for admission. In the high-risk group, the highest rate of CHD was detected in 9 (50%) of 18 fetuses with fetal karyotype anomaly (7 of 10 fetuses with Down syndrome [5 AVSD, 1 VSD, 1 tetralogy of Fallot], two of four fetuses with DiGeorge syndrome [2 truncus arteriosus]) and in 47 (22.9%) of 205 fetuses with suspected fetal cardiac anomaly in obstetric ultrasonography. In the low-risk group, CHD was detected in 5 (12.8%) of 39 fetuses with anomaly in the umbilical cord or placenta, and in one (12.5%) of 8 pregnant women who used anticonvulsants, SSRI and NSAI in the first trimester (**Table 4**).

CHD was detected in 109 (12.7%) of 855 pregnant women who underwent FE. The rate of CHD in patients in the high-risk group was 15.2%, while it was 9% in patients in the low-risk group (0.008). Significant CHD was 6.2% in the high-risk group versus 2.7% in the low-risk group (0.016). There was no statistical difference between the two groups in terms of the incidence of complex and minor CHD (**Table 5**).

The most common structural cardiac anomaly in FE examination was VSD (42 of 109 fetuses with CHD; 38.5%), the second most common cardiac anomaly was AVSD (20 of 109 fetuses with CHD; 18.3%). Complex cardiac anomalies were found in 43 (30.5%) of 109 fetuses with CHD, significant cardiac anomalies in 41 fetuses (37.6%) and minor cardiac anomalies in 25 fetuses (22.9%) (**Table 6**).

Table 4. Distribution of structural cardiac heart disease ratios in high-risk and low-risk pregnancies[1]

High-risk group	n	CHD n (%)
Maternal indications		
Maternal pregestational diabetes mellitus	35	2 (5.7)
Diabetes mellitus diagnosed in the first trimester	3	0 (0)
Maternal phenylketonuria (uncontroled)	2	0 (0)
Maternal autoantibodies (SS-A ve SS-B)	2	0 (0)
ACE inhibitors-Retinoic acid and NSAIDs in third trimester	18	1 (5.6)
Maternal first trimester rubella infection	1	0 (0)
Maternal infection with suspicion of fetal myocarditis	12	0 (0)
Assisted reproduction technology	14	0 (0)
Familial indications		
CHD in first degree relative of fetus (maternal, paternal or sibling with CHD)	119	10 (8.4)
First or second degree relative with disorder with Mendelian inheritance with CHD association	4	0 (0)
Fetal indications		
Fetal cardiac abnormality suspected on obstetrical ultrasound	205	47 (22.9)
Fetal extracardiac abnormality suspected on obstetrical ultrasound	35	6 (17.1)
Fetal tachycardia or bradycardia, or frequent or persistent irregular heart rhythm	20	1 (5)
Fetal karyotype abnormality	18	9 (50)
Fetal increased NT >95% (≥3 mm)	6	2 (33)
Monochorionic twinning	2	0 (0)
Fetal hydrops or effusions	24	2 (8.3)
Total (High-risk group)	**520**	**79 (15.2)**
Low-risk group		
Maternal use of anticonvulsants, SSRIs (only paroksetin) and NSAIs in the first trimester	8	1 (12.5)
CHD in second degree relative of fetus	27	2 (7.1)
Fetal abnormality of the umbilical cord or placenta	39	5 (12.8)
Maternal infection other than rubella with seroconversion only	15	1 (6.7)
Failure to clearly evaluate the fetal heart in obstetric ultrasonography	98	8 (8.2)
Maternal age > 35 years	132	12 (9.1)
Multiple pregnancies other than monochorionic twinning	16	1 (6.3)
Total (Low-risk group)	**335**	**30 (9)**
Total (High-risk and low-risk group)	**855**	**109 (12.7)**

CHD, congenital heart disease; SS-A, anti–Sjögren's syndrome-related antigen A; SS-B, anti-Sjögren's syndrome type B; ACE, angiotensin-converting enzyme; NSAID, nonsteroidal anti- inflammatory drug.

Table 5. Distribution of structural cardiac heart disease types in high-risk and low-risk pregnancies.

	High-risk n/n (%)	Low-risk n/n (%)	Total n/n (%)	p
Complex	31/520 (6)	12/335 (3.6)	43/855 (5)	0.091
Significant	32/520 (6.2)	9/335 (2.7)	41/855 (5)	0.016
Minor	16/520 (3)	9/335 (2.7)	25/855 (2.9)	0.625
Total CHD	79/520 (15.2)	30/335 (9)	109/855 (12.7)	0.008

CHD, congenital heart disease,

Intracardiac echogenic focus was present in 158 (18.5%) of 855 pregnants who underwent FE examination, and the majority (80.4% in 127 pregnants) comprised the echogenic focus within the left ventricle. While intracardiac focus was detected in 101 (19.4%) of 520 high-risk pregnant women, intracardiac echogenic focus was found in 57 (17%) of 335 low-risk pregnants (p=0.387). CHD was detected in 21 (13.3%) of 158 fetuses with intracardiac echogenicity, and 88 (12.6%) of 607 fetuses without intracardiac echogenicity were found (p=0.826). CHD was found in 15 (14.9%) of 101 fetuses in the high-risk group with intracardiac echogenicity, and in 6 (10.5%) of 57 fetuses in the low-risk group with intracardiac echogenicity (p=0.442).

We did not detect CHD in any of the 12 pregnant women who had covid 19 infection. Two had mild sinüs tachycardia. There was no any cardiac problem in the postpartum controls.

Table 6. Distribution of structural heart diseases detected as a result of fetal echocardiography

CHD	n	%
Complex		
AVSD	20	18.3
HLHS	7	6.5
Truncus arteriozus	6	5.5
Tricuspid atresia	5	4.6
DORV + TGA	2	1.8
Ebstein abnomality	1	0.9
DILV	1	0.9
TAPVR	1	0.9
Total (Complex)	43	39.5
Significant		
Large VSD (requiring operation)	20	18.3
TGA	6	5.5
Critical PS	5	4.6
Tetralogy of Fallot	5	4.6
Coarctation of aorta	3	2.8
Critical AS	1	0.9
DORV	1	0.9
Total (Significant)	41	37.6
Minor		
Small VSD	22	20.2
Less severe PS	2	1.8
Less severe AS	1	0.9
Total (Minor)	25	22.9
Total CHD (Complex + Significant + Minör)	109	100

CHD, congenital heart disease; AVSD, atrioventricular septal defect; HLHS, hypoplastic left heart syndrome; DORV, double outlet right ventricle; TGA, transposition of great arteries; DILV, double inlet left ventricle; TAPVR, total anomalous pulmonary venous connection; VSD, ventricular septal defect; PS, pulmonary stenosis; AS, aortic stenosis,

Cardiac arrhythmia was detected in 20 fetuses. Fetal supraventricular tachycardia (SVT) was found in 12 fetuses, premature atrial and ventricular beats were found in 4 fetuses, and sinus tachycardia and sinus bradycardia were found in two fetuses each.

DISCUSSION

Most of the newborns with CHD can be detected with a high accuracy in the prenatal period by FE.[5,6] Therefore, it is very important which pregnant women need FE examination. Tegnander et al.[3] found CHD with a rate of 14.6% in the prenatal and postnatal period in their study consisting of 29460 fetuses. In various studies on FE in the literature, fetal CHD is present at different rates such as 4.9%, 11.1%, 2.7% and 1.9%.[6-9] In studies conducted in our country, it was reported that CHD was found at rates such as 13.1%, 5.6%, 9.4%, 13.3% and 7% as a result of fetal echocardiography.[10-14] In our study, we found the rate of CHD as 12.7% in 855 fetuses. Since the rates of consanguineous marriages differ between countries, the incidence of genetically inherited heart diseases may vary. Indications can be chosen differently when referring pregnant women to FE. Finally, the knowledge and skills of obstetricians and radiology specialists who send patients for FE examination as a result of obstetric ultrasonography examination may be different. For all these reasons, we think that the rates of CHD detected in FE may have been reported differently.

There are quite different publications regarding the incidence of CHD in high and low risk pregnant women who underwent FE. Hallıoğlu et al.[10] reported a rate of 13.3% (complex CHD 5.1%, significant CHD 2.3% and minor CHD 5.9%) in the high-risk group and 16.3% (complex CHD 6.1%, significant CHD 2.8%, and minor CHD 7.4%) in the low-risk group. Özbarlas et al.[11] reported a rate of 7.8% (complex CHD 4.1%, significant CHD 2.3%, and minor CHD 1.4%) in the high-risk group and 2.7% (complex CHD 0.6%, significant CHD 0.8%, and minor CHD 1.3%) in the low-risk group. In most of the generally reported publications, the most common CHD detected in FE was reported as VSD and AVSD.[7,10,11,13,15,16] In our study, we also had a statistically significantly higher rate of CHD in the high-risk group (15.2%) than in the low-risk group (9%). Likewise, we found that the rate of complex CHD (6%) and significant CHD (6.2%) in the high-risk group were statistically significantly higher than the rate of complex CHD (3.6%) and significant CHD (2.7%) in the low-risk group. The most common CHD detected was VSD with a rate of 38.5% and AVSD with a rate of 18.3%.

If fetal chromosome testing reveals a genetic mutation, deletion, trisomy or aneuploidy, the risk of congenital anomalies is generally high and FE should be performed in addition to detailed obstetric ultrasonography examination. Likewise, increased nuchal thickness also increases the risk, especially in terms of Down syndrome.[17] In our study, half of 18 fetuses with fetal karyotype anomaly had CHD. Of the fetuses with karyotype anomaly, 10 had Down syndrome and four had DiGoerge syndrome. CHD was detected in 7 of 10 fetuses with Down syndrome (5 AVSD, 1 VSD, 1 tetralogy of Fallot). Truncus arteriosus was detected in half of four fetuses with DiGeorge syndrome. CHD was detected in 2 of 6 patients whose nuchal translucency was above the 95% percentile (both were AVSD and prenatal diagnosis could not be made because the family did not allow amniocentesis, but they were found to have Down syndrome after birth).

In the presence of extracardiac anomaly in obstetric ultrasonography examination, CHD has been reported with a rate of 20-45% depending on the type of malformation and the gestational week at which FE examination was performed.[18,19] In our study, we found CHD in 6 (17.1%) of 35 patients with extracardiac anomalies (two each, central nervous system, gastrointestinal system and musculoskeletal system anomalies). Interestingly, five of the six patients had complex CHD and one had significant CHD. This shows us that in the presence of extracardiac malformation, accompanying cardiac anomalies can be severe; and in this respect, it is necessary to be more careful in terms of CHD in pregnancies with extracardiac anomaly and FE echocardiography should be performed.

