Journal of Contemporary Medicine

YEAR:2021 VOLUME:11 ISSUE:4

JOURNAL OF CONTEMPORARY MEDICINE

e-ISSN 2667-7180

Formerly Çağdaş Tıp Dergisi

VOLUME 11 ISSUE 4 YEAR 2021

The Owner and Publishing Manager on behalf of
the Journal of Contemporary Medicine

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Journal article on the Internet

Abood S. Quality improvement initiative in nursing homes: The ANA acts in an advisory role. Am J Nurs [serial on the Internet] 2002 [cited 12 Aug 2002]; 102. Available from: www.nursingworld.org/AJN/2002/june/wawatch.htm

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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The Intensive Care Society of Australia and New Zealand. Mechanical ventilation strategy in ARDS: Guidelines. Int Care J Aust 1996;164:282-4.

Acknowledgements

The source of financial grants and the contribution of colleagues or institutions should be acknowledged.

Tables

Tables should be complementary, but not duplicate information contained in the text. Tables should be numbered consecutively in Arabic numbers, with a descriptive, self-explanatory title above the table. All abbreviations should be explained in a footnote. Footnotes should be designated by symbols in the following order: *,†, ‡, §, ¶.

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ORIGINAL ARTICLES

CASE REPORT

JOURNAL OF
CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.870631
J Contemp Med 2021;11(4):428-432

Orjinal Araştırma / Original Article

The Effect of Hyperemesis Gravidarum on Pregnancy Outcomes

Hiperemezis Gravidarumun Gebelik Sonuçlarına Etkisi

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Abstract

Objective: We evaluated the clinical characteristics of the patients followed with the diagnosis of hyperemesis gravidarum (HG). We aimed to determine the effects of HG on pregnancy outcomes in this study.

Material and Method: This retrospective study was conducted in the department of obstetrics and gynecology between January 2018–2020. The study group consisted of pregnant women who were diagnosed with HG before the 20th gestational week and were treated and delivered at our hospital. The patients were divided into two groups based on the presence of HG. Both groups were compared in terms of placental dysfunction and newborn outcomes. The severity of the HG was assessed and classified. A sub-analysis of the HG group comparing mild and severe cases was performed.

Results: The study included 213 patients diagnosed with HG and 218 healthy pregnant women without HG diagnosis. Preterm birth (p=0.034) and small for gestational age (SGA) (p=0.016) were significantly higher in the HG group compared to the control group. 78.8% of the pregnant women diagnosed with HG were mild and 21.1% were severe HG. When women in the severe HG group and mild HG group were compared, we found that severe HG is associated with a higher chance of SGA (p=0.042), preterm birth (p=0.001) and admission to Neonatal Intensive Care Unit (p=0.031).

Conclusions: Babies born from hyperemetic pregnant women are at a significant risk for SGA and preterm birth compared to babies born from healthy pregnant women. This risk increases especially in pregnant women with severe HG.

Keywords: Hyperemesis gravidarum, pregnancy outcomes, small for gestational age,

Öz

Amaç: Hiperemezis gravidarum (HG) tanısı ile takip edilen hastaların klinik özelliklerini değerlendirdik. Bu hastalarda HG'nin gebelik sonuçları üzerindeki etkilerini belirlemeyi amaçladık.

Gereç ve Yöntem: Bu retrospektif çalışma 2018-2020 yılları arasında hastanemiz kadın hastalıkları bölümünde gerçekleştirildi. Çalışma grubu, 20. gebelik haftasından önce HG tanısı alan ve hastanemizde tedavi edilerek doğum yapılan gebelerden oluşturuldu. Hastalar HG varlığına göre iki gruba ayrıldı. Her iki grup plasental disfonksiyon ve yenidoğan sonuçları açısından karşılaştırıldı. HG'nin şiddeti değerlendirildi ve sınıflandırıldı. Hafif ve ağır vakaları karşılaştıran HG grubunun bir alt analizi yapıldı.

Bulgular: Çalışmaya HG tanısı almış 213 hasta ve HG tanısı olmayan 218 sağlıklı gebe dahil edildi. Preterm doğum (p=0.034) ve gestasyonel yaşa göre küçük (SGA) (p=0.016) HG grubunda kontrol grubuna göre anlamlı olarak yüksek bulundu. HG tanısı alan gebelerin % 78,8'i hafif,% 21,1'i ağır HG idi. Ağır HG grubundaki kadınlar ile hafif HG grubundaki kadınlar karşılaştırıldığında, şiddetli HG'nin daha yüksek SGA (p=0,042), erken doğum (p=0,001) ve Yenidoğan Yoğun Bakım Ünitesine yatış (p=0,031) ile ilişkili olduğunu bulduk.

Sonuçlar: Hiperemetik hamile kadınlardan doğan bebekler, sağlıklı hamile kadınlardan doğan bebeklere kıyasla SGA ve erken doğum için önemli bir risk altındadır. Özellikle ağır HG'li gebelerde bu risk artar.

Anahtar Kelimeler: Hiperemezis gravidarum, gebelik sonuçları, gebelik yaşına göre küçük,

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Received *(Geliş Tarihi)*: 29.01.2021 **Accepted *(Kabul Tarihi)*:** 25.03.2021

INTRODUCTION

Hyperemesis gravidarum (HG) is a syndrome characterized by nausea, vomiting and dehydration, ketosis, electrolyte and acid-base imbalances, and sometimes hepatic and renal failure, resulting in weight loss (≥5% of body weight).[1] HG is seen in approximately 0.3-2% of pregnant women and is one of the most common reasons for hospital admission during the first half of pregnancy.[1] Although the HG clinics differ, this disorder is generally manifested by nausea and vomiting that starts in the 6-8th week of pregnancy, peaks around the 12th week and disappears until the 16-20th week. However, symptoms may continue in 5% of patients until delivery.[2]

It is often difficult to clarify the etiology in these patients given the increasing number of HG admissions today, but may be attributed to hormones, gastrointestinal dysfunction, thyrotoxicosis, serotonin, hepatic abnormalities, autonomic nervous dysfunction, nutritional deficiencies, asthma, allergies, helicobacter pylori infection, or psychosomatic causes.[3,4] The results differ among different studies in the literature investigating the effect of HG on pregnancy outcomes. The studies have shown that HG may be associated with increased small for gestational age (SGA) and preterm birth and increases the length of hospitalization in newborns.[5-8] On the other hand, some studies show that HG is not associated with adverse pregnancy outcomes. These studies have found that HG is not a risk factor for preterm birth, SGA, intrauterine growth restriction (IUGR), and low Apgar score.[8-11]

The present study has evaluated the clinical characteristics of the patients followed with the diagnosis of HG based on the conflicting results in the literature. We aimed to determine the effects of HG on pregnancy outcomes in these patients.

MATERIAL AND METHOD

Patient selection

This retrospective study was conducted in the department of Obstetrics and Gynecology of our hospital between January 2018 and January 2020. Local ethics committee approval was obtained for the study (Ethics committee number: 2020/03-53). The study group consisted of pregnant women who were diagnosed with HG before the 20th gestational week and were treated and delivered at our hospital.

Inaccessibility to full medical records, births before 24th week, gestational week or birth weight being less than 500g, hypertension, diabetes mellitus, thyroid hormone disorder, psychiatric disease, multiple pregnancy, gastrointestinal system disease, and fetal congenital malformation were reasons for patients to be excluded from the study.

Data collection and processing

The study population was determined using the electronic medical database of the obstetrics clinic. Patients age, parity, pre-pregnancy body mass index, maternal weight at birth, gestational week at birth, type of delivery, gestational outcomes and complications, fetal weight at birth, Apgar score, laboratory results, and obstetric ultrasonography results were recorded.

While benign nausea and vomiting in early pregnancy are closely related to temporarily increased human chorionic gonadotropin (hCG) levels, it has been argued that in women with hyperemesis, the persistently high hCG level dysregulates normal stimulation of trophoblast migration, which consequently alters placentation. Ultimately abnormal placentation could lead to placental dysfunction that clinically manifests as gestational hypertension, preeclampsia, as well as miscarriage, stillbirth and IUGR.[12-14] The patients were divided into two groups based on the presence of HG. Patients diagnosed with HG were included in the first group, and healthy pregnant women followed in our clinic were in the second group. Both groups were compared in terms of placental dysfunction (gestational diabetes, preeclampsia, and stillbirth), and newborn outcomes (birth weight, SGA, Apgar score at the 5th minute, and gestational week at birth).

Definitions

Severe HG was defined as a process accompanied by at least two of the following criteria in addition to severe vomiting three or more times per day before the 20th gestational week. These criteria are as follows: 1) Three or more days of hospitalization due to HG, 2) Finding of dehydration in physical examination, 3) At least one hepatic enzyme elevation (alanine aminotransferase [ALT], aspartate aminotransferase [AST]), 4) Having sodium or potassium abnormality at least once, 5) Total weight gain being below 7kg during the whole pregnancy, 6) Urine ketone level being ≥2+.[5,10] Mild HG was defined as lack of severe HG criteria. SGA was defined as a situation where birth weight is below 10 percentiles at a certain gestational age.[15] Preterm delivery was defined as giving birth before the 37th gestational week while stillbirth refers to babies born without a heartbeat after the 24th gestational week.[16]

Statistical Methods

All statistical data were analyzed using SPSS for Windows version 15.0 (SPSS Inc.; Chicago, IL, USA). First of all, descriptive statistics (number (n), frequencies (%), mean, and standard deviation) of the variables in the study group were calculated. Pearson's Chi-Square or Fisher's test was used for the comparison of the categorical data. The normal distribution of data was tested with the Kolmogorov-Smirnov test. Student's t-test was used to compare the normally distributed data, and the Mann-Whitney U test was used to compare the non-normally distributed data. P values of <0.05 were regarded as statistically significant.

RESULTS

The study included 213 patients diagnosed with HG and 218 healthy pregnant women without HG diagnosis. The mean age of the HG cases was 26.8±4.7, and the mean age of the control group was 25.6±4.6. There was no statistically significant difference between the two groups (p=0.061). 73.7% (n=157) of the pregnant women diagnosed with HG

were in the first trimester and 26.2% (n=56) were in the second trimester of pregnancy. The demographic characteristics and laboratory results of the women with HG and control group are presented in **Table 1**. The possibility of HG was higher in women with a history of HG (p=0.001). When laboratory results were compared, there was a statistically significant difference between HG and control group in terms of AST and urine ketone bodies. All the other laboratory results were similar between the two groups.

Table 1. Demographic characteristics and laboratory values of women with and without hyperemesis gravidarum

Variables	Hyperemesis (n=213)	Control (n=218)	P value
Maternal age (years)	26.8±4.7	25.6±4.6	0.061
Age>35 years	18 (8.4%)	14 (6.4%)	0.542
Body mass index (kg/cm²)	24 (21-26)	25 (22-27)	0.350
Parity			0.092
Nulliparous	62 (29.1%)	57 (26.1%)	
Multiparous	151 (70.9%)	161 (73.8%)	
Fetal sex			0.163
Female	130 (61%)	113 (51.8%)	
Male	83 (38.9%)	105 (48.1%)	
Artificial pregnancy	4 (1.8 %)	5 (2.3%)	0.746
Previous miscarriages	12 (5.6%)	8 (3.6%)	0.402
Previous cesarean section	16 (7.5%)	22 (10%)	0.345
HG in previous pregnancy	27 (12.6%)	4 (1.8%)	**0.001**
Smoking	5 (2.3%)	7 (3.2%)	0.512
Gestational age at first visit			0.856
First trimester (<12 weeks)	157 (73.7%)	155 (71.1%)	
Second trimester (12-20weeks)	56 (26.2%)	63 (28.9)	
Gestational age at delivery	38.8±2.2	39.1±2.6	0.441
Labor induction	19 (8.9%)	25 (11.4%)	0.059
Mode of delivery			0.487
C/S	68 (31.9%)	58 (26.6%)	
NSD	145 (68.1%)	160 (73.3%)	
Laboratory findings			
Hemoglobin (g/dl)	12.6±1.1	11.7±1.4	0.335
Hematocrit (10^3/ml)	36.7±2.5	35.7±3.5	0.447
Aspartate aminotransferase(U/l)	27.2±22.5	18.4±6.9	0.318
Alanine aminotransferase(U/l)	37.4±40.1	12.1±4.4	**<0.001**
Sodium (mmol/l)	135.4±2.6	136.6±1.3	0.189
Potassium (mmol/l)	3.8±0.2	4.0±0.3	0.248
Creatinine (mg/dl)	0.65±0.1	0.61±0.1	0.741
Urea (mg/dl)	22.5±8.7	20.7±5.2	0.226
Urine ketone bodies	3.1±1.4	0	**< 0.001**

Data are presented as mean±STD, Median and 25–75 percentiles or N (%), HG: Hyperemesis gravidarum, C/S: Cesarean delivery, NSD: Normal spontan delivery

Pregnancy outcomes of the HG and control group are presented in **Table 2**. Preterm birth (p=0.034) and SGA (p=0.016) were significantly higher in the HG group compared to the control group. All the other pregnancy outcomes were similar between groups. 78.8% (n=168) of the pregnant women diagnosed with HG were mild and 21.1% (n=45) were severe HG. When women in the severe HG group and mild HG group were compared, a higher rate of preterm birth (p=0.001), admission to Neonatal Intensive Care Unit (NICU) (p=0.031) and SGA (p=0.042) was observed in women with severe HG (**Table 3**).