There are different reports in the literature regarding CHD rates detected as a result of FE performed due to suspected cardiac anomaly in obstetric ultrasonography (48.7%, 27.7%, 32%, 16% and 68%).[8,10,11,20,21] In our study, we detected 22.9% CHD in 45 out of 205 fetuses, who were suspected of fetal cardiac anomaly in the obstetric ultrasonography examination and performed FE examination. Intracardiac focus was present in 189 (70%) of the remaining fetuses and therefore they were consulted. We can attribute the great difference in this regard to the fact that the knowledge and skills of the obstetricians and radiologists who perform the obstetric ultrasonography examination and the pediatric cardiologists who perform the FE examination may differ. In addition, another reason may be the different levels of accessibility of centers that can perform FE.

CHD was detected in 8 (8.2%) of 98 fetuses who were consulted to our outpatient clinic because the fetal heart could not be seen clearly in obstetric ultrasonography. One of them was complex and important cardiac anomalies such as tricuspid atresia and the other tetralogy of Fallot. Therefore, if the fetal heart cannot be seen clearly on obstetric ultrasonography, consultation from a fetal echocardiography specialist should be sought. By providing continuous training to all obstetricians and radiology specialists who perform obstetric ultrasonography examination, on how to evaluate the fetal heart, it will be possible to diagnose babies with CHD more frequently in the prenatal period.

CHD in the mother, father or siblings may increase the likelihood of CHD in the next pregnancy. CHD is seen at 2-3% in the baby to be born when the father has CHD, 2-6% when the siblings have CHD.[22] The risk of recurrence of nonsyndromic, nonchromosomal CHD is >2 times as high if the mother is affected versus the father or a sibling.[22,23] In our study, we

found CHD in four (5.7%) of 70 fetuses with siblings with CHD, in one (5.3%) of 19 fetuses with fathers with CHD, and in five (16.6%) of 30 fetuses with CHD in their mothers.

Advanced maternal age (>= 35 years) is accepted in the low-risk group for CHD.[3] Best et al.[24] reported the rate of CHD in advanced age pregnancies as 0.99% and Özbarlas et al. (0%). [11] as a result of FE. Pierpoint et al.[25] found in their studies that chromosomal disorders was increased in pregnancies at advanced ages and the probability of CHD was high in pregnancies with chromosomal disorders. In our study, 12 (9.1%) of the fetuses of 132 pregnant women over 35 years of age had CHD. Seven of these patients had Down syndrome. These data show us that the risk of chromosomal disorders such as Down syndrome, increases in advanced age pregnancies, and therefore, caution should be taken in terms of CHD.

Today, Covid 19 infection is seen as a pandemic all over the world. It is very severe in pregnant women and can cause problems in the cardiovascular system as in many systems. Myocarditis is also a complication seen in Covid 19 infection. [26] There are a few published cases of COVID-19 occurring during pregnancy and due the possibility of mother-fetal vertical transmission. In our study, we performed FE examination to 12 pregnant women with Covid 19 infection; two of them had mild sinus tachycardia and none of them had decreased systolic functions, insufficiency of atrioventricular and semilunar valves, pericardial fluid and CHD. All of the pregnancies resulted in live births and there was no problem that required hospitalization afterwards.

In our study, we found a similar rate of intracardiac echogenic focus in high-risk and low-risk groups; we found no difference in the frequency of CHD between those with and without an intracardiac echogenic focus. In addition, we did not detect any difference in the frequency of CHD in high-risk or low-risk groups with an intracardiac focus.

Fetal arrhythmia may develop due to ischemia, inflammation, electrolyte disturbances, stress, structural cardiac anomalies and gene mutations, and these patients present as fetal tachycardia, bradycardia or arrhythmia in obstetric examination.[27] Fetal arrhythmias are found in 2% of normal pregnancies and can be detected up to 16.6% in high-risk pregnancies.[28,29] Antiarrhythmic drugs such as digoxin, sotalol, and flecainide are administered alone or in combination to pregnant women with fetal supraventricular tachycardia. [30] In our study, fetal arrhythmia was present in 20 (2.3%) of 855 pregnant women with a mean gestational week of 36 (min 33- max 39). While 12 (2.3%) of 520 high-risk pregnants had fetal arrhytmia, 8 of (2.4%) of 335 low-risk pregnants had fetal arrhythmia. We gave medical treatment to 12 pregnant women who were found to have fetal SVT. Eight pregnant women were given digoxin and one pregnant woman sotalol. Three pregnant women whose tachycardia did not improve with single treatment were given digoxin + sotalol treatment. Ten of the patients recovered during the antenatal period and two continued to receive postnatal treatment.

CONCLUSION

We performed FE examination on pregnant women who were colsulted with various indications. As a result we found a higher rate of CHD in pregnant women in the high-risk group than in the low-risk group and especially significant CHD was more common in pregnant women in the high-risk group. Therefore, we strongly recommend performing FE examination, especially in high-risk pregnant women.

The most important limitation of our study was that autopsy could not be performed due to the fact that families did not allow medical abortion due to their socio-cultural structure. In addition, the number of our cases was insufficient for epidemiological data. Therefore, multicenter studies with higher numbers of cases will enable the prediction of high and low risk pregnancies in terms of CHD.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was obtained from Ministry of Health and the local Ethics Committee (Decision No: 2021-10/13).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

Evaluation of The Relationship between the Mastoid Process and Some Anthropometric Points on the Skull with Computed Tomography

Processus Mastoideus ile Kafatasında Bulunan Bazı Antropometrik Noktalar Arasındaki İlişkinin Bilgisayarlı Tomografi ile Değerlendirilmesi

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Abstract

Aim: Facial reconstruction is a method that estimates the face shape of the unidentified person using clay and similar material in cases where only the skull is present. Due to natural events and animals, the integrity of the skeletal remains can be disrupted and this makes identification hard. The aim of the study is to estimate the skull shape by reference to the mastoid process in case of fragmentation of the skull at the scene.

Material and Methods: In the study, computerized tomography images of a total of 96 adult individuals of 51 females and 45 males which were obtained from Bursa Uludag University Faculty of Medicine, Department of Radiology, were used. The variables determined in the images taken in the Frankfurt Horizontal plan were measured using the Image J program. Statistics of the data obtained were carried out using SPSS 22.0 program.

Results: The descriptive values of the variables were given. While it was seen that linear distances differed between males and females, it was seen that angular variables did not show a gender difference. Regression formulas were developed to predict missing parts and the formulas which have the highest accurate percentage is for males; M5=-2.945 + (0.548xM4) + (0.404xM6) and for females M5= -7.457 + (0.409xM4) + (0.619xM6).

Conclusion: In this study, we tried to evaluate the facial reconstruction from a different point of view. We have developed regression formulas with high reliability, taking into account the correlation coefficients between deciduous variables. We believe that all this data will benefit especially forensic anthropologists. In addition, we think that the fact that the angular values did not show a gender difference can be accepted as an indicator from a different perspective that the face develops at a certain rate of development.

Keywords: Skull, regression, temporal bone, mastoid process, facial reconstruction

Öz

Amaç: Yeniden yüzlendirme, yalnızca kafatasının var olduğu durumlarda kil ve benzeri materyal ile kimliklendirilmesi yapılamayan kişinin yüz şeklinin tahmin edildiği bir yöntemdir. Doğa olayları ve hayvanlar nedeniyle iskelet kalıntılarının bütünlüğü bozulabilmektedir bu da kimliklendirmeyi zor hale getirmektedir. Çalışmanın amacı, kafatasının olay yerinde fragmente olması durumunda, processus mastoideus referans alınarak kafatası şeklinin tahmin edilmesidir.

Gereç ve Yöntem: Çalışma, Bursa Uludağ Üniversitesi Tıp Fakültesi Radyoloji Anabilim Dalı'ndan elde edilen erişkin 51 kadın ve 45 erkek olmak üzere toplam erişkin 96 bireyin bilgisayarlı tomografi görüntüleri kullanıldı. Frankfurt Horizontal planında alınan görüntülerde belirlenen değişkenler Image J programı kullanılarak ölçüldü. Elde edilen verilerin istatistikleri SPSS 22.0 programı kullanılarak gerçekleştirildi.

Bulgular: Değişkenlerin betimleyici değerleri verildi. Lineer mesafelerin kadın ve erkeklerde fark gösterdiği görülürken açısal değişkenlerin cinsiyet farkı göstermediği görüldü. Eksik parçaları tahmin etmek için regresyon formülleri geliştirildi ve en yüksek doğruluk yüzdesine sahip formüller erkekler için; M5= -2,945 + (0,548xM4) +(0,404xM6); kadınlar için M5= -7,457 + (0,409xM4) + (0,619xM6) olarak bulunmuştur.

Sonuç: Çalışmada yeniden yüzlendirmeyi farklı bir bakış açısıyla değerlendirmeye çalıştık. Değişkenler arasındaki korelasyon katsayılarını dikkate alarak yüksek güvenilirliğe sahip regresyon formülleri geliştirdik. Tüm bu verilerin özellikle adli antropologlara fayda sağlayacağına inanıyoruz. Ayrıca açısal değerlerin cinsiyet farkı göstermemiş olması yüzün belirli bir oranda gelişim gösterdiğinin farklı bir açıdan göstergesi olarak kabul edilebilir olabileceğini düşünmekteyiz.

Anahtar Kelimeler: Kafatası, regresyon, temporal kemik, processus mastoideus, yeniden yüzlendirme

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INTRODUCTION

Identification is one of the priority subjects of the forensic sciences. Age, gender, ethnicity and height form the biological profile of the individual and they are the basis of the identification.[1] There are so many methods to assess the identification of the person but DNA analysis is the most reliable among these. The only disadvantage is that after a long time and if the corpse is fully skeletonized, the appropriate quality and quantity of the DNA cannot be reached at the crime scene. In this case, skeletal forensic identification is preferred as the last method.[2] Because the skeletal elements are affected by taphonomic factors in a longer time, it usually takes longer times for them to disappear completely.[2,3] One of the methods that used to identify skeletal remains of unknown origin or to obtain information about the identity of the corpses in cases where there is little or no evidence at the crime scene is facial reconstruction. In this method, it is estimated that only the skull exists at the scene, and in cases where soft tissue cannot be obtained, the shape of the person's face. Depending on the tissue thickness at various anatomical points on the face, tissue depth markers such as vinyl or rubber are used in different lengths. Then, organs such as lips, cheeks, eyes and nose are placed.[4]

In facial reconstruction, the position of the soft tissue relative to the underlying bone structure and the consistency of the anatomical connection between it is an important issue. To assess this consistency, a comprehensive understanding of the anatomy of the skull and the relationship between the skull and the face is thoroughly required.[2] It causes deterioration of the integrity of skeletal remains due to natural events such as climate, wind and surrounding animals. For this reason, working with fragmented bones with impaired integrity makes identification hard.[5] In human skull sex determination, the petrous part of the temporal bone has a special importance among the bones used as the base due to its compact structure that can withstand mechanical effects and other destructive factors such as temperature.[6] By using the morphological features of bones, mathematical models can be made by means of morphometric methods, and an individual's age, height and gender can be estimated. Studies indicate that bones differ according to gender and ethnicity, so regression formulas for each population should be produced.[7,8]

The aim of the study is to give descriptive values for the estimation of the skull shape and to produce regression formulas, by taking the mastoid process as reference in case of fragmented or missing parts of the skull at the scene.

MATERIAL AND METHOD

The study was conducted as a result of the decision of the Bursa Uludağ University Faculty of Medicine Clinical Research Ethics Committee dated 20 July 2020 and numbered 2020-12/23. Cranial, face and neck computed tomography (CT) images taken using Siemens Somatom Definition 128-section multi-detector computed tomography device in the xxx University Faculty of Medicine, Department of Radiology are used. Images, protocol numbers, and three-dimensional computed tomography images obtained with Centricity RIS 6.0 Plus PACS system (General Electric Company, USA) were brought to jpeg format on Workstation. After selecting the 1.5 mm thick thin-section axial images in the GFPACS system, reformat images were created with the AW Suite 2.0 program and evaluated in the bone window. Sagittal and coronal images of skulls rendered in 3D with the volume are rendering option on the program. It was brought to the Frankfurt Horizontal Plan separately and recorded in the PACS system via AW Suite 2.0. Afterwards, images of adult females and males individuals were filed separately in jpeg format and made ready for measurement.

Study Group

In the retrospective study, 1260 computed tomography images that the report files could be accessed were examined. Individuals with fractures, deformities, or any pathological findings and a history of surgery and trauma were excluded from the study. A total of 96 adult individuals, 51 females and 45 males, were included in the study. The age range for males was 19-65, and the mean age was 36.82±14.18 years. The age range for females was 18-66, and the mean age was 35.76±14.18.

Measurements

Variables were chosen by selecting anthropometric points that reveal the convexity and concavity of facial features with reference to the mastoid process. The linear distances from the mastoid process to the anthropometric points that glabella, nasion, rhinion, nasospinale, A point, prosthion, infradentale, B point, pogonion, menton and gonion and the angles formed between the linear distances were measured.[9-12] The reference points were shown in **Figure 1**, the linear variables included in the study were shown in **Figure 2** and angular variables were shown in **Figure 3**. After calibrating in the ImageJ program with the help of the ruler on the images recorded as jpeg, linear distances were measured in millimeters. The measured parameters are:

M1: The linear distance between mastoid process and glabella

M2: The linear distance between mastoid process and nasion

M3: The linear distance between mastoid process and rhinion

M4: The linear distance between mastoid process and nasospinale

M5: The linear distance between mastoid process and A point

M6: The linear distance between mastoid process and prosthion

M7: The linear distance between mastoid process and infradentale

M8: The linear distance between mastoid process and B point

M9: The linear distance between mastoid process and pogonion

M10: The linear distance between mastoid process and menton

M11: The linear distance between mastoid process and gonion

M12: The linear distance between mastoid process and inion

M13: The linear distance between mastoid process and ophistocranion

M14: Angle between glabella, mastoid process and nasion

M15: Angle between nasion, mastoid process and rhinion

M16: Angle between rhinion, mastoid process and nasospinale

M17: Angle between nasospinale, mastoid process and A point

M18: Angle between A point, mastoid process and prosthion

M19: Angle between prosthion, mastoid process and infradentale

M20: Angle between infradentale, mastoid process and B point

M21: Angle between B point, mastoid process and pogonion

M22: Angle between pogonion, mastoid process and menton

M23: Angle between menton, mastoid process and gonion

M24: Angle between gonion, mastoid process and inion

M25: Angle between inion, mastoid process and ophistocranion

M26: Angle between ophistocranion, mastoid process and glabella

In the first phase of the facial reconstruction stages, the missing or broken parts of the skull must be completed. The parts that are broken or missing one side are completed by using the mirror method technique by accepting them as symmetrical with respect to the existing side.[13] Accordingly, the lateral measurements of the variables on the right side of the skull were taken as reference.

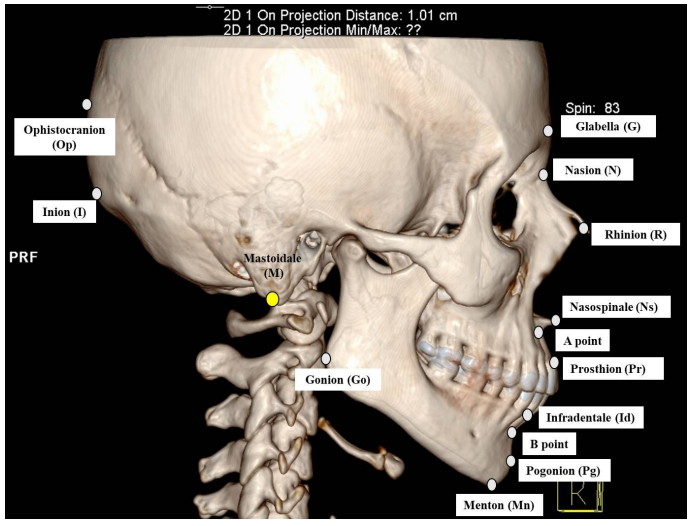

Figure 1. Anthropometric points used as reference

Mastoidale -(M): Lowest point of the mastoid process; Glabella -(G): The most prominent point between the superciliar arcs on the midline; Nasion-(N): Intersection point of midline and frontonasal sutur; Rhinion-(R): The junction of the nasal bone and lateral nasal cartilages on the midline; Nasospinale-(Ns): anterior nasal spine crest; A point (Subspinale): Deepest point below the nasospinale; Prosthion (Supradentale)-Pr: The most anterior point of the alveolar process between the maxillary anterior incisors; Infradentale-(Id): The most anterior point of the alveolar process between the mandibular anterior incisors; B point (Supramentale): Deepest point between infradentale and pogonion; Pogonion-(Pg): The most prominent point of the mental tubercle on the midline; Menton-(Mn): The lowest point of the mandible on the midline; Gonion-(Go): The point on the outermost edge of the angle of mandible; Inion-(I): The most prominent point of the external occipital protuberance; Ophistocranion-(Op): The most prominenet point of the occipital bone on the midline

Statistical Analysis

Descriptive statistical values in the form of mean±standard deviation were examined for all variables in males and females individuals. Independent sample t-test was used to reveal the difference between gender. Pearson correlation analysis was performed to determine the relationship between the variables ($p<0.05$). Regression formulas were produced by using highly correlated variables as a result of correlation analysis. With these formulas, it was aimed to determine the shape of the face from broken or fragmented skulls. All statistical analyzes were performed using SPSS 22.0 (IBM).

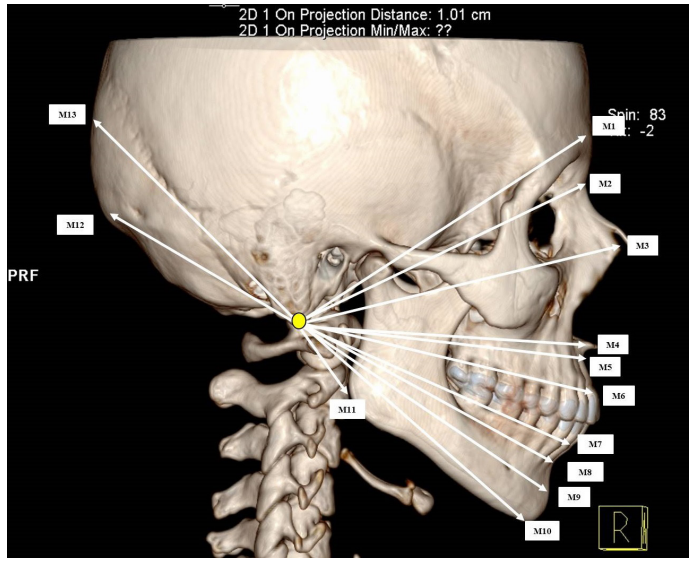

Figure 2. Parameters measured with reference to the mastoid process

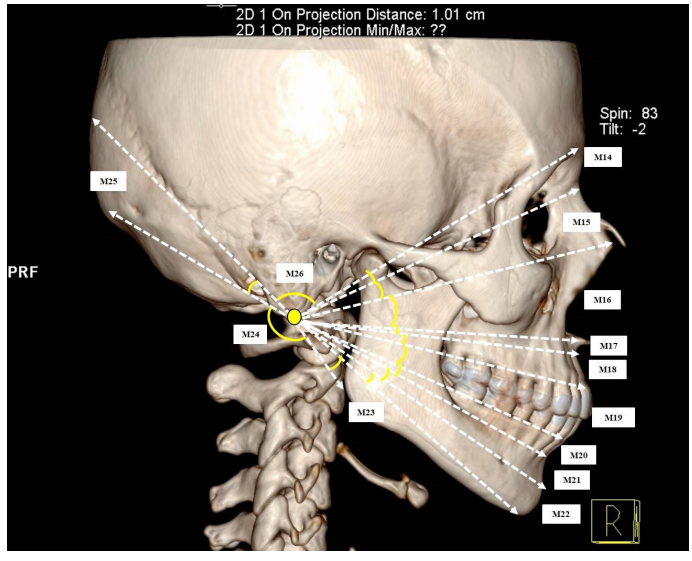

Figure 3. Angular parameters measured with reference to the mastoid process

RESULTS

Descriptive statistical values of the variables for adult females and males individuals were examined. In males and females, the linear distances of the mastoid process to the glabella, nasion, rhinion, nasospinale, A point, prosthion, infradentale, B point, pogonion, menton and gonion, and the angles formed between the distances were shown in **Table 1**. It was determined that the linear distances of the mastoid process to other points differ between gender while the angle between glabella-mastoid process-nasion, nasospinale-mastoid process-A point and menton-mastoid process-gonion angles showed gender difference ($p<0.05$).