Table 2. Pregnancy and perinatal outcomes in patients with and without hyperemesis gravidarum

	Hyperemesis (n=213)	Control (n=218)	P value
Diabetes (gestational)	4 (4.9%)	5 (2.3%)	0.514
Preeclampsia	5 (2.3%)	3 (1.4%)	0.349
Placental abruption	3 (1.4%)	1 (0.5%)	0.303
Delivery <37 wks	21 (9.9%)	10 (4.6%)	**0.034**
Birth weight in grams	3096±451	3188± 558	0.178
SGA (<10th percentile)	17 (8.0%)	6 (2.8%)	**0.016**
Apgar score <7 at 5 min.	7 (3.3%)	6 (2.8%)	0.746
Fetal distress	6 (2.8%)	4 (1.8%)	0.361
Meconium at delivery	14 (6.6%)	13 (6.0%)	0.794
Stillbirth*	1 (0.5%)	0	0.494
Admission to NICU	5 (2.3%)	4 (1.8%)	0.486

Values are presented as mean SD or n (%). * Only births >24 gestational weeks were included, SGA, small for gestational age; NICU, neonatal intensive care unit

Table 3. Pregnancy and perinatal outcomes in patients with mild hyperemesis gravidarum and severe hyperemesis gravidarum

	Hyperemesis		P value
	Mild (n=168)	Severe (n=45)	
Diabetes (gestational)	3 (1.8%)	1 (2.2%)	0.848
Preeclampsia	3 (1.8%)	2 (4.4%)	0.285
Placental abruption	2 (1.2%)	1 (2.2%)	0.511
Delivery < 37 wks	10 (6.0%)	11 (24.4%)	**0.001**
Birthweight in grams	3108±558	3074±451	0.791
SGA (<10th percentile)	10 (6.0%)	7 (15.6%)	**0.042**
Apgar score < 7 at 5 min.	4 (2.4%)	3 (6.7%)	0.165
Fetal distress	4 (2.4%)	2 (4.4%)	0.459
Meconium at delivery	9 (5.4%)	5 (11.1%)	0.148
Stillbirth*	0	1 (2.2%)	0.211
Admission to NICU	2 (1.2%)	3 (6.7%)	**0.031**

Values are presented as mean SD or n (%). * Only births >24 gestational weeks were included, SGA, small for gestational age; NICU, neonatal intensive care unit

DISCUSSION

HG is a serious complication of pregnancy characterized by severe nausea and vomiting. There is no standard process in the diagnosis and treatment of HG, as the underlying mechanisms are not fully known. However, it can have both maternal and fetal adverse effects when it is not properly treated. The relationship of HG with adverse pregnancy outcomes has been discussed for a long time.[10] We found that severe HG is associated with a higher probability of SGA, preterm birth and admission to NICU. However, there was no relationship between other adverse pregnancy outcomes including low 5-min Apgar score, stillbirth, fetal distress, meconium at delivery and placental abruption.

Studies conducted with pregnant women with HG have conflicting results. Some studies report that there is no significant relationship between HG and adverse pregnancy outcomes.[17,18] On the other hand, some studies report that

excessive weight loss and malnutrition caused by HG are more likely to result in SGA, preterm birth and low Apgar score compared to healthy pregnant women.[5-9] Veenendaal et al.[19] reported that insufficient weight gain during pregnancy is associated with a higher female/male birth rate and the incidence of SGA and premature babies in women with HG. Bailit et al.[20] showed that malnutrition during pregnancy is associated with adverse fetal outcomes. Peled et al.[21] found that women with HG who received total parenteral nutrition (TPN) support had a lower rate of preterm birth and SGA than women who did not receive TPN support. The present study found a statistically significant difference between the HG group and the control group in terms of SGA and preterm birth rates. The treatment given to pregnant women with HG is planned based on the severity of the symptoms and their effects on the mother. Pregnancy-related vomiting is not teratogenic; however, untreated electrolyte imbalance, malnutrition, and maternal weight loss can cause adverse pregnancy outcomes.

Some studies argue that HG may be associated with increased SGA risk and preterm birth, as well as causing a decrease in birth weight and an increase in hospitalization after delivery.[20-23] Bailit et al. found a significant relationship between HG and stillbirth.[20] On the other hand, Fiaschi et al. found that HG causes an increase in fetal and neonatal mortality rates, but there is no significant difference between HG and stillbirth rates.[24] We did not find a significant difference in stillbirth rates between women with HG and the control group. Peled et al. found that HG was associated with adverse short-term neonatal outcomes (admission to NICU, low Apgar score at 5th minute).[21] Fiaschi et al.[24] found that the need for NICU admission of babies born to mothers with HG increased slightly. We did not find a significant relationship between the HG and control group in terms of admission to NICU and low Apgar score at 5th minute. However, we found that admission rate to NICU was higher in severe HG patients among women with HG.

Although there are limited and inconsistent data for more severe fetal and perinatal outcomes, some studies have reported a relationship between HG and preeclampsia, placental abruption, and SGA.[12,23] On the other hand, some studies point out that there is no relationship between HG and placental dysfunction (i.e. preeclampsia, placental abruption, stillbirth, and SGA).[25,26] The present study did not find a significant relationship between HG, and preeclampsia and placental abruption.

There are some limitations of this study. First of all, the retrospective nature of the study limited the data to those that are routinely collected. The exclusion of patients with incomplete data on obstetric outcomes in women with HG was another important limitation. This retrospective study may relate to selection bias as it only includes hospitalized patients. Secondly, this was a single-center study. Further studies involving multiple centers are needed to validate our results.

CONCLUSION

Although nausea and vomiting are common in pregnant women, only a small part of it makes up the clinical picture of HG. Babies born from hyperemetic pregnant women are at a significant risk for SGA and preterm birth compared to babies born from healthy pregnant women. This risk increases especially in pregnant women with severe HG. The results of the present study revealed that pregnant women with HG need more frequent follow-up.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study protocol was approved by Clinical Research Ethical Committee of Aksaray University Faculty of Medicine with a protocol number of 2020/03-53 and conducted in accordance with the Declaration of Helsinki and Good Clinical Practices.

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

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.

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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JOURNAL OF
CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.752747
J Contemp Med 2021;11(4):433-439

Orjinal Araştırma / Original Article

Follow Up of The Growth in the Term Small for Gestational Age Infants and the Factors that Influence Growth

Term SGA (Small for Gestational Age) İnfantlarda Büyümenin İzlemi ve Büyümeyi Etkileyen Faktörler

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Abstract

Aim: Infants born small for gestational age (SGA) confront many problems in adulthood. Most of them catch up with their peer as growth in the first six months. In this study, we investigated the perinatal predictive factors that influence postnatal catch-up growth in the term SGA infants.

Material and Method: The study included seventy-three term, healthy infants. Prenatal, natal, and postnatal information forms were filled for each infant. Infants were examined in 0, 1, 6, and 12th months. The information form was recorded. At the examination time parameters concerning growth like weight, length, and head circumference were recorded. Postnatal growth catch-up was defined as above the 10th centile according to the reference population growth curves. By the SPSS 10,0 version for windows prenatal, natal and postnatal factors that influence postnatal catch-up growth were investigated.

Results: Infants in the Catch up (CU) group at the first month were significantly taller than the non-catch-up (NCU) group. APGAR scores of the group CU at the sixth month were significantly more increased than group NCU. Length and head circumference of the sixth month and body length of the twelfth month were significantly more increased than the NCU group at the sixth month. Other infections and usage of vitamin D in the group NCU in the twelfth month were significantly more increased than the group CU. Length and head circumference at the twelfth month in group CU were significantly more increased than group NCU.

Conclusion: For infants with born SGA, it is very important to follow up postnatal growth patterns and growth velocity. Body length, head circumference, and APGAR scores can be a positive predictor for the postnatal growth catch up for healthy term SGA infants. The usage of vitamin D and other infections can also be negative predictors. Infants that catch up growth first few months may anticipate that will be continued growth velocity for six months.

Keywords: SGA infant, growth catch up, perinatal predictors

Öz

Amaç: SGA doğan infantlar yetişkin hayatta birçok riskle karşı karşıyadırlar. Postnatal hayatta çoğu ilk 6 ay içerisinde hızlı bir büyüme göstererek yaşıtlarının büyüme yüzdelerini yakalarlar. Bu çalışmada sağlıklı term SGA infantların büyümeyi yakalamaya etkisi olan perinatal prediktif faktörler incelendi.

Gereç ve Yöntem: Çalışmaya sağlıklı 73 term SGA infant katıldı. Her hasta için prenatal, natal ve postnatal bilgi formu dolduruldu. İnfantların 0, 1, 6 ve 12. aylarda fiziki incelemeleri yapıldı ve geçmişe yönelik anamnez formu dolduruldu. Muayene sırasında kilo, boy ve baş çevresi gibi büyüme ile ilgili parametreler kaydedildi. Postnatal dönemde büyümeyi yakalama kriteri olarak referans toplumun büyüme eğrilerinde 10. persentilin üzerine çıkma olarak tanımlandı. Büyümeyi yakalama üzerine SPSS 10.0 kullanılarak perinatal, natal ve postnatal faktörlerin etkisi araştırıldı.

Bulgular: Bulgular 1. ayda catch-up (CU) grubundaki infantların boyu non-catchup (NCU) grubundakilerden anlamlı derecede daha uzun idi. 6. aydaki CU grubunun APGAR skorları, 6.ayda ölçülen boy ve baş çevresi, 12. ayda boy ölçümleri NCU grubuna göre daha fazla bulundu.12. aydaki NCU grubunda diğer enfeksiyonlar ve D vitamini kullanımı CU grubuna göre daha fazla bulundu. Vakaların 12. aydaki boy ve baş çevreleri NCU grubuna göre daha fazla bulundu.

Sonuç: SGA'lı doğan infantların postnatal büyüme paternlerini ve büyüme hızlarını takip etmek son derece önemlidir. Sağlıklı term SGA infantlar için postnatal büyümeyi yakalamada boy ve baş çevresi ve APGAR skorunun pozitif belirleyici, D vitamini ve diğer enfeksiyonların negatif belirleyiciler olarak kullanılabilir. Ve ilk aylarda büyümeyi yakalayan infantların büyüme hızlarını özellikle ilk 6 ay koruyabilecekleri öngörülebilir.

Anahtar Kelimeler: SGA infant, büyümeyi yakalama, perinatal belirleyiciler

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Received *(Geliş Tarihi)*: 16.06.2020 **Accepted *(Kabul Tarihi)*:** 24.03.2021

INTRODUCTION

Fetal development is affected by many factors that affect growth. Fetal factors are more prominent in the first half of pregnancy, and maternal environment and uteroplacental factors are more prominent in the second half of pregnancy. In this growth process, factors affecting the fetus cause growth retardation. SGA (Small for gestational age) definition is used to define infants whose birth weight or birth height is below –2 SD (Standard Deviation) for that gestational age according to the data of the reference society.

While the SGA incidence is observed at an average rate of 16% in societies, this rate has been detected as 7% in industrial areas and 41, 5% in South Asia.[1,2] Approximately 90% of all SGA births are term SGA infants.[2] Infants born SGA face increased risks in adult life in terms of persistent short stature, insufficient intellectual functions, and chronic diseases such as Type-2 DM (Diabetes Mellitus) and ischemic heart disease.[3] Most infants with SGA catch up with the growth percentages of their peers after birth gradually. Mostly, this catch-up growth is achieved in the first 6 months of life.[4] Only a small portion of infants; especially premature babies continue to catch up towards the second years of their lives. Many factors play a role in postnatal growth. Early detection of babies who cannot catch growth parameters after birth and follow-up of such babies in terms of the risks they will be exposed to in both adolescence and adult life are very important. In this study, it was aimed to evaluate catch-up growth and factors that influence catch-up growth by making anthropometric measurements such as height, weight, and head circumference at the first 1, 6, and 12 months in healthy term SGA babies.

MATERIAL AND METHOD

Term infants born in Selçuk University Meram Medical Faculty and Faruk Sukan Maternity Hospital between October 2004 and October 2005 were included in our study. Ethical approval was obtained from the ethics committee of the Selcuk University Medical Faculty with the decision dated July 1, 2004, and numbered 2004/078. Those who are between 38 and 42 weeks according to the last menstrual period, whose term and birth weight or height are below 10% according to the Lubchenko curve as SGA (small for gestational age), those between 10 - 90% as AGA (appropriate for gestational age), those above 90% as LGA (Large for gestational age)" were accepted.[5] Gestational age was determined according to the last menstrual period or ultrasound measurements. For babies who were not followed up during pregnancy and mothers who did not know the first day of their last menstrual period, the gestational ages on the first day of life were determined by Ballard scoring.[6] The infants included in the study group were physically examined on the day of birth, at the 1st, 6th, and 12th months, and anthropometric measurements such as height, weight, and head circumference were performed. Follow-up was done with the growth chart of Turkish children made by Neyzi and her friends.[7] Identity information, family information, prenatal, natal, and postnatal information forms of each baby's family were filled at the time of delivery. If they were hospitalized, the length of stay and the reason were recorded. Babies with dysmorphic findings, anomaly, prematurity, stage III hypoxic-ischemic encephalopathy, and major congenital abnormalities that would affect growth during follow-up were excluded from the study. Routine nutritional recommendations were given to all babies on nutrition issues. They were also advised to take 400 units/day of vitamin D. Iron supplements were recommended to each family at 4-6 months. During the follow-up of all babies, records including the measurement of growth, nutritional history, starting age and type of supplementary food, use of vitamin D, use of iron preparations, previous illness, and chronic disease were recorded. Catch-up growth was considered as the weight and height increase over the 10th percentile according to age and gender during follow-up.[8] The group that caught the growth was called catch-up (CU), the group that couldn't catch it was called non-catch - up (NCU). Variables in prenatal, natal, and postnatal periods that may affect growth between the CU and NCU groups were investigated. 73 term SGA babies were included in the study group. Physical examinations were performed after the height, weight and head circumference of the babies were recorded at birth. The information form has been filled in. The weight measurement was done naked by the same person with the baby scale. Height measurement was measured with a height measuring board with a fixed head and a movable foot part. Head circumference was measured using a non-flexible plastic measuring tape using the glabella and the area where the occipital region is the most protruding. Babies who lost their lives in the neonatal period and those with a deficiency in anthropometric measurements such as height, weight, and head circumference were not excluded from the study due to the presence of demographic data. Statistical analyzes were performed using SPSS version 10.0. Parametric data were recorded as mean±standard deviation. Categorized data were compared using Chi-square analysis. T test was used to evaluate the effect of independent variables on growth patterns. For statistical significance, $p<0.05$ was accepted.

RESULTS

73 term SGA newborns were included in the study. The study group was re-evaluated at 1, 6, and 12 months. The group that reached the 10th percentile by weight was defined as catch-up (CU), and the group that could not catch it as non-catch-up (NCU). Due to the nature of the study, it was a prospective and follow-up study, and the number of patients attending regular controls decreased, and 73, 38, 29, and 23 infants participated in the study at 0, 1, 6, and 12 months, respectively. CU and NCU groups were compared for each control period. The general characteristics of the cases are shown in **Table 1**.

Table 1. Fundamental characteristics of the study group

Characteristics	N (Number)	Mean±SD
Birth weight (gr)	73	2255±195
Birth length (cm)	71	46.7±2.2
Birth head circumference (cm)	62	32.8±1.2
HC at 1st month	35	35.2±1.2
Length at 1st month	37	50.75±2.05
Weight at 1st month	38	3355±553
HC at 6th month	19	42.1±1.4
Length at 6th month	23	63.2±2.5
Weight at 6th month	29	6480±800
HC at 12th month	20	46.05±1.5
Length at 12th month	22	73±2.6
Weight at 12th month	24	9014±1021
Breastfeeding		
Yes (%)	47(97)	
No (%)	1 (3)	
Breastfeeding for 3 months (%)	3 (6.3)	
Breastfeeding for 6 months (%)	4 (8.3)	
Breastfeeding for 12 months (%)	30 (62.5)	
Breastfeeding duration		9.43±2.7
Formula use		
Yes (%)	23 (51)	
No (%)	22 (49)	
For 1 month (%)	21 (46.7)	
For 3 months (%)	1(2.2)	
For 12 months (%)	1 (2.2)	
Formula duration	45	2.73±3.63
Vitamin D use duration	45	8.39±4.05
The rates of vitamin D use		
Yes (%)	43 (95.6)	
No (%)	2 (4.4)	
For 1 month (%)	3(6.8)	
For 6 month (%)	2 (4.5)	
For 12 months (%)	20 (45.5)	
Iron use		
Yes (%)	32 (74.4)	
No (%)	11 (25.6)	
For 3 months (%)	6 (14)	
For 6 months (%)	10 (23.3)	
For 8 months (%)	2 (4.7)	
Duration of iron use		3.67±2.67
The history of infection		
Yes (%)	27 (61.4)	
No (%)	17 (38.6)	
URTI (%)	19 (43.2)	
1 time	14 (31.8)	
2 times	3 (6.8)	
4 times	2 (4.5)	
UTI (%)	1 (2.3)	
LRTI (%)	13 (29.5)	
1 time	9 (20.5)	
2 times	4 (9)	
CNS infection (%)	0(0)	
Acute gastroenteritis (%)	1 (2.3)	
Other infections (%)	4 (9)	

Abbreviations: HC: Head circumference; URTI: Upper respiratory tract infection; UTI: Urinary tract infection; LRTI: Lower respiratory tract infection; CNS: Central nervous system

The number of cases evaluated in the first month was 38. Achieving growth was detected at a rate of 55.3% among all cases. When the groups that achieved growth and those who failed to achieve growth were compared, their height at the end of the first month was 51.7±1.46 cm in the CU group and 49.5±2.98 cm in the NCU group. There was a statistically significant difference between the two groups ($p<0.05$). Infants in the CU group were taller. There was no significant difference between the two groups in terms of other variables.

Height and head circumference measured at 6 months were significantly higher in the CU group. The 6th month height and head circumference in the CU and NCU groups were 64.18±1.46 cm, 61.67±3.2 cm and 42.74±0.96 cm, 41.07±1.53 cm, respectively ($p<0.05$). In the follow-up of the cases, height and weight measurements at 12 months were significantly higher in the CU group ($p<0.05$).

Significant associations were found between height at 6th month, head circumference at 12th month, height at 12th month, head circumference, and duration of vitamin D use related to achieving growth at 12th month. At the sixth month, head circumference was 43±1 cm and 39.8±1.2 cm, respectively, in the CU and NCU groups, while height measurements were 63.6±2 cm and 59±1 cm, respectively. The height and head circumference of the cases at 12 months were significantly higher in the CU group. The height was 73.7±2.2 cm in the CU group, 69±1 cm in the NCU group, 46.5±1.3 cm in the head circumference in the CU group, and 43.8±0.7 cm in the NCU group, and this difference was found to be significant ($p<0.05$). While there was no significant difference between the two groups in terms of the use of breast milk, formula, and Fe preparations during the first year of life ($p>0.05$), the duration of vitamin D use was significantly higher in the NCU group ($p<0.05$). The mean duration of vitamin D use was 7.75±4.9 months in the CU group, while it was 12±0 months in the NCU group ($p<0.05$).

DISCUSSION

Many factors related to SGA birth have been identified. These include fetal, maternal, uteroplacental, and demographic factors. Demographic factors; Groupings can be made such as maternal age too advanced or too young, mother's weight and height, born of mothers with low birth weight, nulliparity or grand multiparity, mother's inability to gain enough weight during pregnancy, maternal history of a baby with SGA before.

The average height of the mothers was 160.9±7.17 cm. All of the infants in the study thought that when babies with SGA, maternal height was found close to the average height of women in Turkey. Since the comparison of AGA and SGA groups was not made in our study, the relationship between maternal height and SGA birth was not evaluated. However, when the effect of maternal height on growth catch-up was evaluated, it was observed that there was no significant effect on the groups. Since the birth weights of the mothers of the infants participating in the study were not known, the mother's

birth SGA and the relationship between the participants in the study group and growth catch-up could not be evaluated. In the literature, nulliparity and grand multiparity SGA have been associated with birth and considered as risk factors.[9] Considering that 55.4% of the mothers of babies with SGA in our study were their first pregnancy, it is consistent with the literature. There were no grand multipara mothers among our cases. Previous SGA sibling or stillbirth history has been associated with SGA birth.[10] In the history of our cases, 7.7% had a previous sibling history with SGA and a stillbirth history in 5.9%.

Chronic diseases in the mother, placental, uterine and cervical anomalies are other risk factors for the development of a baby with SGA. No chronic disease, placental, uterine and cervical anomalies were found in the mothers of the babies with SGA who participated in our study. Smoking and alcohol consumption of the mother are also important risk factors. None of the mothers consumed alcohol during their pregnancy, only 7.7% of the mothers had smoked. In the study of Harding et al.[8], It was shown that only the mother's use of aspirin and the gestational age, when diagnosed with SGA, had significant effects on growth catch-up between antenatal variables. In our study, no positive or negative effects of antenatal variables on growth catch-up could be detected.

One of the factors that is thought to have an effect on postnatal growth is nutritional status of the infants. Different results were obtained in breast milk and formula comparisons. In the study by Ounsted et al.[11] , They reported that infants who were breastfed showed faster growth than those fed with formula. A study by Fewtrell et al.[12] , who investigated the effect of breast milk, term standard formula, and enriched term formula on postnatal growth in term SGA infants, showed that the type of nutrition did not affect the linear growth process. They suggested that those who catch the growth in the first months maintain their growth rates until the 9th month, and they found that the earlier catch-up growth is associated with longer duration of this process. In our study, 55.3% of the cases achieved growth cutch-up in the postnatal 1st month. They maintained similar rates to these rates in the 6th month. The rate of those who achieved growth in the 6th month was 62.1%. In the same study, they found that the 9th-month head circumference was greater than those using formula.[11] In our study, 97.9% of the infants used breast milk, and 46.6% used formula. The mean duration of breast milk intake was 9.43±3.7 months and 62.5% of the infants had maintained breast milk consumption for 12 months. Similar to the study conducted by Fewtrell et al.[12], We did not find a significant difference between the groups that caught up and failed catch-up growth in terms of breast milk and formula use. In the study of Arefeen et al.[13], Data related to breast milk and nutrition effect on growth catch-up were found similarly. It has been shown that among those receiving breast milk, those with good birth weight and full-term AGA infants continued to stay above -2 SD almost throughout the infantile period. In other words, birth weight was shown in the foreground rather than breast milk. In our study, we did not find a positive relationship between breast milk intake and growth catch-up. In the studies of Arefeen et al.[13], In which premature babies with SGA were included and the growth follow-up of infants was investigated, over 1000 infants were followed, it was shown that the growth rate got slower as the birth weight decreased. Since premature babies were also evaluated in this study, the complications of preterm birth and problems associated with prematurity may have affected the growth rate. In our study, although there was no statistically significant difference for each control period, the average birth weight was higher in the groups that achieved growth catch-up. In the same study, there were differences in the general characteristics of the population and the selection of cases. More than half of the selected infants were males. In our study, 46% of the infants were male. 75% of the mothers are illiterate, 60% of the fathers did not have any level of education. 83.6% of the mothers of the infants in our study were primary school graduates. It is known that SGA birth rates in African countries with low levels of education increase up to 70%, although the education level and SGA vary according to the societies studied on SGA birth.[21] Studies have shown that maternal education level does not affect catch-up growth.[15] Similarly, we did not find a relationship between maternal education level and achieving growth catch-up. Also, while 26% of the mothers of infants born SGA were the first pregnancy, 23% were the second pregnancy, 55.4% of the mothers in our study were the first and 24.6% were the second pregnancy. While 31% of the mothers had a stillbirth history before, 5.9% of the mothers included in our study had a stillbirth history. Basic differences such as education level, history of stillbirth, development level, and perinatal health services seem to be related. In their studies conducted in Bangladesh, there were significant differences between the average birth weights of infants. While the mean birth weight of the babies was 2516±404 gr, the mean birth weight of the infants in our study was 2255±195 gr. The average height at birth was similar. It was 47.7±2.3 cm and 46.7±2.28 cm, respectively. In their study, a strong relationship was found between growth patterns and anthropometric measurements at birth. They did not find a significant difference at any measurement time between the groups that were allocated to every 500 grams according to their birth weight. While there was little difference between preterm AGA and term SGA infants, the mean birth weight of preterm SGA infants at any point was significantly lower than the other groups. The reason for this may be due to the negative effects of problems such as prematurity and low birth weight on growth. Although premature babies were not included in our study, we found that the group that achieved growth catch-u in the measurements made at birth and in the following months had a significantly higher regarding height and weight than the group that failed to achieve growth. Accordingly, better height and weight at birth and early follow-up may be a determining factor in achieving postnatal growth. Term AGA infants were also included in the studies of Arefeen et al.[13] They found that heavier infants grew

faster in the first months of life, especially in the first 3 months, compared to lighter infants, and they maintained this growth pattern until the second half of life. Infants with normal birth weight showed an average monthly weight gain of 73 g more than low birth weight infants. In our study, although there are no babies above 2500 gram, it is understood that the rate of catching postnatal growth of infants in the 1st month and 2nd month is 55% and 70%, and it is understood that rapid growth is observed in the first months and the growth potential of this group is better.