Regression analysis based on the estimation of the face shape due to fractured or fragmented skull sections was performed using variables with high correlation between the variables, separately for males and females. While performing the regression analysis, formulas are created by testing more than one variable and its combinations. It has been tried to take into account the possibility that any part of the skull is absent or missing. The adjusted R2 value shows us the prediction rate of the formula as a percentage. It has been achieved to produce formulas with an accuracy of 90% and above in both genders. The regression formulas produced for males were shown in **Table 2,** and the formulas were produced for females were shown in **Table 3**. The formula which has the highest accuracy percentage is for males and females respectively:

M5=-2.945+(0.548xM4)+(0.404xM6) Adjusted R2 Value: 0.945; S.E.: 1.432

M5=-7.457+(0.409xM4)+(0.619xM6) Adjusted R2 Value: 0.955; S.E.: 1.006

Table 2. Regression formulas for males

Regression Formula	Adjusted R2 Value	Standart Error
M1=4.552+(1.047×M2)	0.898	2.063
M2=7.555+(0.860×M1)	0.898	1.869
M3=14.337+(0.459×M²)+(0.506×M4)	0.907	1.731
M4=10.144+(0.943×M5)	0.905	0.835
M4=3.886+(0.136×M1)+(0.836×M5)	0.915	1.758
M4=-3.341–(0.028×M1)+(0.381×M3)+(0.658×M5)	0.933	1.569
M4=4.077+(0.14×M1)+(0.901×M5)–(0.07×M6)	0.914	1.772
M5=-0.761+(0.965×M4)	0.908	1.857
M5=-11.616+(0.386×M3)+(0.629×M6)	0.927	1.656
M5=-2.945+(0.548×M4)+(0.404×M6)	0.945	1.432
M6=-7.174+(0.652×M5)+(0.439×M7)	0.931	1.688
M6=-6.551+(0.766×M5)+(0.325×M8)	0.903	1.996
M7=-0.558+(0.341×M6)+(0.669×M8)	0.909	1.743
M7=1.344–(0.228×M5)+(0.551×M6)+(0.661×M8)	0.914	1.690
M8=0.943+(0.243×M6)+(0.694×M9)	0.903	1.652
M8=1.143+(0.457×M7)+(0.492×M9)	0.929	1.412
M8=2.429+(0.477×M7)+(0.453×M10)	0.938	1.326
M9=8.446+(0.908×M10)	0.929	1.448
M9=6.818+(0.175×M7)+(0.762×M10)	0.938	1.352
M10=-0.753+(1.025×M9)	0.929	1.539
M10=-1.24+(0.233×M8)+(0.813×M9)	0.934	1.489

Table 1. Descriptive statistical values of distance (mm) and angle values between mastoid process and other parameters

Variable	Female			Male		
	Mean±S.D.	Median	Min. – Max.	Mean±S.D.	Median	Min. – Max.
M1	117.036±5.496	117.189	98.393 – 128.908	125.038±6.459	125.662	107.916 – 141.596
M2	108.573±5.339	108.528	91.405 – 120.453	115.047±5.852	115.170	99.253 – 129.168
M3	113.112±5.140	113.720	98.166 – 123.419	120.070±5.690	120.288	105.541 – 133.002
M4	100.462±4.807	100.260	91.158 – 114.265	104.722±6.048	103.990	91.193 – 120.000
M5	96.267±4.762	96.521	86.358 – 107.619	100.322±6.120	99.581	88.752 – 115.302
M6	101.141±4.587	101.185	90.625 – 111.519	104.172±6.418	103.574	90.814 – 120.731
M7	100.363±5.020	100.933	89.258 – 109.452	104.628±5.763	104.017	94.672 – 118.436
M8	99.009±5.535	99.606	86.580 – 108.689	104.112±5.309	103.368	94.234 – 114.716
M9	106.141±5.670	106.470	93.025 – 116.678	112.153±5.443	111.540	100.253 – 124.290
M10	107.726±5.977	108.084	94.206 – 118.869	114.227±5.784	113.205	103.636 – 126.416
M11	46.650±5.470	34.197	46.742 – 56.545	51.097±7.496	51.235	35.234 – 77.217
M12	70.595±10.909	73.301	33.861 – 91.942	79.910±8.435	77.881	67.612 – 114.964
M13	100.383±9.330	99.451	80.716 – 120.946	110.651±8.926	112.551	91.467 – 133.061
M14	5.258°±1.179°	5.461°	2.407°-7.762°	4.451°±1.101°	4.218 °	2.827° – 8.374°
M15	11.785°±1.771°	11.570°	7.086°-17.667°	11.743°±1.963°	11.734°	8.273° – 16.189°
M16	15.782°±1.765°	15.844°	10.431°-21.256°	15.488°±1.795°	15.660°	11.780° – 18.836°
M17	3.541°±0.846°	3.386°	1.787°-5.678°	3.198°±0.869°	3.063°	1.728° – 5.869°
M18	6.432°±1.702°	6.116°	3.498°-11.302°	6.432°±1.497°	6.582°	3.112° – 10.274°
M19	11.538°±1.359°	11.568°	8.491°-14.804°	12.069°±2.080°	11.730°	8.163° – 17.361°
M20	5.402°±1.732°	5.343°	1.879°-9.712°	4.844°±1.607°	4.877°	1.570° – 8.133°
M21	5.640°±1.499°	5.625°	1.700°-10.238°	5.821°±1.368°	5.875°	0.818° – 8.497°
M22	4.794°±1.150°	4.723°	2.649°-7.028°	4.703°±1.122°	4.779°	2.605° – 7.519°
M23	18.017°±3.983°	18.393°	9.982°-26.220°	20.167°±5.025°	20.175°	8.584° – 32.724°
M24	144.37°±11.564°	145.954°	108.211°-166.04°	144.984°±9.344°	146.38°	116.243° – 166.48°
M25	23.525°±6.695°	23.480°	8.721°- 41.897°	23.777°±5.431°	23.957°	14.201° – 34.481°
M26	103.942°±7.512°	105.241°	90.337°-120.64°	102.201°±6.086°	102.58°	86.131° – 135.35°

SD. Standart devaition; Min.-Max., Minimum and Maximum

Table 3. Regression formulas for females

Regression Formula	Adjusted R2 Vlaue	Standart Error
M1=10.025+(0.986×M2)	0.927	1.472
M2=-5.261+(0.721×M1)+(0.261×M3)	0.938	1.331
M5=-4.279+(0.994×M6)	0.915	1.386
M5=-11.937+(0.227×M3)+(0.816×M6)	0.945	1.112
M5=-7.457+(0.409×M4)+(0.619×M6)	0.955	1.006
M5=-3.438+(0.752×M4)+(0.24×M7)	0.903	1.480
M5=0.491+(0.771×M4)+(0.185×M8)	0.891	1.570
M5=-3.42+(1.045×M6)–(0.057×M9)	0.916	1.328
M5=-3.772+(1.028×M6)-(0.037×M10)	0.915	1.391
M6=16.89+(0.15×M3)+(1.051×M5)	0.924	1.262
M6=8.322+(0.768×M5)+(0.188×M7)	0.931	1.205
M6=10.629+(0.789×M5)+(0.147×M8)	0.926	1.245
M6=8.405+(0.818×M5)+(0.132×M9)	0.929	1.222
M6=9.264+(0.831×M5)+(0.11×M10)	0.926	1.251
M6=12.344+(0.922×M5)	0.915	1.335
M7=13.852+(0.874×M8)	0.927	1.357
M7=9.402+(0.13×M6)+(0.786×M8)	0.930	1.325
M8=-12.163+(0.133×M4)+(0.974×M7)	0.933	1.436
M8=-8.135+(0.292×M4)+(0.722×M10)	0.909	1.671
M8=-9.589+(0.345×M5)+(0.711×M9)	0.901	1.745
M8=-7.522+(0.338×M5)+(0.687×M10)	0.916	1.603
M8=-9.585+(0.077×M6)+(1.004×M7)	0.927	1.498
M8=-9.751+(0.37×M6)+(0.662×M10)	0.915	1.618
M8=-3.181+(0.961×M7)+(0.123×M11)	0.932	1.443
M9=7.286+(0.918×M10)	0.935	1.451
M9=6.271+(0.173×M8)+(0.768×M10)	0.937	1.423
M9=11.984+(0.814×M10)+(0.138×M11)	0.939	1.397
M10=-0.518+(1.020×M9)	0.935	1.529

DISCUSSION

Understanding the relationship between skull and soft facial tissue is important for forensic facial reconstruction.[2] There are so many studies about facial reconstruction, especially estimation of the facial organs like ear, nose, eye etc. for the various gender, age, and races. It is seen that these studies accept the skull as a whole without any deformity and reconstruction it in this way. Given that mass catastrophes, wars, and animal activity at the scene have disrupted the integrity of the skeletal remains, situations are likely to arise where it may be necessary to reveal the shape of the skull before attempting reconstruction The study aims to estimate the anatomical points that make up the facial contours using the mastoid process in case the skull is fractured or fragmentary.

In the literature, there are studies that tried to estimate gender using many variables such as the length of the mastoid process and its distances from the neighboring anatomical structures.[14,15] In the study, unlike the literature, the linear distances between the mastoid process to the anthropometric points on the midline of the face and the angles between these distances were measured. When the difference between males and females individuals with comparative statistics were examined, it is seen that all linear distances showed gender differences. Among the angles, it was determined that the angle between glabella-mastoid process-nasion, the angle between nasospinale-mastoid process-A point and the angle between menton-mastoid process-gonion showed gender differences, and all the other angles did not differ between males and females. It is not surprising that angular variables do not show gender differences since the rate of development of the face is constant in males and females.[16] It made us think that some points might not have been able to adapt to this rate of development. It is seen that some angular variables differ in the study.

Considering the stability of the skull bones, the harmony between the facial bones, the maxilla, and the mandible and the effect of these bones on the vertical development of their face it is usual to find differences between males and females individuals. In male, the sharp edge of the supraorbital margin of the orbita and its extension towards the region causes the glabella to have a more prominent appearance.[17] This explains to us the gender difference in the angle between the glabella-mastoid process-nasion.

The mandibular angle shows dimorphism due to the antero-inferior displacement of the gonion, which shortens the length of the gonial region, and the slight upward movement of the preangular notch. A longer lower margin (lower edge of the basal bone) in males and an allometric downward orientation of the preangular notch in females causes the lower margin to display a more curved appearance. These structures are also thought to be related to the enlargement of the nasopharyngeal cavity as a whole as a result of its clockwise rotation.[18] In the study, the angle between the menton-mastoid process-gonion which shows the gender difference think that it may be due to a functional difference originating from the chewing muscles as well as being an individual. The nasal cavity shows a gender difference in males and females due to their energy requirements.[19] We think that the shape and direction of anterior nasal spine in this region may show a gender difference because of the great differences in individuals.

In a study that use computed tomography images in the Turkish population, the distance between the mastoid process and the glabella was reported as 131.1±5.86 mm in males and 123.5±4.69 mm in females. In the same study, the distance between the mastoid process and the nasion was 121.7±5.60 mm in males and 115.1±4.20 mm in females; the distance between the mastoid process and the rhinion was 125.8±5.50 mm in males and 119.5±4.23 in females. The distance between the mastoid process and the nasospinale was 110.7±5.54 mm in males and 106.1±3.66 mm in females; the distance between the mastoid process and the prosthion was specified as 109.0±5.92 mm in males and 105.3±3.33 mm in females.[4] When the data of our study is compared with the thesis study, it is seen that the values are lower. Apart from this study, no study using dry bone has been encountered in the literature.