In the study conducted by McCowan et al.[15] In which perinatal markers were investigated on the growth parameters of SGA infants at the 6th month; infants who have catch-up growth at the 6th months of age, in terms of maternal factors such as maternal age, height, weight at birth, being married, maternal education, having their first pregnancy, hypertension during pregnancy, smoking; There was no statistically significant difference between normal and short groups. They found that among the maternal factors, mothers had significantly more European ethnicity in the group with normal height than in the group with a short height. Although there is no significant difference between maternal heights, some racial factors may determine the postnatal growth pattern. In our study, although ethnic origin was not taken into account, we obtained similar results in terms of general characteristics of maternal factors other than maternal education and smoking. Although no statistical significance was found in terms of these factors in our study, the smoking rate of mothers was found to be between 20 and 30% in their study, and 7.7% in our study. In their study, while the rates of secondary education and tertiary education were around 45 and 50%, 83.6% of the mothers in our study were only primary school graduates. In the same study, when intrauterine and fetal factors that may affect growth were examined, in the group whose height was normal in the 6th month, the fetal abdominal circumference was larger, the gestational week was better, the birth weight was better, the birth weight and the height had smaller Z scores had positive predictive values. They found that the use of antenatal steroids, being under 32 weeks at birth, being hospitalized in the neonatal period, staying in the hospital for a longer period, and having a chronic lung disease had negative predictive values.[15] In our study, premature babies were excluded from the study and none of the cases received steroids during the antenatal period. Similarly, birth weights and heights were higher in the CU group. However, no significant difference was found between the groups in terms of the reason for hospitalization and the day of hospitalization in the neonatal period.

Although vitamin D was not investigated as a marker in studies on growth catch-up, the reason why vitamin D use was among the negative determinants in our study; The mothers in the group NCU thought that their babies were not growing and took care of the use of vitamin D, which may be due to the neglect of the mothers in the other group because their babies seem healthy.

In the study of McCowan et al.[15], In which groups with normal and slow growth according to weight in the 6th month were compared, they found significant differences in terms of height and head circumference Z scores at birth, among the parameters listed above. They observed that the group whose weight was normal for the 6th month had better birth height and head circumference Z scores.[15] Especially in the follow-up of infants born with SGA, published by Albertson et al.[16] in 1993, they showed that the male gender achieved faster growth than girls in terms of weight.[16] In our study, we did not find any significant difference in terms of gender, as in McCowan's study. Many different studies have shown that infants with low birth weight, especially those below 1500 g, exhibit very slow and late growth in the postnatal period, especially in the first year, and face great risks in the growth period.[17-19] In some studies on premature infants, data showing that inappropriate nutritional regimens after hospital discharge are determinative in terms of growth failure have been obtained.[20,21] In our study, we did not find any significant difference between the groups that caught up in growth and failed growth in terms of nutrition. In a similar study by Harding et al.[8], SGA infants were followed for 18 months and prenatal and postnatal markers were examined on growth catch-up. Unlike our study, the groups were divided into 4 subgroups as early catch up, transient catch up, late catch-up, and non catch up. Variables were including similar parameters to our study. Most of the cases, 74%, were in the early catch-up group which they were the group that reached the 10th percentile by weight in the first 6 months. 8% was in the group that caught up with growth temporarily, 7% was in the group that caught up with growth late, and 11% was in the group that failed to achieve growth. The infants participating in our study were followed for 12 months, and our groups were divided into two groups, the group that could catch-up growth or not. In our study, the rate of those who achieved catch-up growth in the 6th month was determined as 66.2%. In their study, in which infants were followed for 18 months, significant differences were found regarding the gestational week when SGA was diagnosed, and the use of aspirin during pregnancy. The week of gestation, when diagnosed with SGA, was found to be significantly lower in the non-catch-up group and the late catch-up group. This parameter was not included in the study variables since the parents of the infants included in our study were diagnosed with SGA only at birth and in the near-term period due to low sociocultural levels or due to irregular follow-up. Making the diagnosis of SGA in the early weeks of gestation may be related to the etiological factors causing symmetrical SGA. It is a known fact that the rate of catch-up growth is lower in symmetrical SGA babies. In our study, only one mother used aspirin during the antenatal period, and that infant was included in the group that achieved catch-up growth at the 4th month and maintained its place in the group that achieved catch-up growth until the end of the 12th month. When the effect of postnatal variables in Harding's study on catching growth is examined; they found significant

differences between the groups in terms of the gestational week, birth weight, height, and head circumference; standard deviation scores (SDS) of birth weight, height, and head circumference; placental weight, placenta/birth weight ratios, oxygen support requirement, hospitalization rates and length of hospital stay. The NCU group had significantly lower birth weight, height, and head circumference. In our study, premature babies were not included, and no significant difference was found between the group that caught up in growth and the group that failed in terms of these parameters at birth. However, some parameters such as height, weight, and head circumference in the follow-up were found significantly higher in the group that achieved catch-up in growth in some months. In Harding's study, SDS of birth weight, height, and head circumference were found to be significantly lower in the NCU group. Many of the parameters listed above may be due to prematurity and its complications, immaturity of many systems, and consequent problems of adaptation to postnatal life and nutritional deficiencies. In the study mentioned above, hospital duration, oxygen support duration, and hospitalization rates in the postnatal period were found to be significantly higher in the group that failed to achieve growth. In our study, we did not find any significant difference between the groups in terms of the cause of hospitalization and length of stay in the postnatal period. There may be several reasons why there was no significant difference in our study. Since the groups consist of term infants, it can be interpreted as the absence of complications of prematurity, the shorter length of hospitalization, and to be neonatal jaundice among the most common causes of hospitalization. The average hospital stay of the infants in our study was 2.76 days. In their study involving premature babies, this difference can be understood more easily considering that the average hospital stay of the group that failed to achieve catch-up growth was 35 days.[8]

In the group that failed to achieve catch-up growth which an average birth week of 33 weeks this group, supplemental oxygen was significantly higher than the other groups. Only one of the patients required hospitalization due to respiratory problems in our study. It was observed that this baby was also in the NCU group in his 12-month follow-up. As a result, it is a known fact that the foundations of many problems observed in adolescence and advanced stages of life are laid in intrauterine life.[22,23] In this context, it is very important to know what problems await babies born with IUGR, prediction, and follow-up of growth patterns in the postnatal period, and measures that can be taken regarding preventive medicine. Especially pediatricians should discuss with their parents of infants born with SGA in all aspects of IUGR and the problems awaiting these babies, including psychological support. Furthermore, these babies face increased risks in terms of neurological development, poor school performance, and socialization deficiencies. Another known risk Metabolic Syndrome in which include type 2 DM, hypertension, obesity, and hyperlipidemia, is observed in adolescents and adults. Consequently, the increased risk of cardiovascular system diseases should be discussed with parents. Another important problem is also the persistent short stature observed in 10% of babies born SGA. It is a known fact that most SGA infants catch up in growth compared to their peers in the first 6 months of life. Infants who fail to catch up with their peers, especially in the 18th month, may also have a shorter adult final height.

CONCLUSION

Factors related to SGA birth and postnatal growth should be well known and timely and on-site interventions should be made in terms of both medical and psychological support to deal with these problems. Multi-center and detailed studies with a large number of cases should be planned to determine the factors related to evaluate catch-up growth in the postnatal period.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval was obtained from the ethics committee of the Selcuk University Medical Faculty with the decision dated July 1, 2004, and numbered 2004/078.

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

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.

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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JOURNAL OF
CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.901361
J Contemp Med 2021;11(4):440-444

Orjinal Araştırma / Original Article

Parameters That May Indicate Early Postoperative Rejections in Patients with Liver Transplantation

Karaciğer Nakli Yapılan Hastalarda Postoperatif Erken Dönemdeki Rejeksiyonların Göstergesi Olabilecek Parametreler

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Abstract

Aim: We aimed to investigate the importance of inflammatory parameters in determining acute rejection in the early post-operative period in liver transplant patients.

Material and Method: When rejection was developed and after pulse steroid therapy, Preoperative, Hemoglobin, Neutrophil / Lymphocyte rate, AST / Lymphocyte rate, AST / Neutrophil rate, ALT / Lymphocyte rate, ALT / Neutrophil rate, CRP / Albumin rate, Glucose, tacrolimus and GRWR levels of patients who developed rejection in the early period after liver transplantation performed Yeditepe University Hospital in 2020 were measured. Preoperative and discharge values of the group without rejection were also evaluated.

Results: Acute rejection developed in the first one month in the early postoperative period at eight (23.5%) of 34 patients who underwent liver transplantation. It was observed that there were significant differences in terms of changes in ALT and AST values at different stages of treatment in clients who developed rejection (p=0.01). The preoperative albumin value of the patients who developed rejection was significantly lower than the patients who did not develop rejection (p=0.040). The difference among pre-transplantation CRP values was significant (p=0.035). In the multiple analyzes performed, the ratio of neutrophil/lymphocyte (p=0.026), AST/lymphocyte (p=0.003), ALT/lymphocyte (p<0.001) and ALT/neutrophil (p=0.003) at the rejection stage according to the pre-transplantation period was significant.

Conclusion: Acute rejection can occur days after transplantation and may lead to graft failure. The importance of parameters that supports the correct diagnosis in treatment is increasing day by day.

Keywords: Liver transplantation, rejection, immunosuppression

Öz

Amaç: Karaciğer nakli yapılan hastalardaki postoperatif erken dönemde gelişen akut rejeksiyonların belirlenmesinde enflamatuar parametrelerin önemini araştırmayı amaçladık.

Gereç ve Yöntem: 2020 yılında Yeditepe Üniversitesi Hastanesinde yapılan karaciğer nakilleri sonrası erken dönemde rejeksiyon gelişen hastaların, preoperatif, rejeksiyon geliştiğinde ve pulse steroid tedavi sonrası taburculuğundaki hemoglobin, Nötrofil/Lenfosit oranı, AST/Lenfosit oranı, AST/Nötrofil oranı, ALT/Lenfosit oranı, ALT/Nötrofil oranı , CRP/Albumin oranı, Glukoz, tacrolimus ve GRWR düzeylerine bakıldı. Rejeksiyon gelişmeyen grubun da preoperatif ve taburcu edildiğindeki değerlerine bakıldı.

Bulgular: Karaciğer nakli yapılan 34 hastadan sekizinde (%23,5) postoperatif erken dönemde ilk bir ayda akut rejeksiyon gelişti. Rejeksiyon gelişen hastalarda ALT ve AST değerlerinin tedavinin farklı aşamalarındaki değişimleri açışından anlamlı farklılıkların olduğu görüldü (p<0.005). Pre-transplantasyon ve taburculuk öncesi ölçülen hemoglobin, trombosit, nötrofil, lenfosit, ALT, AST ve serum glukoz değerleri arasında anlamlı farklılık tespit edilmedi (p>0.05). Rejeksiyon gelişen hastaların preoperatif albümin değeri, rejeksiyon gelişmeyen hastalardan anlamlı olarak daha düşüktü (p=0.040). Pre-transplantasyon CRP değerleri arasındaki fark anlamlı idi (p=0.035). Yapılan çoklu analizlerde, pre-transplantasyon dönemine göre rejeksiyon aşamasında nötrofil/lenfosit (p=0.026), AST/lenfosit (p=0.003), ALT/lenfosit (p<0.001) ve ALT/nötrofil (p=0.003) oranlarında anlamlı idi.

Sonuç: Akut rejeksiyon transplantasyondan günler sonra ortaya çıkabilen ve greft kaybı ile sonuçlanabilen bir tablodur. Tedavisinde doğru tanıyı destekleyecek parametrelerin önemi her geçen gün daha da artmaktadır.

Anahtar Kelime: Karaciğer transplantasyonu, rejeksiyon, immünsupresyon

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Received *(Geliş Tarihi)*: 22.03.2021 **Accepted *(Kabul Tarihi)*:** 02.04.2021

INTRODUCTION

Transplantation is the only treatment method for end-stage organ failure such as liver, heart, lungs, and pancreas. The method of the follow-up and treatment of these patients requires a multidisciplinary approach among related patients. One of the most important problems after liver transplantationis that an acute rejection picture occurs days later. T lymphocytes that respond to alloantigenes such as MHC molecules in vascular endothelial and parenchymal cells cause the development of an acute reaction. Activated T lymphocytes kill the graft cells directly by destroying them or by activating the inflammatory cells that cause necrosis and secreting cytokines. The effects of T lymphocytes in acute rejection can be reduced by immunosuppressive therapy. Therefore, early diagnosis and treatment of rejection is very significant.[1,2]

In our study, we aimed to investigate the importance of inflammatory parameters and their contribution to the early diagnosis and treatment process in patients who developed acute rejection after liver transplantation.