Macroscopic and radiographic measurements of dry bones or teeth are problematic due to changes in the skeleton because of taphonomic reasons. Huxley stated that postmortem shrinkage was observed in human fetal diaphyseal lengths when compared dry bones with the fresh bones.[20] This means that indicators based on fresh bones cannot be applied directly to dry bones.[21] The association of facial soft tissues with dry skulls is important for forensic identification or for inferring the facial morphology of extinct forms. It is known that the soft tissue of the face shows serious differences between individuals due to reasons such as embryology, growth and aging, and aesthetics.[22] It is seen that the compatibility of the data obtained from living individuals with the dry skull or the fact that the data obtained from the cadavers do not reflect the real image, and the large differences between individuals due to environmental conditions show that facial reconstruction cannot give us a definite result.

Forensic facial reconstruction is a method for predicting possible face shape. Especially estimation of the soft tissue thickness is the main point of the studies. Before the reconstruction, restoration of the skull can be necessary and in this study, we tried to evaluate the issue from a different point of view with the mastoid process. We believe this study set an example for future studies and help the forensic sciences.

Limitations of the study: The number of the images are can be increased by dividing them into the age groups. It is recommended to examine the study with other age groups as well as the adult group and also it is possible to estimate the soft tissue with the skull.

CONCLUSION

In the case of fragmentation of the skull in the study, we tried to evaluate the skull from a different perspective in the light of the studies in the literature. In the study, we aimed to reveal the face shape on the bone by using mastoid process on the temporal bone. For this purpose, we have developed regression formulas with high reliability, taking into account the correlation coefficients between deciduous variables. We believe that all this data will benefit different disciplines, especially forensic anthropologists.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was obtained from Ethics Committee of Bursa Uludag University School of Medicine (Date: 20/07/2020-Decision No: 2020-12/23).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

Radiological Evaluation of Allergic Fungal Sinusitis: Novel Findings

Alerjik Fungal Sinüzitin Radyolojik Değerlendirmesi: Yeni Bulgular

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Abstract

Aim: Fungal sinusitis is a disease that was previously considered a rare disease, but has recently been reported with increasing frequency in warm climates. Fungal sinusitis classification has evolved over the past two decades and is said to include five subtypes. Discrimination of different subtypes and knowing their radiological features are important for accurate and rapid diagnosis and initiation of appropriate treatment. In our study, we aimed to investigate whether there is a difference between the radiological findings of allergic fungal sinusitis (AFS) with a newly defined finding that may help the diagnosis of AFS; serrated turbinate and those reported in the literature.

Material and Method: Our study included 120 patients who underwent paranasal sinus computed tomography examination in our center between January 2019 and September 2021. Patients diagnosed with AFS as a result of allergic tests and/or fungal culture examinations were included in the first group, and patients diagnosed with non-AFS rhinosinusitis were included in the second group. Presence of serrated turbinate appearance, polyps, bone erosion, CT hyperdensity were evaluated in the images.

Results: The radiological features of AFS and non-AFS were compaired and serrated turbinate appearance was found to be statistically signifant in AFS ($p<0.05$). Bone erosion, presence of polyps and CT hyperdensity did not differ between the groups ($p>0.05$).

Conclusion: Our findings showed that serrated turbinate appearance may be a useful radiological marker in the diagnosis of AFS. Bone erosion should be evaluated seperately from other morphological and structural changes in the bone structure, and the bone density measurements should be specified for sinus opacification.

Keywords: Allergic fungal sinusitis, serrated turbinate, bone erosion, radiology

Öz

Amaç: Fungal sinüzit daha önceleri nadir görülen bir hastalık olarak kabul edilen, ancak son zamanlarda sıcak iklimlerde artan sıklıkta bildirilen bir hastalıktır. Fungal sinüzit sınıflandırması son yirmi yılda gelişmiştir ve beş alt tip içerdiği söylenmektedir. Farklı tiplerinin anlaşılması ve bunların radyolojik özelliklerinin bilinmesi doğru ve hızlı tanı ile uygun tedavinin başlatılması açısından önemlidir. Çalışmamızda Alerjik Fungal Sinüzit (AFS) tanısına yardımcı olabilecek yeni bir bulgu olan serrated konka varlığı ile ılıman iklim kuşağında yer alan ülkemizde AFS'nin radyolojik bulgularının literatürde belirtilenler ile farklılığının bulunup bulunmadığını araştırmayı amaçladık.

Gereç ve Yöntem: Çalışmamıza Ocak 2019 – Eylül 2021 tarihleri arasında merkezimizde paranazal sinüs BT incelemesi yapılan 120 hasta dahil edilmiştir. Hastalardan alerjik testler ve/veya fungal kültür incelemeleri sonucu AFS tanısı konulanlar birinci grup, AFS dışı rinosinüzit tanısı konulan hastalar ikinci gruba dahil edilmiştir. Görüntülerde serrated konka görünümünün varlığı, polip varlığı, kemik erozyon varlığı ve CT hiperdansitesi varlığı araştırılmıştır.

Bulgular: Çalışmamızda AFS'nin radyolojik özellikleri diğer rinosinüzitlerle karşılaştırılmış olup serrated konka görünümünün AFS için istatistiksel farklılığını tespit ettik ($p<0.05$). Kemik erozyon, polip mevcudiyeti ve CT hiperdansitesi ise farklılık göstermemekteydi ($p>0.05$).

Sonuç: Ortaya koyduğumuz bulgular AFS tanısı için serrated konka görünümünün ayırıcı tanıda faydalı bir belirteç olabileceğini göstermiştir. Kemik erozyonun kemik yapıdaki diğer şekil ve yapı değişikliklerinden ayrı değerlendirilmesi, sinüs opasifikasyonu için de dansite değerinin belirtilmesi gerekmektedir.

Anahtar Kelimeler: Alerjik fungal sinüzit, serrated konka, kemik erozyon, radyoloji

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INTRODUCTION

Fungal sinusitis is a disease that was previously considered a rare disease, but has recently been reported with increasing frequency, especially in warmer climates such as the Southern USA and Australia.[1-3] The fungal sinusitis classification has evolved over the past two decades and includes 5 subtypes. Acute invasive fungal sinusitis, chronic invasive fungal sinusitis, chronic granulomatous invasive fungal sinusitis constitute the invasive group whereas allergic fungal sinüsitis (AFS) and fungal ball (fungal mycetoma) are classified as non-invasive fungal sinusitis.[1,4] These five subtypes have different clinical and radiologic features. The treatment strategies and prognosis of each type are also different.[1] Differentiation of fungal sinusitis subtypes with their specific radiological features is important to distinguish them from bacterial sinusitis subtypes and to initiate correct, rapid diagnosis and treatment.[1,5]

The idea of AFS first appear when Safirstein et al described a clinical picture in allergic bronchopulmonary aspergillosis in 1976 in with nasal polyposis, nasal mucosal crust formation resembling sinusitis and Aspergillus was isolated in sinus cultures.[6] The same clinical picture was described by Millar et al as allergic aspergillosis of the paranasal sinuses in 1981, and as allergic aspergillus sinusitis by Katzenstein et al in 1983.[7,8] However, the pathology first expressed by Robson et al with the term allergic fungal sinusitis (AFS) showing that it can also be caused by non-aspergillus fungi, is a newly defined disease that is generally seen in atopic individuals and is different from other types of sinusitis.[9] As a result, AFS is an Ig-E mediated hypersensitivity reaction to fungal elements, not an infection of the mucosa, and is the most common form of fungal sinusitis.[10,11]

AFS diagnostic criteria established by Bent and Kuhn in 1994 are positive allergy tests, nasal polyposis, characteristic computed tomography (CT) scan findings, presence of eosinophilic mucin, and detection of fungus in the culture. However, as stated by the authors, first of all, there should be suspicion about the presence of AFS in the patient.[5] In later studies on the subject, heterogenous mucin-induced areas in the paranasal sinuses in CT examinations were accepted as relatively characteristic features of the disease, although they were not specific for AFS.[12,13] It is stated that in magnetic resonance (MRI), hypointense appearance in the centre in T1W sequence, presence of central signal gap and peripheral signal increase in T2W sequence are significant for AFS when compaired with invasive fungal sinusitis subtypes, and combined CT and MRI findings provide a radiographic appearance that is highly specific for AFS.[14] However, recently there are opinions that radiological findings alone are not significant in the diagnosis of AFS.[15]

Although Bent and Kuhn diagnostic criteria for AFS is extremely useful, according to the information that we have gained in recent years about AFS, this disease is much more common than expected in some parts of the world and there may be a need for a re-evaluation in the radiological diagnostic criteria due to increased number of diagnoses of AFS.[5] In our study, we aimed to investigate the presence of serrated turbinate, which is a new radiological finding that can help the diagnosis of AFS, and whether there is a difference between the radiological findings among AFS and non-AFS in our study.

MATERIAL AND METHOD

This study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and was approved by the Ethical Committee of noninvasive Clinical Research of the Mardin Artuklu University (2021/2). Our study included 120 out of 186 patients who underwent paranasal sinus CT examination with a preliminary diagnosis of sinusitis in our center between January 2019 and September 2021. 26 patients under 18 years age, 32 patients who had a previous operation involving paranasal sinuses, 8 patients with a mass or invasive pathology were excluded from the study. Patients diagnosed with AFS as a result of allergic tests and/or fungal culture examinations were included in first group, and patients diagnosed with non-AFS rhinosinusitis were included in the second group. The CT examinations were performed with General Electric IQ™ 32-Detector Spiral MSCT device with 120–130 kV tube voltage using 80-160 mAs value within 0,625 mm section thickness. The images taken in axial plane and evaluated together with coronal and sagittal reformat images by an otolaryngologist experienced in radiological anatomy and a radiologist retrospectively. Presence of serrated turbinate morphology, presence of polyps, presence of bone erosion and hyperdensity in the sinus are investigated on CT images (**Figure 1-4**).