MATERIAL AND METHOD

The records of 34 patients who underwent liver transplantation between January and December 2020 in the Yeditepe University Organ Transplant Clinic were retrospectively analyzed after receiving the approval of the Ethics Committee of the Yeditepe University Faculty of Medicine (Clinical Research Ethics Committee Decision No: 1391). Signatures of all patients included in the study were obtained on the informed consent form. According to the results obtained, the patients were divided into two groups. The first group (Group I) included patients who developed acute rejection, while the second group (Group II) included clients who did not develop acute rejection. Hemoglobin, Neutrophil / Lymphocyte rate, AST/Lymphocyte rate, AST/Neutrophil rate, ALT/Lymphocyte rate, ALT/Neutrophil rate and CRP/Albumin ratios, glucose, tacrolimus levels were compared by statistical methods among the groups when were patients discharged preoperatively, rejection developed, and after pulse steroid therapy.

Statistical Analysis

In summarizing the data obtained from the study, descriptive statistics were tabulated as average±standard deviation or median, minimum and maximum, depending on the distribution for numerical variables. Categorical variables were summarized as numbers and percentages. The normality of numerical variables was controlled by Shapiro-Wilk, Kolmogorov-Smirnov and Anderson-Darling tests. In comparing two independent groups; Mann Whitney U test was used in cases where numerical variables did not show normal distribution. In comparing the differences between categorical variables according to groups, Pearson Chi-Square was used in 2×2 tables with expected cells of five and above, Fisher's ExactTest was used in tables with expected cells below five, while Fisher Freeman Haltontest was used in R×C tables where expected cells were below five. The Wilcoxon test was used in numerical variables that did not show normal distribution to evaluate the differences between tacrolimus (ng/mL) rejection and pre-discharge measurements. Friedman Test was used to evaluate the statistical differences between pre-transplantation, rejection and pre-discharge measurements. Durbin-Conover test was used to detect differences between measurements.

Statistical analyzes were made by "Jamovi project (2020), Jamovi (Version 1.6.16.0) [Computer Software] (Retrieved from https:// www.jamovi.org) and JASP (Version 0.14.1.0) (Retrieved from https: // jasp- stats.org) programs and the significance level was taken into account as 0.05 (p-value) in statistical analysis.

RESULTS

The average age of the patients (n=34) included in the study was 51.9±12.1 years. Male patients constituted the majority (61.8%) and median BMI (body mass index) was calculated as 26.9 kg/m². The groups were similar in terms of age, gender distribution and BMI (**Table 1**).

Table 1. Demographic characteristics of the patients in the groups

	All patients (n=34)	Patients who developed rejection (n=8)	Patients who did not developed rejection (n=26)	p
Age (year)	51.9±12.1 54 [22-72]	55.1±7.9 54.5 [45-68]	50.9±13.1 54 [22-72]	0,563*
Gender				
Male	21 (61.8)	5 (62.5)	16 (61.5)	0.999**
Female	13 (38.2)	3 (37.5)	10 (38.5)	
Height (cm)	165 [145-187]	163.5 [157-186]	166.5 [145-187]	0,858*
Weight (kg)	72 [46-104]	74 [60-100]	72 [46-104]	0,563*
BMI (kg/m²)	26.9 [17.7-37.7]	27.4 [24-32]	26.7 [17.7-37.7]	0,647*

Descriptive statistics were tabulated as average±standard deviation or median, minimum and maximum, depending on the distribution for numerical variables. Categorical variables were summarized as numbers and percentages..
*. Mann-Whitney U test used. **. Pearson Chi-Square, Fisher's Exact or Fisher Freeman Halton test used. BMI: Body mass index

As a result of the statistical evaluations, significant differences were observed in ALT and AST values in patients who developed rejection (Group I) in terms of changes at different stages of treatment ($p<0.001$ and $p=0.010$). In multiple analyzes, ALT and AST values at the rejection stage were significantly higher than pre-transplantation values. The average ALT 25 IU/mL and 44.5 IU/L AST values before transplantation, increased to average values that 190.5 IU / mL and 186.5 IU / mL at the rejection stage ($p <0.001$ and $p=0.001$). Significant decreases were observed in ALT and AST values at the discharge process compared to the rejection process($p <0.001$ and $p=0.003$). There were no significant differences in terms of other variables in terms of pre-discharge, rejection process and pre-transplantation change. Neutrophil and lymphocyte counts, ALT and CRP values before discharge were significantly higher in patients who did not develop rejection (Group II) compared to pre-transplantation values ($p<0.05$).

The preoperative albumin value of the patients with rejection (Group I) was significantly lower than the patients who did not developed rejection (Group II) (median value 3.2 g/dL etc. 4 g/dL, p=0.040).

While pre-transplantation CRP value was 11 mg/dL in patients with rejection (Group I), it was measured as 3.5 mg/dL in patients who did not developed rejection (Group II). The difference between them was significant (p=0.035). Neutrophil / lymphocyte, AST/lymphocyte, AST/neutrophil, ALT/lymphocyte, and ALT/neutrophil rates in patients with rejection (Group I) were found to show significant changes at different stages of the treatment process (p<0.005) (**Table 2**). In multiple analyzes, the rejection process compared to the pre-transplantation period when significant increase was present in neutrophil / lymphocyte (p=0.026), AST/lymphocyte (p=0.003), ALT/lymphocyte (p<0.001) and ALT/neutrophil (p=0.003) rates, significant decreases were found in AST / lymphocyte (p=0.001), AST/neutrophil (p<0.001), and ALT/lymphocyte (p=0.003) rates in the pre-discharge period compared to the rejection process (**Table 2**).

CRP/albumin and thrombocyte / lymphocyte rates did not show significant changes at different stages of treatment in patients with rejection (Group I) (p>0.05). In patients who did not developed rejection (Table II), ALT/lymphocyte and CRP/albumin rates were found to be significantly higher in the pre-discharge period compared to the values in the pre-transplant period (p=0.023 and p=0.016). It was observed that the AST/Neutrophil rate decreased before discharge (p=0.001).

When tacrolimus level was taken into account in patients with rejection (Group I) and who did not developed rejection (Group II), pre-discharge values were similar (p=0.714).

Table 2. Comparison of the treatment process of patients with and without rejection in terms of proportional laboratory values in the pre-transplantation, rejection and pre-discharge stages

	Patients who developed rejection (n=8)	Patients who did not developed rejection (n=26)	p***
Neutrophil / Lymphocyte rate			
Pre-transplantation	3.8 [1.8-10]	3.1 [1.3-9.3]	0.307
Rejection	8.2 [2.6-73.8]	[-]	
Discharge value	7.9 [3.5-38.2]	4.3 [1-15.3]	0.008
p	0.030*	0.521**	
AST/Lymphocyte rate			
Pre-transplantation	49.2 [16.5-257.6]	52.2 [12.3-112.1]	0.705
Rejection	194.8 [55.2-2187.5]	[-]	
Discharge value	41.2 [31.9-671.4]	31 [8.2-151.2]	0.053
p	0.010*	0.078**	
AST/Neutrophil rate			
Pre-transplantation	14 [3-82.5]	16.5 [3.1-54.3]	0.765
Rejection	20.1 [10.5-88.2]	[-]	
Discharge value	7 [1-33.8]	8 [1.3-28]	0.796
p	0.011*	0.001**	
ALT/Lymphocyte rate			
Pre-transplantation	28 [6.3-220.8]	44.9 [13-86.4]	0.618
Rejection	434.9 [108.4-2525]	[-]	
Discharge value	151.5 [80.9-1414.3]	50.1 [14.4-288.4]	0.002
p	0.002*	0.004**	
ALT/Neutrophil rate			
Pre-transplantation	10.1 [1.1-70.7]	11.9 [4.2-33]	0.253
Rejection	45.2 [20.6-110]	[-]	
Discharge value	29.5 [3.2-71.2]	13.9 [2.7-95.6]	0.177
p	0.021*	0.424**	
CRP/Albumin rate			
Pre-transplantation	3.2 [0.7-9.6]	1.2 [0.2-19.5]	0.253
Rejection	4.7 [1.3-30.5]	[-]	
Discharge value	3.8 [0.4-19.7]	3.8 [0.5-17.9]	0.984
p	0.197*	0.014**	
Platelet/Lymphocyte rate			
Pre-transplantation	69419.7 [34285.7-475949.4]	134440.7 [21311.5– 414457.8]	0.205
Rejection	195844.4 [76562.5-562500]	[-]	
Discharge value	158367.7 [121276.6-634482.8]	102274.9 [28571.4-389090.9]	0.031
p	0.223*	0.501**	
Tacrolimus (ng/mL)			
Pre-transplantation	8.7 [6.2-11.9]	[-]	
Discharge value	10.2 [3.1-12.6]	11,2 [3.7-18.9]	0.714
p	0.675**	N-a-N	

Descriptive statistics were tabulated as average ± standard deviation or median, minimum and maximum, depending on the distribution for numerical variables. *. Friedman Test used. **. Wilcoxon test used. ***. Mann-Whitney U test used. ALT: alanine aminotransferase, AST: aspartate aminotransferase, CRP: C-reactive protein, N-a-N: Not-A-Number

DISCUSSION

In liver transplantation, rejection is a common complication, especially in the first 12 months, and is associated with increased morbidity and mortality . The number of acute rejection attacks, histological severity, and low drug levels are seen as risk factors for graft loss.[3] Recently, many studies have been conducted on markers that play a role in the inflammatory process to predict postoperative events.[4] Similarly, there are studies on genomic markers alternative to invasive liver biopsy associated with many risks for diagnosis in acute cellular rejection.[5]

In a study evaluating the effect of hematocrit on the blood tacrolimus level, a significant positive correlation was found between the hematocrit rate and the tacrolimus rate. The hematocrit has a significant effect on the tacrolimus level. It is important to consider hematocrit levels in better dose adjustment for patients.[6,7] In a study in which hematopoietic stem cell transplantation was used and tacrolimus was used for graft-versus-host disease prophylaxis, it was reported that changes in blood tacrolimus concentration were significantly associated with hemoglobin levels, but not with changes in white blood cell and platelet count.[8] Hemoglobin values in our patients were 9.5 g/dL [8.4-11.6] (P=0.419). However, we believe that the hematocrit must be at a sufficient level to arrive an effective blood tacrolimus level.

Acute rejection is generally reported in patients with tacrolimus blood concentrations below 10 ng/mL.[9] In another study, a statistically significant (p=0.046) relationship was found between increasing tacrolimus blood concentrations in a 7-day period and a decrease in the risk of acute rejection. [10] In the experimental liver transplant rat model, it has been shown that tacrolimus has important effects on the acute rejection table on the 7th day.[11] In a study conducted, it was reported that the decrease in chronic rejection rates in many centers may be associated with effective immunosuppression therapies.[12] In our patients, we aimed to reach a drug level of 10 ng/ml in the blood within an average of 7 days by starting tacrolimus at a low dose of 0.5 mg on the postoperative day and giving it in increasing daily doses. When acute rejection developed, the average tacrolimus levels of the patients were 8.7 ng/mL [6.2-11.9] and (P=0.675).

It has been shown in national cohortt studies that the incidence of acute rejection is significantly lower in patients with liver transplantation with hepatocellular carcinoma compared to with benign end-stage liver disease. In the same study, parameters such as neutrophil/lymphocyte rate, monocyte/lymphocyte rate, thrombocyte/lymphocyte rate, aspartate aminotransferase/lymphocyte rate, C-reactive protein/albumin rate and fibrinogen level were examined.[13] In our study, neutrophil/lymphocyte (p=0.026) and AST/lymphocyte (p=0.003) were significant in those who developed rejection. However, CRP/albumin and thrombocyte/lymphocyte rates were not significant at different stages of treatment (p>0.05).

Feng et al; did not see a significant difference in associating low and normal graft-to-recipient weight rate (GRWR) with perioperative mortality, biliary complications, postoperative bleeding, and the risk of acute rejection.[14] No significant statistical relationship was found in our study, either.

We see that the limitations of this study are the lack of histopathological verification and the small sample size to support the diagnosis when we think that rejection has developed. We think that the diagnosis and treatment approach in acute rejection should be in the light of clinical, radiological, immunological and pathological data.

CONCLUSION

Liver transplantation is the most effective treatment for those with end-stage liver disease. However, acute rejection is still a major source of concern. The mechanisms underlying acute rejection remain uncertain. More research is needed on biochemical parameters that may be indicative of acute rejection.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study permit was obtained from Yeditepe University Clinical Research and Ethical Committee, 17/02/2021 No: 1391

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

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.