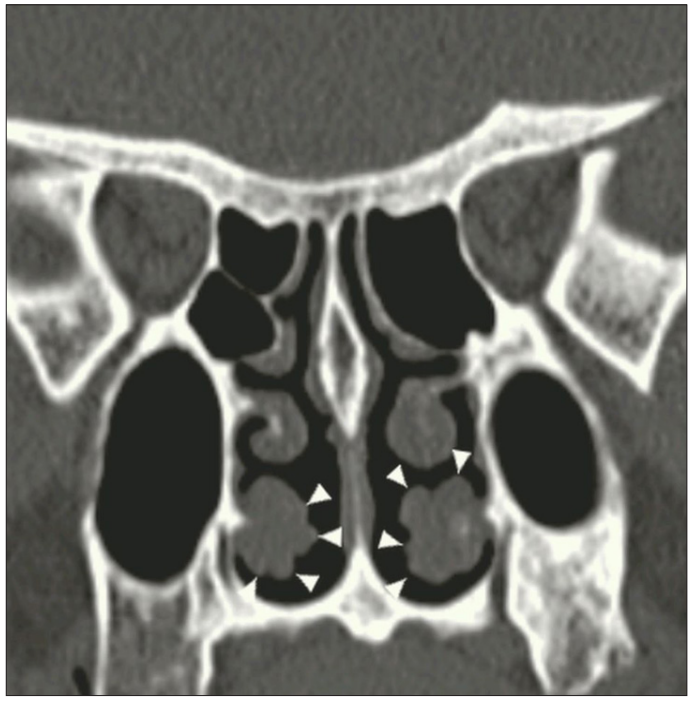

Figure 1. Serrated turbinate (white arrowheads)

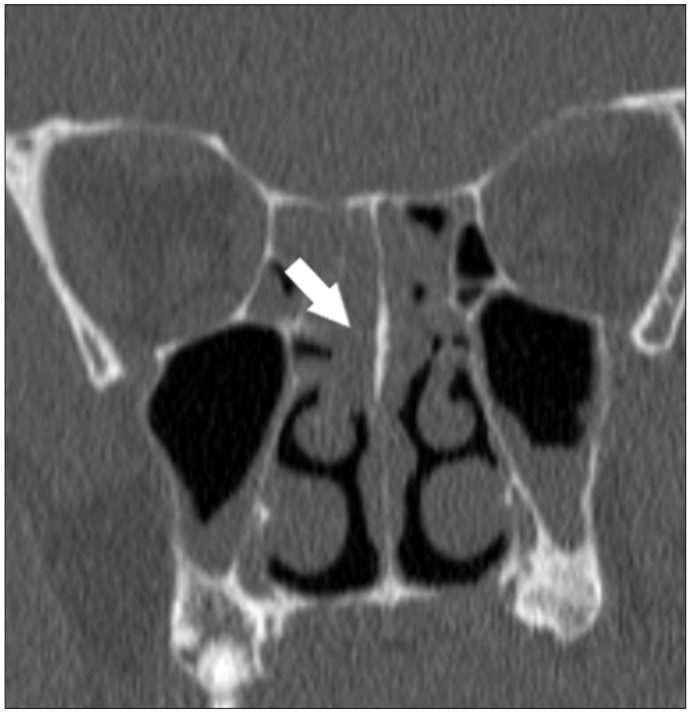

Figure 2. Polypoid lesion (white arrow)

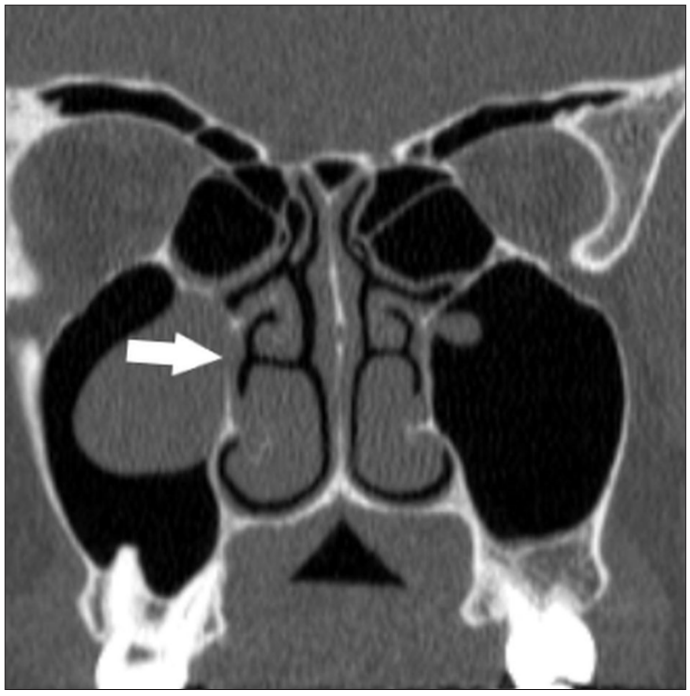

Figure 3. Bone erosion (white arrow)

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 22 (IBM Corp. Armonk, NY). Distribution of variables, were analyzed using Shapiro Wilk test. Variables were not found to be distributed normally in Shapiro Wilk test. Categorical data were also analyzed by chi-square test. A p value of <0.05 was considered significant.

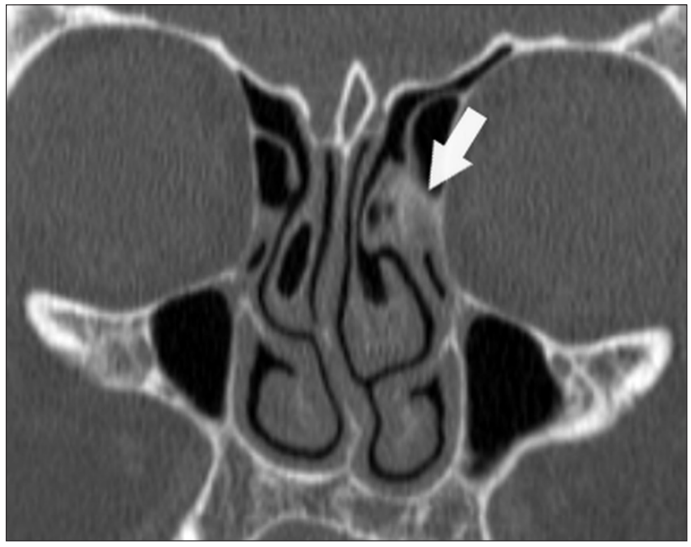

Figure 4. Hyperdense lesion (white arrow)

RESULTS

120 adult patients (50% male, 50% female; 18 to 63 years old) met the inclusion criteria for our study. The distribution of age is normal with mean of 36.81 years and standard deviation (SD) 11.24 years. Of the 120 patients; 86 patients (72%) are AFS (-) and 34 patient (28%) are AFS (+). Among AFS (+) patients; 19 patients (16%) are female and 15 patients (12%) are male.

AFS (+) patients are compaired with AFS (-) patients among gender, polyp formation, serrated concha appearance, bone erosion and hyperintensity on CT. None of the parameters were found to be statistically significant except serrated concha morphology on CT (p<0.05) (**Table 1**).

Polyp formation, bone erosion and hyperdensity on CT is compaired between serrated concha positive and negative patients. Statistical difference was found between serrated concha positive and negative patients. However there were no statistically significant relation between positive and negative patients in bone erosion and hyperdensity parameters on CT (p>0.05) (**Table 2**).

Table 1. Comparison of AFS (+) and AFS (-) patients according to gender, presence of polyp, serrated concha, bone erosion and hyperdensity.

	AFS		p
	Positive	**Negative**	
Female	19 (15.8%)	41 (34.2%)	p>0.05
Male	15 (12.5%)	45 (37.5%)	
Polyp			p>0.05
Positive	15 (12.5%)	26 (%21.7)	
Negative	19 (15.8%)	60 (50%)	
Serrated Turbinate			p<0.05*
Positive	19 (15.8%)	5 (4.2%)	
Negative	15 (12.5%)	81 (67.5%)	
Bone Erosion			p>0.05
Positive	2 (1.7%)	1 (0.8%)	
Negative	32 (26.5%)	85 (70.8%)	
Hyperdensity			p>0.05
Positive	5 (4.2%)	6 (5%)	
Negative	29 (24.2%)	80 (66.2%)	

Chi-square test.

Table 2. Comparison of serrated concha morphology on CT between polyp formation, bone erosion and hyperdensity.

	Serrated		p
	Positive	Negative	
Polyp			p=0.021*
Positive	13 (10.8%)	28 (23.3%)	
Negative	11 (9.2%)	68 (56.7%)	
Erosion			p=0.1
Positive	2 (1.7%)	1 (0.8%)	
Negative	22 (18.3%)	95 (79.2%)	
Hyperdensity			p=0.6
Positive	2 (1.7%)	9 (7.5%)	
Negative	22 (18.3)	87 (72.5%)	

Chi-square test.

DISCUSSION

AFS is a type of chronic sinusitis associated with the presence of eosinophilic mucin with fungal hyphae in the sinuses and type I Ig E-mediated hypersensitivity to fungi.[16] Pathological findings in AFS may vary due to eosinophil predominant inflammation, Charcot-Leyden crystals, and inflammatory response to various fungal species.[17] The most common fungal species seen in AFS Aspergillus, Alternaria, Bipolaris and Curvularia (18). The rate of AFS in chronic sinusitis was found to be between 4-24% in various studies, and it is said to be even higher in temperate climates.[19,20]

Although AFS is a relatively newly defined disease, there are many studies in the literature, especially on radiological imaging features. Studies provide very useful information about CT and MRI images in AFS.[4,21] Bent and Kuhn criteria consisting of major and minor criteria are used in diagnosis of AFS. The main criteria are history, history of type I hypersensitivity by skin test or in vitro test, nasal polyposis, characteristic CT scan findings (areas of serpiginous hyperattenuation), presence of eosinophilic mucin without evidence of invasion, and presence of fungal cell in the operation material removed during surgery. Patients must meet all the major criteria for diagnosis except the positive fungal cell culture. Minor criteria include unilateral predominance of disease, history of asthma, Charcot-Leyden crystals, and peripheral eosinophilia. Minor criteria support the diagnosis but are not diagnostic.[5] Although CT is also useful in diagnosis of sinusitis and in demonstrating bone erosion, it was not found to be sufficient to determine the etiology of sinusitis.[21] Although ''starry-sky'' ''ground-glass'' or ''serpiginous'' patterns, but commonly referred to as the ''double-density'' images in CT scan are associated with AFS, it has been reported that this appearance is also seen in other fungal pathologies.[22] Three findings in particular (nasal polyps, hyperattenuation foci in the sinuses on CT scan, and high Aspergillus-directed IgE antibody titers) were identified as reliable and specific indicators for the preoperative diagnosis of AFS in subsequent studies.[23] All AFS patients had polyposis and hyperattenuation on CT reported by Bent and Kuhn.[5] It has been reported that nasal polyps are not associated with allergies, but may be associated with AFS.[2] The most likely cause of hyperdensity in CT is the presence of heavy metal (eg iron and manganese) deposits and calcium salt precipitation in the allergic fungal mucin.[12] The presence of hyperattenuation and polyp formation was not statistically significant in our study. Although the CT finding was named hyperdensity in the literature review, no specific Hounsfield Unit (HU) value was given in any study. We can not use the term sinus opacification which we used to evaluate sinus radiographs because the inflammatory sinus contents are in soft tissue density. We think that this proportional difference may be due to the difference in the use of terminology, it may be useful to give specific HU values in subsequent studies to overcome this issue.