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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JOURNAL OF
CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.884444
J Contemp Med 2021;11(4):445-451

Orjinal Araştırma / Original Article

The Presence of Mef (E) and Erm (B) Genes in Throat Samples of Children Infected with *Streptococcus pyogenes*

Streptococcus pyogenes ile Enfekte Çocukların Boğaz Örneklerinde Mef (E) ve Erm (B) Genlerinin Varlığı

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Abstract

Aim: Antibiotic resistance studies about the Streptococcus have a great importance for the treatment of especially child throat infections in terms of public health and rational antibiotic use. For this purpose, we aimed to identify the macrolide resistance genes mef(E) and erm(B).

Material and Method: The throat culture samples taken from 51 children presenting to the hospital with the complaint of sore throat were evaluated in the laboratory, and *S. pyogenes* was diagnosed using tests; gram staining, catalase, bacitracin and PYR. Susceptibility profile was determined with the Kirby-Bauer disk-diffusion method and minimum inhibitor concentration(MICs) of erythromycin and clindamycin was determined by VTEC 2 System.

Results: *S. pyogenes* was possible macrolide resistance genes of mef(E) and erm(B) was determined by PCR. Macrolide resistance in *S. pyogenes* are determined in 51 pateients as follows; benzylpenicillin 0%, erytromycin 74.5%, clindamycin 31.4%. In patients with *S. pyogenes*, the genetic determinants of macrolide resistance mef(E) and erm(B) genes was investigated with the PCR method using primers specific to each gene. Total of 48% of the isolates (n=24) were positive for erm (B), 10% (n=5) for mef(E), in 42% (n=21) of the isolates both genes were detected.

Conclusion: When the anamnesis of these patients was examined, it was determined that there were patients that frequently presented to the hospital with throat infections and experienced re-infection within a few weeks after receiving treatment. Due to the threat of antimicrobial resistance in *S. pyogenes*, especially in children, national and city surveillance studies are needed to detect resistance. This should be supported by our research, new hypotheses and studies that are open to development.

Keywords: Resistance genes, PCR, *Streptococcus pyogenes*, molecular epidemiolgy

Öz

Amaç: Streptococcus ile ilgili yapılan antibiyotik direnç çalışmaları, özellikle çocuk boğaz enfeksiyonlarının tedavisinde halk sağlığı ve akılcı antibiyotik kullanımı açısından büyük önem taşımaktadır. Biz de çalışmamızda bu amaçla makrolid direnç genleri mef (E) ve erm (B) 'yi tanımlamayı amaçladık.

Gereç ve Yöntem: Boğaz ağrısı şikayeti ile hastaneye başvuran 51 çocuktan alınan boğaz kültürü örnekleri laboratuvarda değerlendirildi ve gram boyama, katalaz, basitrasin ve PYR testleri ile *S. pyogenes* tanısı konuldu. Duyarlılık profili Kirby-Bauer disk difüzyon yöntemi ile ve eritromisin ile klindamisinin minimum inhibitör konsantrasyonu (MİK), VITEK 2 Sistemi ile saptandı.

Bulgular: *S. pyogenes*, mef (E) ve erm (B) 'nin olası makrolid direnç genleri PCR ile belirlendi *S. pyogenes*'te ki makrolid direnci 51 hastada aşağıdaki gibi saptandı; benzilpenisilin %0, eritromisin %74,5, klindamisin %31,4. *S. pyogenes* hastalarında makrolid direnci mef (E) ve erm (B) genlerinin genetik belirteçleri her gene özel primerler kullanılarak PCR yöntemi ile araştırıldı. İzolatların toplam %48'i (n=24) erm (B) için pozitif, %10'u (n=5) mef (E) için pozitif, %42'sinde (n=21) her iki gen birlikte tespit edildi.

Sonuç: Çalışmamızın sonuçlarına göre makrolid direnç genleri pozitif hastaların anamnezleri incelendiğinde, hastaneye sık sık boğaz enfeksiyonu ile başvuran ve tedavi aldıktan sonraki birkaç hafta içinde tekrar enfeksiyon yaşayan hastaların olduğu belirlendi. *S. pyogenes*'te özellikle çocuklarda antimikrobiyal direnç tehdidi nedeniyle, direnci saptamak için ulusal ve şehir sürveyans çalışmalarına ihtiyaç vardır. Bu nedenle araştırmamız, geliştirmeye açık yeni hipotezler ve çalışmalarla desteklenmelidir.

Anahtar Kelimeler: Direnç genleri, PCR, *Streptococcus pyogenes*, moleküler epidemiyoloji

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Received *(Geliş Tarihi)*: 24.02.2021 **Accepted *(Kabul Tarihi)*:** 31.03.2021

INTRODUCTION

Streptococcus pyogenes is beta hemolytic, gram-positive bacteria in Group A streptococcus (GAS) according to the Lancefield classification and caused several infections for centuries. Although it is associated with a wide range of diseases that can progress from skin infections to sepsis, it is largely known as being the most common infectious agent in throat and upper respiratory tract infections. [1] In addition to causing acute diseases, it can also lead to serious complications, such as acute rheumatic fever and glomerulonephritis. Especially in newborns, it is observed that the frequency of infection increases after the gradual decrease of immunity acquired through breast milk. In school children (aged 5-15 years), the incidence of GAS pharyngitis is not negligible, with the presence of GAS being asymptomatic in about 15-20% of this age group.[2] It is very important to detect bacteria to eradicate the disease and prevent associated complications with antibiotic treatment, as well as stopping its spread, especially in environments with a high contagion risk, such as schools and nurseries.[3,4]

For many years, macrolides have been used as a second option when there is no response from penicillin treatment against gram-positive bacteria. Despite this situation being commonly observed in practice, there is some studies conclusively reporting that streptococci have reduced susceptibility to beta lactam antibiotics.[5] In some clinical studies, it has been observed that 30% of the patients did not respond to penicillin treatment in tonsillopharyngitis caused by GAS.[6] This situation is considered to occur as a result of the evolution of bacteria, especially in terms of their mechanisms of escape from antibiotics.[6] Macrolides, which are used as the second treatment choice in patients, are also globally becoming increasingly resistant to antibiotics.[7] In our study we aim to find some genes which has roles in macrolide resistance. For this reason, it is of great importance to detect virulence factors, antibiotic escape mechanisms, microorganism subtypes, and resistant genes of streptococcus infections. As is known, M protein is among the main virulence factors in GAS, and strains detected with the use of M antisera in species differentiation are called 'M serotypes'. However, today, it is known that there are streptococcal groups that cannot be defined based on M protein alone. For this reason, genotype determination and especially 16s rRNA are used in the differentiation of streptococci.[8] According to the conducted studies, there is often unnecessary antibiotic use without a culture analysis in infections for which GAS bacteria are possibly responsible.[9] Despite seeming simple, it is actually very difficult to eradicate GAS infections considering their clinical implications while also avoiding unnecessary antibiotherapy and preventing resistance to antibiotics. [10] To date, there is no vaccine for this bacterium, and this presents a serious risk in certain conditions of neonatal sepsis and infant mortality.[10]

This study has recently been conducted to examine *S. pyogenes* macrolide resistance and resistant genes taken from children admitted to our hospital with sore throat. In case of penicillin allergy or treatment response problems other options are macrolides, beta-lactams, clindamycin or oral cephalosporins are used. Our aims were to find *S. pyogenes* antibiotic resistance and investigate the mef (E) and erm (B) genes which cause macrolide resistance.

MATERIAL AND METHOD

Collection of Samples, Identification of *S. pyogenes* and Susceptibility

Throat cultures of 78 patients who applied to the Kafkas University Research and Application Hospital outpatient clinic with a complaint of sore throat were taken by clinicans and sent to the microbiology laboratory. The samples were first inoculated onto blood agar, put bacitracin disc and then kept in an etuve for 24 hours, PYR test was applied to beta hemolytic colonies. All streptococcus suspected colonies adjusted to 0.5 MacFarland standart in indol broth and were seeded on Muller Hinton Agar. All patients with S.pyogenes detected were included to the study. Penicillin G (benzylpenicillin), Eritromycin, Clindamycin disks were placed on the medium. Susceptibility of cephalosporins and carbapenems is inferred to the benzypenicillin in EUCAST 2020. The susceptibility limits of antibiotics according to the Eucast criteria are given in **Table 2**. Minimum inhibitor concentration(MICs) of erythromycin and clindamycin was determined by VTEC 2 (BioMerieux, France). Bacteria stored at -80°C for genetic examination.[11]

Genomic DNA Isolation Protocol

The samples were placed into eppendorf tubes, to which 200 µl dH_2O, 50 µl 0,5 M EDTA, 10 µl %20 sarkosyl, 10 µl proteinase K (10 mg/ml), 10 µl 1 M Tris- HCl (pH:8), and 5 µl 5 M NaCl were added. The mixture was vortexed for 5 min and kept in a water bath set at 65 °C for 30 min. During this period, the mixture was vortexed every 10 minutes. Phenol: chloroform: isoamyl alcohol (25:24:1) was added to the cell suspension. It was then centrifuged at 13,000 rpm for 5 min. The supernatant layer was removed with a Pasteur pipette (or a 1,000 µl micropipette the tip of which was cut with a razor blade) and transferred to a new tube. The phenol: chloroform: isoamyl alcohol procedure was performed three times as described above. In each step, the supernatant was removed from the products obtained at the end of centrifugation and transferred to a clean eppendorf tube, to which 3M NaAc at 1/10 of its volume and absolute ethanol at two times of its volume were added, and this mixture was kept overnight at -20°C. At the end of this period, the sample was centrifuged at 13,000 rpm for 10 min. The supernatant was removed, and the pellet was dried. After adding 200 µl dH_2O, the pellet was thawed and 0.3 M NaOAc and 440 µl ethanol were added

at 1/10 volume and kept overnight at -20°C. At the end of this period, the sample was centrifuged at 13,000 rpm for 5 min. The supernatant was removed, and the pellet was allowed to dry. After drying, the pellet was thawed in 100 µl dH_2O. Genomic DNA obtained was examined for quality, RNA contamination and integrity according to the spectrophotometric measurement first, followed by imaging in 0.8% agarose gel.[12]

Gene Sequences used for the Detection of Resistance Genes

In this study, primers containing the following gene sequences were used.[13]

erm (B): F5'-ATTGGAACAGGTAAAGGGC-3' and
R5'-GAACATCTGTGGTATGGCG-3'
mef (E): F5'-GGGAGATGAAAAGAAGGAGT-3' and
R5'-TAAAATGGCACCGAAAG-3'.

Genomic DNA Replication

Genomic DNA was used as source DNA in the PCR reaction. The PCR reaction was established with macrolid resistant genes specific (F and R) primers. A solution containing 2.5 µl 10X buffer, 2.5 µl 25 mM MgCl2, 2 µl 2.5 µM dNTP mixtures, 2.5 µl F, 2.5 µl R, 0.5 µl genomic DNA, and 0.2 µl Taq DNA polymerase enzyme (5 u/µl) was completed to a total volume of 25 µl by adding 12.3µl ddH_2O. The PCR program used for products was as follows: at 94°C for 2 min, at 94°C for 1 min, at 55°C for 1 min, at 72°C for 1 min, at 72°C for 4 min, and at 4°C for ∞.

Agarose Gel Analysis And Gel Imaging

The DNA fragments run in the agarose gel were checked in a UVP transilluminator device, and the data were recorded using a UV-photometer gel documentation device (UviTec).

The study permit was obtained from ''Kafkas University, Faculty of Medicine Ethics Board with the decision dated 25.04.2018 and numbered 80576354-050-99

RESULTS

Antibiotic Susceptibility Results

With Kirby Bauer disc diffusion method; The antibiotic resistance rates of *S. pyogenes* strains are determined in 51 pateients as follows; benzylpenicillin %0, erytromycin 74.5%, clindamycin 31.4%. In order to determine the macrolide resistance in more detail, the MICs of the *S. pyogenes* strains were examined with VTEC 2 (bioMerieux) and minimum inhibitory concentrations (MIC) were noted. Clinical breakpoints - breakpoints and guidance EUCAST 2020 was used for determine the resistance. Samples which were resistant to two or more antibiotics were considered as multi drug resistant. Demographic distrubution of patients are in **Table 1** and Macrolide resistance in **Table 2**.

Table 1. Demographic Details of Patients

Age	Gender	Multidrug Resistant Strains	Non-Multidrug Resistant Strains
(0-18)	Male (n:39)	N:6	N:33
	Female (n:12)	N:3	N:9

Table 2. Distrubution of Macrolide Resistance and Sensitivity in 51 Patients Throat Sample.

Antibiotic	Sensitive/ Resistance	Number of Resistance Patients (n)	Percentage
Erytromycin	Resistant	38	74.5%
Clindamycin	Resistant	16	31.4%
Erytromycin + Clindamycin	Resistant	9	17.6%
Erytromycin + Clindamycin	Sensitive	6	11.8%

Antibiotic susceptibility was identified in 51 patients with *S. pyogenes* and their resistant genes are on **Table 3**. Samples are taken from pediatric patients incoming to our hospital with sore throat.