Although AFS is accepted among non-invasive sinusitis, bone erosion and expansion are still included in radiological imaging findings.[24] The incidence of bone erosion is between 20-80% in various studies.[12,25,26] It is speculated that as the amount of mucin in the sinus increases, decalcification may occur with mucocele formation and bone remodelling in the involved paranasal sinus.[24] Presence of mucin and local inflammatory changes can cause enlargement of the sinuses thereby causing remodelling.[27] Local bone resorption is much more common in AFS than in other forms of chronic rhinosinusitis, and bone erosion does not always denote invasive disease. It may be caused by pressure effects of mucin.[27] Therefore, in this context it is incorrect to accept bone erosion as a indicator of AFS. In fact, as Bent and Kuhn said it is unfortunately not possible to disagree with the authors who stated that there are many misunderstandings about AFS due to the novelty of disease, and misdiagnosis of AFS is prevalent despite the intervening 27 years.[5] The incidence of bone erosion was also not statistically significant in our study. This may be due to the fact that we did not consider remodelling as erosion in our study.

Serrated turbinate appearance, one of the incidental findings in paranasal sinus tomographies shared by Zain-Alabdeen and El Khateeb in their article attracted our attention.[28] During discussions about serrated turbinate with clinicans, serrated turbinate appearance might be interpreted as the cobblestone appearance of the mucosa. However, we noticed that this morphology was not mentioned as a radiological finding in the literature. We included serrated turbinate morphology in our study, and surprisingly, we found the statistical association of this morphology with AFS ($p<0.05$). However, since our study only focus on AFS, larger series of studies are needed about the relation of serrated turbinate morphology with other allergic rhinitis and fungal sinusitis subtypes.

Our current opinion, like Pillai et al, is that CT imaging alone will not be sufficient to accurately diagnose one subtype of fungal sinusitis, perhaps only helping us to differentiate it from non-fungal sinusitis.[15] Combined CT and MRI findings have also been reported to provide a radiographic appearance that is highly specific for AFS.[14]

Our study has some limitations. MRI images were not included in our study, as it is a retrospective study and MRI images of the patients were not available. In addition, the low number of patients diagnosed with AFS are another drawback of our study. This study is the first study analyzing paranasal serrated turbinate morphology with AFS and more research is needed for further evaluation with larger patient groups.

CONCLUSION

Although AFS is a clinical entity that has been recently described, the presence of fungal infection in immunocompetent individuals should be suspected in order to diagnose AFS, and it should be evaluated radiologically, immunologically, microbiologically and histopathologically with ENT examination. In our study, no diagnostic criteria was found in cases treated as AFS, that is consistent with the literature. We argue that we need large and objective studies that will fully demonstrate the value of radiological findings including serrated turbinate for the diagnosis of AFS.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Ethical Committee of Noninvasive Clinical Research of the Mardin Artuklu University (2021/2).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Case Report / Olgu sunumu

A Rare Cause of Hypoxemia: Hereditary Methemoglobinemia

Nadir bir Hipoksemi Sebebi; Herediter Methemoglobinemi

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Abstract

Hereditary methemoglobinemia is one of the rare causes of hypoxemia. Mutations in the CYB5R3 gene cause autosomal recessive hereditary methemoglobinemia. Mostly, symptoms such as shortness of breath, bruise and and fatique occur. It may not display any symptoms until adult ages. Our case was at the age of 18 and had sometimes recurring bruise in hands and lips, shortness of breath, palpitations and oxygen saturation (SaO_2) was 85%. Methemoglobin (Methb) level was %20 (N;0-1.5) No cardiac or pulmonary cause could be detected, which could account for dyspnea and cyanosis, and due to low saturation and high Methb. levels, metheglobinemia was considered and high dose IV ascorbic acid was administered. In follow up period, saturation increased and Methb. level gradually decreased and with genetic tests, homozygous missense c.136C> T (p.R46W) mutation was detected with CYB5R3 gene sequence analysis. Patient was diagnosed with autosomal recessive hereditary methemoglobinemia type 1. This case is presented ın order to emphasize that hereditary methemoglobinemia should be kept in mind when shortness of breath, hypoxia and cyanosis, occur together and can not be attributed to pulmonary and cardiovascular causes.

Keywords: Hereditary methemoglobinemia, CYB5R3 gene mutation, hypoxemia, dyspnea, cyanosis

Öz

Herediter Methemoglobinemi hpokseminin nadir sebeplerinden biridir. CYB5R3 geninde oluşan mutasyonlar otozomal resesif herediter methemoglobinemiye neden olur. Çoğunlukla nefes darlığı, morarma, halsizlik gibi semptomlar görülebilir. Bazen erişkin yaşa kadar semptom vermeyebilir. Onsekiz yaşında ellerinde ve dudaklarında zaman zaman tekrarlayan morluk, nefes darlığı, çarpıntısı olan olgumuzun, pulseoksimetre ile ölçülen oksijen satürasyonu (SpO_2) %85 saptandı. Methemoglobin (Methb) düzeyi %20 (N;0-1,5) idi. Dispne ve siyanozu açıklayacak kardiyak ve pulmoner neden saptanmayan olguda satürasyonu düşüklüğü ve methb yüksekliği nedeniyle methemoglobinemi düşünülerek, yüksek doz ıntravenöz askorbik asit verildi. Satürasyonu yükselen ve methb düzeyi tedricen düşen hastanın takiplerinde genetik testler sonucunda CYB5R3 geni sekans analizi ile homozigot missense c.136C>T (p.R46W) mutasyonu saptandı. Hasta otozomal resesif herediter methemoglobinemi tip 1 olarak kabul edildi. Pulmoner ve kardiyovasküler nedenlerle açıklanamayan nefes darlığı, hipoksi, siyanoz birlikteliğinde nadir görülen herediter methemoglobineminin akla gelmesi gerektiğini vurgulamak için bu vakamızı sunuyoruz.

Anahtar kelimeler: Herediter methemoglobinemi, CYB5R3 gen mutasyonu, hipoksemi, dispne,siyanoz

INTRODUCTION

Hereditary Methemoglobinemia, is one of the rare causes of hypoxemia. Methemoglobin (MetHb), is the non functional form of hemoglobin produced by transformation of ferrous (Fe^{+2}) hemoglobin iron to ferric form (Fe^{+3}) by oxidation. Methemoglobin can not transport oxygen and hence tissue hyoxia and cyanosis arises. In normal metabolism, due to erithrocyte enzyme systems (NADH-cytochrome b5 reductase and NADPH Methb reductase), MetHb level is kept under 1%. Congenital deficiency or acquired impairment of these systems lead to Methemoglobinemia, which may be innate or acquired.[1]

Hereditary methemoglobinemia is a rarely occurring disease all over the world and its prevalence and incidence is unknown. Hereditary methemoglobinemias may not exhibit any symptoms until adult ages.[2] The CYB5R3 gene, located in the chromosome 22q13.2 region, is involved in

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the synthesis of the enzyme named Nicotinamide-adenine dinucleotide (NADH) -cytochrome b5 reductase.[3,4] The CYB5R3 gene, which consists of nine exons, is 32 kb in size. [5] There are two known isoforms of (NADH) -cytochrome b5 reductase enzyme, the membrane-bound form found in all somatic cells, and the soluble form found only in erythrocytes. Its membrane-bound form functions in the elongation and desaturation of fatty acids, cholesterol biosynthesis, and the metabolism of various molecules and drugs. The soluble form found in erythrocytes takes place in the electron transport system to reduce methemoglobin to functional hemoglobin. [6] Mutations in the CYB5R3 gene cause autosomal recessive congenital methemoglobinemia.[7] There are two different phenotypes of thedisease, type 1 and type 2, depending on the functional change caused by the mutation in gene function. CYB5R3 gene mutations that cause autosomal recessive congenital methemoglobinemia type 1 typically decrease enzyme activity or stability, and the only finding observed in the sick individual is cyanosis.[7] Ferric iron (Fe^{3+}) cannot be converted effectively to ferrous iron (Fe^{2+}), which causes an increase in the erythrocyte's methemoglobin. Autosomal recessive congenital methemoglobinemia type 2 occurs if the mutation in the CYB5R3 gene leads to a complete loss of function in the enzyme, resulting in a more severe clinical picture.[8-11]

This case is presented to emphasize that hereditary methemoglobinemia, which is one of the rare causes of hypoxemia, should be borne in mind in cases presenting with dyspnea, cyanosis and hypoxemia.

CASE

An 18 year old female patient presented with the symptoms of bruise in lips and hands and dyspnea. In history, it was learned that she had recurrent bruise in the past and underwent investigation a few times for this reason since childhood, but the cause could not be found. Patient did not receive any drug or anesthetic before admission for any reason. In physical examination, cyanosis was detected in finger tips and lips and respiratory system examination were normal. In cardiovascular system examination, tachycardia was observed (120/min). In ambient air, with pulse oximeter, oxygen saturation was found to be (SpO_2)%85. Hematological and biochemical parameters were unremarkable. Lung graphy and respiratory function tests were normal.

In arterial blood gas, partial oxygen pressure (PaO_2) was 99 mmHg, SaO_2 % 96 and Methemoglobin (Methb) level %20 (N;0-1.5). Saturation gap was % 11 (N<%5) In investigations carried out for pulmonary embolism, no pathology was found. Echocardiography results were also normal. No pulmonary or cardiological pathology was detected and peripheral blood smear and hemoglobin electrophoresis yielded normal results as well. Since there was no cause which could explain hypoxia and cyanosis and metHb level was high, methemoglobinemia was considered. Patient was administered high dose IV Vitamin C (3×500mg). This dose was repeated a few times. Subsequent to treatment, cyanosis improved and level of methemoglobin gradually decreased. Pulse oxygen saturation increased to 93%. As a result of the genetic examinations of the patient, homozygous missense c.136C> T (p.R46W) mutation was detected with CYB5R3 gene sequence analysis. The mutation was in the exon 2 region of the gene, resulting in there placement of the positively charged arginine amino acid at codon 46 with the non-polar neutral amino acid tryptophan. The detected variant was evaluated as pathogenic in analysis using public in silico prediction tools such as Mutation Taster and Varsome.

Patient was considered as autosomal recessive hereditary methemoglobinemia type 1 in view of recurrent cyanosis, absence of drug or anesthetic substance use, high Methb level and the presence of mutation in cytochrome b5 reductase (CYB5R3) gene (c.136C>p.R46W) and mild to moderate clinical picture. There is consanguinity in our patient's parents. In the segregation analysis, heterozygous mutations were detected in the same region in both parents of the patient. The absence of any findings related to the disease in the mother and father was found to be compatible with the heterozygous situation. There is no known individual with a history of similar disease in the patient's pedigree. According to the autosomal recessive inheritance pattern, the patient and her family were given genetic counseling, and the patient was informed about the 25% risk of affecting each sibling, 50% risk of being an asymptomatic carrier, and 25% healthy.