Resistant Gene Regions

In this study, we aimed to determine the macrolid resistance of the identified *S. pyogenes* species. The genetic determinants of macrolide resistance were investigated with the PCR method using primers specific to each of the mef (E) and erm (B) genes. Total of 48% of the isolates (n=24) were positive for erm (B), 10% (n=5) for mef (E), in 42% (n=21) of the isolates both genes were detected. Within the scope of the study, it was observed that the expression levels of these genes decreased in some patients (n=5), and this was considered to be the reason for the lack of response to macrolides in these cases (**Figure 1**).

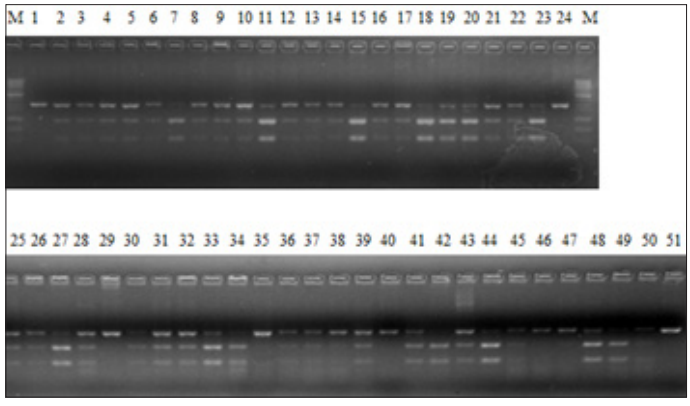

Figure 1. The macrolid resistant genes of the erm (B), mef (E) and erm (B)+mef (E) genes. Ladder 1-51 healty patients. M: 50-1000 bp ladder (Bio Basic GM345). The DNA fragments were separated in 2% agarose gel and visualized with ethidium bromide.

Table 3. Antibiotic and macrolid genes resistant of patients with *S. pyogenes*

Patients/ender	Erytromycin***		Clindamycin		Genes erm (B)	Genes mef (E)	Genes erm (B)+ mef (E)
	*MIC (S/R) mg/L	**KB (S/R) mm	MIC (S/R) mg/L	KB (S/R) mm			
1 F	>0.05 S	22 S	>0.01 S	18 S	+	-	-
2 M	>0.5 R	17 R	>0.15 S	20 S	+	-	-
3 M	>0.75 R	16 R	>0.05 S	23 S	+	-	-
4 M	>1.5 R	14 R	>0.25 S	22 S	-	-	+
5 M	>1.5 R	13 R	>0.1 S	20 S	+	-	-
6 F	>0.55 R	17 R	>0.25 S	23 S	-	-	+
7 M	>0.25 S	22 S	>0.5 R	16 R	+	-	-
8 M	>0.5 R	16 R	>0.5 R	14 R	-	-	+
9 M	>0.5 R	17 R	>0.05 S	20 S	-	+	-
10 M	>0.01 S	23 S	>0.25 S	22 S	+	-	-
11 F	>2.25 R	10 R	>1.5 R	14 R	-	-	+
12 M	>0.5 R	15 R	>0.25 S	22 S	+	-	-
13 F	>0.5 R	14 R	>0.05 S	20 S	+	-	-
14 M	>1.5 R	15 R	>0.25 S	22 S	-	-	+
15 F	>0.75 R	17 R	>0.2 S	20 S	+	-	-
16 M	>250 R	15 R	>1.25 R	15 R	-	-	+
17 M	>0.5 R	16 R	>0.2 S	22 S	+	-	-
18 M	>1. 5 R	16 R	>0.05 S	23 S	-	+	-
19 M	>0.05 S	24 S	>0.5 R	16 R	+	-	-
20 M	>0.05 S	22 S	>0.15 S	20 S	-	-	+
21 M	>0.5 R	14 R	>0.05 S	20 S	+	-	-
22 F	>1.5 R	13 R	>0.25 S	22 S	+	-	-
23 M	>2.5 R	15 R	>1.75 R	16 R	-	-	+
24 M	>0.5 R	15 R	>0.25 S	22 S	-	+	
25 F	>0.5 R	14 R	>0.05 S	24 S	-	-	+
26 M	>0.25 S	23 S	>0.05 S	22 S	+	-	-
27 M	>0.075 S	22 S	>0.5 R	16 R	-	-	+
28 F	>1 R	11 R	>0.75 R	15 R	-	-	+
29 M	>0.75 R	15 R	>0.05 S	24 S	+	-	-
30 M	>1.5 R	13 R	>0.25 S	22 S	+	-	-
31 M	>0.075 S	24 S	>0.1 R	14 R	-	-	+
32 F	>0.25 S	23 S	>0.25 R	16 R	+	-	-
33 M	>2.00 R	10 R	>1.05 R	12 R	-	-	+
34 M	>5.25 R	6 R	>2.25 R	10 R	-	-	+
35 M	>0.02 S	22 S	>0.5 R	14 R	+	-	-
36 F	>0.75 R	11 R	>0.05 S	21 S	-	+	-
37 M	>1.5 R	1 R	>0.25 S	22 S	-	-	+
38 F	>1.25 R	11 R	>1 R	13 R	-	-	+
39 M	>1.0 R	14 R	>0.005 S	25 S	+	-	-
40 M	>0.5 R	15.5 R	>0.25 S	22 S	-	-	+
41 M	>0.25 S	22 S	>0.01 S	18 S	-	+	
42 F	>0.05 S	23 S	>0.5 R	16 R	-	-	+
43 M	>0.75 R	15 R	>0.05 S	24 S	+	-	-
44 M	>0.5 R	17 R	>0.05 S	23 S	+	-	-
45 M	>1.0 R	14 R	>0.25 S	22 S	-	-	+
46 M	>0.5 R	16 R	>0.05 S	24 S	+	-	-
47 M	>1 R	12 R	>25 R	13 R	-	-	+
48 M	>1.0 R	14 R	>0.25 S	22.5 S	+	-	-
49 M	>0.5 R	16 R	>0.05 S	24 S	+	-	-
50 M	>0.05 S	22 S	>0.005 S	18 S	-	-	+
51 M	>0.5 R	17 R	>0.15 S	20 S	+	-	-

*MIC clinical break points for erytromycin S ≤0.25-R>0.5, clindamycin S ≤0.5-R>0.5, **Kirby Bauer break points for erytromycin S≥21-R<18, clindamycin S≥17-R<17 for EUCAST 2020 criteria* [14] ***Erytromycin clindamycin disks take apart 12-16 mm for antagonism(D phenomenon), and erythromycin can be used to determine susceptibility to azithromycin, clarithromycin and roxithromycin.

DISCUSSION

S. pyogenes is the most common cause of throat infections among bacteria. Both acute and chronic forms of GAS infections can be seen at the age of three and over; therefore, they are diseases that frequently occur in a wide age group.[15] Contagion occurs with close contact through infected droplets. In addition to domestic transmission, other environments with a high risk of transmission include public areas, such as schools, barracks, and kindergartens.[16] Especially in acute forms, the disease usually spontaneously regresses in a week without the addition of antibiotics to treatment. However, in the presence of severe complications, including acute rheumatic fever and glomerulonephritis, it is recommended to start penicillin treatment without waiting for the culture result, and Hanage et al. stated that resistant strains were developing in patients that did not respond to treatment.[17] Since studies began to be conducted in 1985, growing experience in clinical practice indicates that some patients have resistance against penicillin treatment and that it does not seem beneficial in eradicating Group B streptococci, but this situation cannot be proven in vitro in real life.[18] Examining the results of some antibiotic resistance studies across the world, erythromycin-resistant *S. pyogenes* was found in 35% of the children admitted to hospital with throat infections in Italy.[19] A study from Turkey by Dundar and friends in 2010, a total of 127 *S. pyogenes* clinical isolates were tested. 11 (9%) isolates were resistant to erythromycin, and 23 (18%) isolates were resistant to tetracycline.[20] In our study, the rate of erythromycin resistance was determined as 74.5%. It is also seen that there is gradually increasing macrolide resistance inversely proportional to age, especially among pediatric patients. Lu and friends study in macrolide-resistance *S. pyogenes* isolates in China from 2009 to 2016, they found *S. pyogenes* isolates were susceptible to penicillin, ampicillin, cefotaxime, and vancomycin and were resistant to erythromycin 131 (93.5%), clindamycin 132 (94.2%), and tetracycline 121 (86.4%), respectively.[21] In our study resistance rates were found erytromycin 74.5%, clindamycin 31.4%, studies show that resistance rates are increasing in the pediatric age group, but when viewed all over the world, it is not as aggressive as in adults, at least in our region. Examining the in vitro effects of antibiotics, we obtained similar results to the literature concerning the distribution and antibiotic susceptibility of *S. pyogenes* strains in the pediatric group.[22] In a study upon GAS isolates from ten European centers; Bulgaria, Croatia, the Czech Republic, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia and Slovenia, detected erm (A) genetic elements of resistance in 2% and mef (A) in 3%, but erm (B) was not reported during the years of 2000–2001 and study is not including Turkey isolates.[23] In our study total of 48% of the isolates (n=24) were positive for erm (B), 10% (n=5) for mef (E), in 42% (n=21) of the isolates both genes were detected. According to our knowledge, this is the first study in which *S. pyogenes* resistance and genes distribution is investigated in east part of Turkey.

When the distribution of resistance among our patients was examined, it was observed that resistance to Clindamycin in *S. pyogenes* was 31.4%. In a study undertaken by Oryaşin et al., it was reported that the erm B and erm TR genes might have this activity of resistance.[24] In our study clindamycin resistant four patients have erm (B) resistance.

Macrolides are used as a second option in patients in case of penicillin allergy or patients who do not respond to penicillin treatment.[25] In an animal study by Samir et al., penicillin and macrolide-resistant *S. pyogenes* was identified, and erm (B), one of the resistance genes, was detected in the whole sample. The authors commented that this situation posed a risk of bacterial transmission to humans through children that are in close contact with animals.[26] Total of 48% of the isolates (n=24) were positive for erm (B), 10% (n=5) for mef (E), in 42% (n=21) of the isolates both genes were detected. Like our study erm(B) is the most frequently reported resistance gene countries such as Germany, Turkey and France.[20,27,28] According to the hospital records, our constituted a population that presented to the hospital several times a year due to throat infections. It was observed that the patients in this group did not respond well to macrolide treatment. It is considered that *S. pyogenes* strains, which have not yet received as much global attention as they require, may gradually become more resistant, to the extent of being described as super-resistant in future.[17]

Some studies have also mentioned the necessity to use secondary treatment options in throat infections that do not respond to antibiotic treatment and emphasized how wrong it was to prescribe medicine for pediatric and adult patients by considering their symptoms alone.[29] In the vast majority of studies, macrolide resistance genes were found at various levels. As stated in the literature on this subject, there are various differences between countries even in relation to the structures of resistance genes.[30] In a study conducted in Norway, the mef A gene found in *S. pyogenes* was observed to differ from that found in S. pneumonia, and this gene was noted to have many subtypes.[31] In another Norwegian study, it was stated that the erm (TR) gene was present in 26 of 44 erythromycin-resistant strains, erm (B) or erm (TR) in six, and mef (E) in one.[32] Resistance genes, mechanisms and increased resistance in *S. pyogenes*, as in all bacteria, cause great economic and moral losses across the world. According to the European Centre for Disease Prevention and Control reports, millions of liras are spent every year for this infection, which easily spreads among children and often requires antibiotic treatment.[33] Nevertheless, there are yet-to-be-proven efficacy problems concerning the first treatment option, penicillin, while at the same time, macrolides, one of the primary alternatives, is also becoming more resistant with each passing day.[34]

CONCLUSION

The results of our study showed the presence of various resistance genes. When the anamnesis of these patients examined, they were seen to represent a pediatric group that visited the hospital due to frequent, long-lasting throat infections and experienced re-infection within a few weeks after receiving treatment. Similarly, due to their reduced susceptibility, macrolides can occasionally be inadequate in eradicating this infection, which seems simple but incurs serious health-related cost across the world. Further comprehensive studies are required to initiate radical changes in the approach of countries to throat infections. Our study should be supported by new antibiotics resistance studies designed for this purpose and open to development

ETHICAL DECLARATIONS

Ethics Committee Approval: The study permit was obtained from ''Kafkas University, Faculty of Medicine Ethics Board with the decision dated 25.04.2018 and numbered 80576354-050-99.

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

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.

Financial Disclosure: This study was financially supported by the Scientific Research Projects Unit of Kafkas University, with the project number 2018-TS–67.

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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JOURNAL OF
CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.860950
J Contemp Med 2021;11(4):452-455

Orjinal Araştırma / Original Article

Investigation of Seroprevalence of Hepatitis B, Hepatitis C and HIV in Hemodialysis Patients

Hemodiyaliz Hastalarında Hepatit B, Hepatit C ve HIV Seroprevalansının Araştırılması

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Abstract

Aim: Impairments in the immune system of patients undergoing hemodialysis cause them to be more sensitive to infectious agents. The purpose of this study was to determine the seroprevalence of HBV, HCV and HIV in patients undergoing hemodialysis treatment.