DISCUSSION

Hereditary methemoglobinemia diagnosis is made with deficiency of cytochrome b5 reductase enzyme or presence of M hemoglobins. Cytochrome b5 reductase gene is located on chromosome 22. To date, 43 different cytochrome B5 reductase gene mutations have been described. Cytochrome b5 reductase enzyme deficiency Type 1 is the most common one. [12] In this patient group, solely enzyme deficiency is present in erythrocytes. Depending upon methemoglobin level, at times, fatigue and dyspnea and cyanosis occur. Blood MetHb level is under 1% in normal conditions. When MetHb level increases over 1.5 g/dl, cyanosis starts to appear and becomes marked when MetHb level reaches 10%. Unless MetHb level rises over %25-40 or cardiopulmonary dysfunction is present, normal life can be expected in this group. However, in Type 2, enzyme deficiency is present in many tissues such as liver, fibroblast and brain in addition to erythrocytes. Neurological syndrome encompassing severe mental retardation, growth delay, opisthotonus and generalized symptoms is encountered. Clinical picture is quite severe.[13,14]

It has been demonstrated that many agents cause acquired methemoglobinemia. The most common causes are sulphonamides, local anesthetic drugs and nitrate containing vegetables. Acquired methemoglobinemia may have a more severe clinical course than hereditary one.[12] While

no symptoms and signs may be observed in mild cases, in severe cases,cyanosis,tachypnea, tachycardia, hypotension, confusion and even death may occur.[13]

In hereditary methemoglobinemia, diagnosis is made based on the appearance of cyanosis, which does not have a respiratory or cardiovascular background and does not respond to oxygen treatment. Recurrent cyanosis and presence of family history suggests hereditary methemoglobinemia, whilst methemoglobinemia produced by drug and chemical substances suggests acquired form. In spite of cyanosis, arterial blood oxygen pressure is within normal range. Oxygen saturation may be low. Definitive diagnosis is made with the measurement of blood level and demonstration of deficiency in cytochrome B5 reductase enzyme. Type 1 enzyme deficiency is in merely erythrocytes, while in type 2, it is in both erithrocytes and leukocytes.[15] At present, there is no cure for hereditary methemoglobinemia. These patients should avoid oxidizing drugs. For cosmetic defects, (blue skin), treatment with ascorbic acid (300-500mg/day), methylene blue (100-30 mg/day and riboflavin (60-120 mg/day) is recommended.[15]

In our patient, dsypnea, cyanosis and hypoxemia, which did not improve despite oxygen treatment, were present. In view of low saturation, high methemoglobin levels and the presence of mutation in cytochrome b5 reductase (CYB5R3) gene and the response to Vitamin C, hereditary methemoglobinemia type 1 enzyme deficiency was considered. Patient was recommended to avoid oxidizing drugs.

CONCLUSION

In the combination of dyspnea, hypoxia and cyanosis, which can not be explained by respiratory and cardiovascular causes, autosomal recessive hereditary methemoglobinemia type 1, which is a rare entity, should be kept in mind.

ETHICAL CONSIDERATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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Case Report / Olgu sunumu

Anesthesia Mumps; A Rare Complication After Surgery

Anestezi Kabakulak; Ameliyat Sonrası Nadir Görülen Bir Komplikasyon

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Abstract

Anesthesia mumps is a rare complication that occurs with sudden swelling of the parotid gland, especially after surgery. It regresses without sequelae within days with symptomatic treatment or spontaneously. It is thought that it may be due to vasodilation, hyperemia, air leakage into the stenone duct, perioperative use of drugs such as atropine, succinylcholine, morphine, and propofol, and the posture position of the patient in the operation. Anesthesia mumps appears within the first few weeks after the operation. In this article, we presented the complication that developed in the event of a short-term procedure such as double J catheter removal.

Keywords: Emergency service, parotid gland swelling, anesthesia mumps, postoperative complications.

Öz

Anestezi kabakulak özellikle ameliyat sonrası parotis bezinin ani şişmesi ile meydana gelen nadir bir komplikasyondur. Semptomatik tedavi veya kendiliğinden günler içerisinde sekel bırakmadan gerilemektedir. Vazodilatasyon, hiperemi, stenon kanalına hava kaçması, perioperatif atropin, süksinilkolin, morfin, propofol gibi ilaçların kullanımı sonucu ve hastanın operasyondaki duruş pozisyonuna bağlı olabileceği düşünülmektedir. Anestezi kabakulak operasyondan sonra ilk birkaç hafta içinde ortaya çıkar. Bu yazı da double j kateter çıkarılması gibi kısa süreli bir işlemin akşamı gelişen komplikasyonu sunduk.

Anahtar Kelimeler: Acil servis, parotis bezi şişmesi, anestezi kabakulak, postoperatif komplikasyonlar

INTRODUCTION

Anesthesia mumps is a rare complication that occurs with sudden swelling of the parotid gland, especially after surgery.[1] It can show unilateral or bilateral involvement and is mostly painless. It regresses without sequelae within days with symptomatic treatment or spontaneously.[1,2] The etiology of anesthesia mumps is unclear, although there are different mechanisms reported. Vasodilation, hyperemia, air leakage into the stenone duct, perioperative use of drugs such as atropine, succinylcholine, morphine, and propofol may ocur.[3] It is also thought that it may depend on the patient's posture during the operation. Anesthesia mumps appears within the first few weeks after the operation.[4] It was first reported in 1968 after various surgical procedures. [4] Although there are publications on this subject from Surgical Clinics and anesthesia[4-7,11] we observed that there were no reports from the emergency department regarding postoperative parotid gland swelling. In this article, bilateral parotid gland swelling is presented after double J catheter intervention (without intubation); This is one of the rare cases of anesthesia mumps in the Emergency Medicine literature.

CASE

A 43-year-old female patient was admitted to the emergency department with sudden swelling behind both ears. The patient stated that she was receiving continuous anti-histamine therapy due to chronic urticaria.

In the morning of the same day, the double J catheter attached to her kidney due to nephrolithiasis was removed. It was learned that the patient had no other medication use during the day and no medication was given other than propofol for sedation. A total 200 mg propofol 1 mg/kg dose, 100 mg IV loading dose in 3 minutes and repeated

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doses of 0.5 mg/kg 2 times with 3 minutes intervals were administered. Ramsey scale was 3 during the procedure. The patient vital signs was monitored before, during, and after the procedure.

There was no pathological feature in our patient's laboratory findings. Edema was detected in both parotid glands on ultrasound imaging.

The patient was diagnosed with anesthesia mumps, which is a rare side effect after sedation. Hydration was given to the patient by taking the opinion of the anesthesia clinic. After 3000 cc of hydration and analgesic application, the patient was discharged with hydration recommendations, as her complaints regressed (**Figure**).

DISCUSSION

Swelling of the parotid gland during or after surgery is a known but rare side effect. Although there are cases published by surgery and anesthesia clinics on this subject, we observed that there are no reports from emergency services regarding postoperative swelling of the parotid gland.

The etiology of anesthesia mumps is still unclear, despite different mechanisms reported. It is thought that breathing with a positive pressure mask may cause an increase in head and neck tone (positional problems), strain and cough, decrease in venous drainage and reverse air flow through the stenone duct.[5] In order to prevent this situation, it is recommended to prevent the compression of the parotid gland or duct by providing the patient with an appropriate position during the operation.[4] Another view is thought to be due to the vascular contraction effects of parasympathetic drugs.[6] Salivary gland enlargement; It has been identified as a unique side effect of many drugs, including analgesics, anti-histamines, muscle relaxants (succinylcholine), sedatives, and phenothiazine derivatives.[7-10] Atropine may play a role in parotid gland enlargement by causing stenosis of the salivary glands, causing thick and viscous saliva.[10] Preoperative dehydration is thought to cause more intense secretion and predispose to salivary duct obstruction.[11,12] In addition, it may cause mechanical obstruction of the parotid canal with fixation of the endotracheal tube after intubation or the inability to evacuate the secretion and temporary parotid gland enlargement due to the traumatization of the parotid canal.[13]

Unfortunately, since the exact cause is not known, there is no method that can prevent the development of anesthesia mumps and treat it directly. Treatment methods in anesthesia mumps mostly include hydration and pain monitoring. Since our patient had chronic urticaria, she frequently used antihistamine medication. In this case, we think that the main factor that triggers anesthesia mumps is the application of propofol (which is frequently used for sedation in the emergency room) during the operation and as she often use antihistaminic and the decrease in the secretions because of propofol,[14] the patient suffer from anesthesia mumps.

Anesthesia mumps can regress in a few days with abundant hydration, symptomatic treatment or no treatment. However, anesthesia mumps should definitely come to our mind in the differential diagnosis of parotitis.

CONCLUSION

Anesthesia mumps is a rare and self-limiting postoperative complication. Usually anti-inflammatory medications go away within a few days with adequate hydration.

We believe that questioning the operation history in the last few weeks in patients presenting to the emergency department with parotid gland swelling may be helpful in the diagnosis of the patients.

ETHICAL CONSIDERATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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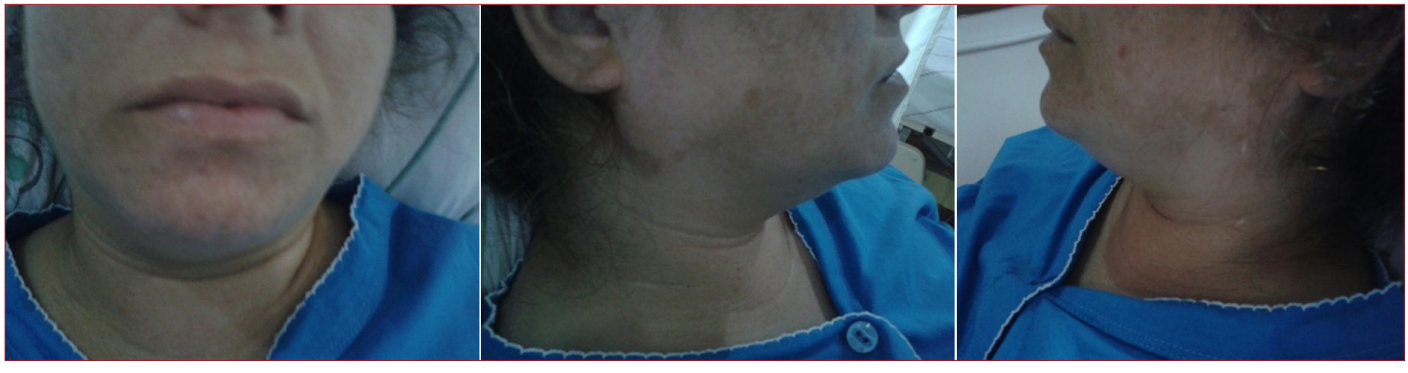

Figure. Images of the relevant case

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