Material and Method: HBsAg, Anti-HBs, Anti-HBc IgM, Anti-HBc IgG, HBV-DNA, Anti-HCV, HCV-RNA and Anti-HIV parameters were analyzed from serum samples of patients with chronic kidney disease (CKD) undergoing hemodialysis treatment in Selçuk University Faculty of Medicine Hospital in Turkey between 2010 – 2020 retrospectively.

Results: From a total of 4155 hemodialysis patients, HBsAg was determined only in 17 (0.40%) while Anti-HBs was positive in 454 (11.2%). Anti-HCV was detected as positive in 14 (0.33%) serums. HBV-DNA was found to be positive in 13 (76.5%) of HBsAg positive patients. HCV RNA was found to be positive in 12 (85.7%) of anti-HCV positive patients. Anti-HIV antibodies were not detected in any of the serum samples.

Conclusions: Proper infection control measures in hemodialysis patients can reduce the contamination of infectious agents. In addition, considering the immunosuppressive status of hemodialysis patients, the vaccination planning for Hepatitis B should be made appropriately.

Keywords: Hemodialysis, chronic kidney patients, hepatitis B, hepatitis C, HIV

Öz

Amaç: Hemodiyaliz (HD) uygulanan hastaların bağışıklık sistemindeki bozulmalar, hastaların enfeksiyon ajanlarına daha duyarlı olmasına neden olmaktadır. Bu çalışmanın amacı; hemodiyaliz tedavisi gören hastalarda HBV, HCV ve HIV seroprevalansını ortaya koymaktır.

Gereç ve Yöntem: Selçuk Üniversitesi Tıp Fakültesi Hastanesi'nde hemodiyaliz tedavisi gören kronik böbrek hastalarının (KBH) serum örneklerinden çalışılmış HBsAg, Anti-HBs, Anti-HBc IgM, Anti-HBc IgG, HBV-DNA, Anti-HCV, HCV-RNA ve Anti-HIV parametreleri 2010-2020 yılları arası retrospektif olarak taranmıştır.

Bulgular: 4155 hemodiyaliz hastasının 17'sinde (% 0,40) HBsAg ve 454'ünde ise (% 11,2) Anti-HBs pozitif bulunmuştur. Anti-HCV 14 (% 0.33) hastanın serumunda pozitif olarak saptanmıştır. HBsAg pozitif HD hastalarının 13'ünde (% 76,5) HBV-DNA pozitif saptanmıştır. Anti-HCV pozitif hastaların 12'sinde (% 85,7) HCV RNA pozitif olarak belirlenmiştir. Serum örneklerinin hiçbirinde anti-HIV antikorları tespit edilmemiştir.

Sonuç: Hemodiyaliz hastalarında uygun enfeksiyon kontrol önlemlerinin bulaşıcı ajanların kontaminasyonunu azaltabileceğini göstermiştir. Ayrıca, hemodiyaliz hastalarının immünosupresif durumu dikkate alınarak Hepatit B'ye karşı aşılama planlaması yapılmalıdır.

Anahtar Kelimler: Hemodiyaliz, kronik böbrek hastalığı, hepatit B, hepatit C, HIV

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Received *(Geliş Tarihi)*: 14.01.2021 **Accepted *(Kabul Tarihi)*:** 07.04.2021

INTRODUCTION

Chronic kidney disease (CKD) is a common health problem all over the world. It is a disease with progressive and irreversible loss of kidney's metabolic and endocrine functions as a result of a decrease in fluid electrolyte balance and a decrease in glomerular filtration. Due to the increasing frequency of CKD in the world, high morbidity and mortality rates are observed.[1]

Chronic kidney disease is a serious public health problem due to its effects on the quality of life and the high cost of renal replacement therapies required for treatment.[2] Many etiological factors are associated with the development of CKD with diabetic nephropathy and hypertension among the top first. Other etiological causes of the CKD include primary glomerular diseases, tubulointerstitial diseases, renal vascular diseases, chronic urinary tract obstruction, collagen tissue diseases and some metabolic diseases.[3]

An effective hemodialysis (HD) has been found to reduce morbidity and mortality in patients with CKD. However, an effective HD depends on dialysis dose, nutritional status of patients, presence of comorbidity, degree of anemia, socio-economic status, compliance, adequate blood flow and membrane type used for hemodialysis.[4]

HD patients are more susceptible to infections than healthy people due to chronic kidney insufficiency. As hemodialysis patients are immunosuppressive, their susceptibility to infections is increased.[5] In particular, these patients are at high risk for infections through the blood. In addition to bacterial infections in these patients, blood-borne hepatitis B virus (HBV), hepatitis C virus (HCV) and Human Immunodeficiency Virus (HIV) may cause high mortality and morbidity.[6] Percutaneous interventions, blood transfusions, hemodialysis machines and infected devices are among the factors that increase the possibility of getting hepatitis infections in each dialysis session. Infection control measures are applied in hemodialysis units to prevent transmission of viral infections.

The vast majority of infection related deaths are caused by vaccine-preventable infections. World Health Organization (WHO) and Turkish Nephrology Association (TND) recommend vaccination of patients with chronic kidney insufficiency against HBV. However, despite all precautionary measures taken during HD sessions, it has however been reported that HBV and HCV infections may still occur.[7] The purpose of this study was to determine the seroprevalence of HBV, HCV and HIV in patients undergoing hemodialysis treatment.

MATERIAL AND METHOD

HBsAg (Hepatitis B surface antigen), Anti-HBs (Hepatitis B surface antibody), Anti-HBc IgM (Hepatitis B core IgM antibody), Anti-HBc IgG (Hepatitis B core IgG antibody), HBV-DNA, Anti-HCV, (Hepatitis C antibody), HCV-RNA and Anti-HIV (Human Immunodeficiency Virus Antibody) parameters were retrospectively screened between 1 July 2010 and 1 July 2020 in Selçuk University Faculty of Medicine. "HIV-1/2Ag/Ab Combo" test was performed by the Architect i1000 sr (Abbott Diagnostics, Germany) device. Patients with confirmed positive serum samples were followed up in our laboratory by HIV -RNA testing (HI Virus-1 RT-PCR, Rotor Gene, QIAGEN, Germany). Architect i1000 sr (Abbott Diagnostics, Germany) device working with the chemiluminescence method was used to detect HBV and HCV. HBV-DNA and HCV-RNA parameters were studied by Real-Time PCR method using Cobas x480 (Roche, Sweden) device. Microsoft Excel software allowed us to compare these results.

The study protocol followed ethical guidelines of the Declaration of Helsinki. The Ethics Committee of Selçuk University Faculty of Medicine (Turkey) approved the ethical standards of our research (02/09/2020 – 2020/348).

RESULTS

Serum samples from 4155 hemodialysis patients were scanned retrospectively. 2405 (58%) of the patients were male and 1750 (42%) were female. HBsAg was positive in 17 (0.40%) patients. Anti-HBs positivity was found in 454 (11.2%) patients. Anti-HBs antibody level was found above 100 mIU/ml in 112 patients (24.7%). Anti-HBc IgG was positive in 10 (0.24%) patients and Anti-HBc IgM in 7 (0.16%) patients. HBV-DNA positivity was found in 13 (76.5%) of the HD patients who were HBsAg positive. Anti-HCV was positive in 14 (0.33%) of the patients (**Table 1**). HCV RNA was found to be positive in 12 (85.7%) of anti-HCV positive patients. Anti-HIV was negative in all samples.

Table 1. Seroprevalence distribution of hepatitis markers in hemodialysis patients

Hepatitis Markers	Seroprevalence (%)
HBsAg	0.40
Anti-HBS	11.2
Anti-HCV	0.33
Anti-HBc IgG	0.24
Anti-HBc IgM	0.16

HBs Ag: Hepatitis B surface antigen; Anti-HBs: Hepatitis B surface Antibody; Anti-HCV: Hepatitis C antibody; Anti-HBc IgG: Hepatitis B core IgG antibody; Anti-HBc IgM: Hepatitis B core IgM antibody

DISCUSSION

Despite the precautionary measures put in place, viral hepatitis remains an important risk factor for both patients and health workers in hemodialysis units. HBV seroprevalence in Turkey varies from region to region. However, the country is located in the middle endemicity zone in terms of HBV infection. In Turkey, reported seroprevalence of HBsAg in chronic hemodialysis patients varied from 3.6% to 8.7%.[8-12]

In a cross-sectional study conducted on 360 HD patients in 5 hemodialysis centers in Tehran (Iran) HBsAg was found to be positive in five (1.39%) patients.[13] HBsAg seroconversion rates were found to be 1.1% in Cameroon.[14] HBsAg positivity was reported to be 7% in 113 HD patients in Vietnam and the

study warned hemodialysis services where universal measures are not taken.[15]

In our study, HBsAg was found to be positive in 17 (0.40%) of hemodialysis patients. This seropervalence was far below those of TND reported in 2016 (3.8%) and 2019 (2.57%).[16] The reason for the low HBsAg seropositivity in hemodialysis patients in our study can be explained by timely implementation of prophylaxis programs associated with erythropoietin therapy, better blood control, separation of dialysis machines for HBsAg patients and good infection control measures.

Because of uremia-related immunosuppression, only 50-60% of HD patients develop an immune response to the vaccine. In addition, the generally developing response in these patients is low antibody titers and is short-term. Although the response to 3 doses of vaccine is 90-95% in people with normal immune system, it was stated that the vaccine response in HD patients is on average 64%.[17]

In our study, Anti-HBs positivity was found in 454 (11.2%) patients and Anti-HBs antibody level was found above 100 mIU/ml in 112 patients (24.7%). Seropositivity of Anti-HBs in HD patients in similar studies carried out in Turkey was reported to range between 33.5-64% [18] while Anti-HBs positivity was reported to be as high in HD patients as 72.2%.[11]

As a whole, serological indicators of hemodialysis patients should be checked and patients with negative serological indicators should be immediately taken into the vaccination program for eventual vaccination. After vaccination, patients should be followed up and researched for Anti-HBs. Anti-HBs titers should be closely monitored and necessary precautions taken to ensure effective prophylaxis in patients. When all serological tests for HBV in HD patients are negative, those with isolated Anti-HBc positivity should be evaluated for occult hepatitis B and HBV DNA testing should be performed.

In Turkey, population-based studies with respect to the epidemiology of HBV and HCV revealed HBsAg positivity in 4%, anti-HCV positivity in 1%, and anti-HDV positivity in 2.8% of HBsAg-positive individuals.[19]

According to current data, it is estimated that more than 170 million people worldwide are infected with HCV. In addition, one million people die each year from cirrhosis or liver cancer due to HCV infection.[20] Liver Studies Association of Turkey reported Anti-HCV positivity as 0.95%. Anti-HCV seropositivity among HD patients has been reported to decrease in some countries over time while increasing in others.[6,21]

HCV infection has a special importance in dialysis patients due to the high risk of transmission in hospitals and studies showed that HCV.[19,20] In a meta-analysis, it has been reported that HCV carriage increases the risk of death in hemodialysis patients. In studies conducted in different countries, anti-HCV positivity rate was determined to vary between 4-59% depending of the geographical regions.[16,21] Five percent (5.2%) of seropositivity for anti-HCV antibodies in chronic hemodialysis patients was reported in Turkey in 2019.[8]

Our study showed anti-HCV positivity in 14 of 4155 hemodialysis patients (0.33%). Low percentage found in our study could be associated to sound implementation of necessary infection control measures in Konya province as well as appropriate training provided to healthcare professionals and patients. However, an effective vaccine has not been developed against HCV to date. For this reason, prevention of transmission and spread of HCV should be of prime importance. In addition, HCV RNA should be investigated in patients who are anti-HCV positive.

HIV-infected people show a broad spectrum from an asymptomatic carrier to a multisystemic disease. The incidence of kidney disease has been reported between 2-10% in HIV-infected patients. Some of these patients have end-stage renal failure or acute renal failure and are under dialysis treatment. HIV infection can also be transmitted to patients with CKD by blood transfusion, renal transplantation, needle stinging, or sexual contact.[22] However, no HIV-positive serum was detected in our study because of strict application of disinfection rules, screening carried out on time and low HIV seroprevalence in Konya. Similar results have been reported in some studies carried out in other countries.[18,23,24] However, HIV-related nephropathy (HIVAN), diabetes, and obstructive nephropathy was reported in Cameroon. The only case of HIV/HCV coinfection. Anti-HIV seropositivity detected in CKD patients was associated with age and history of STI (Sexually Transmissible Infections).[25]

Studies have shown that it is sufficient to apply general disinfection rules in patients with HIV infection in dialysis units. In severe AIDS patients with diarrhea, respiratory problems, isolation should be done to prevent the transmission of community-acquired infections during dialysis.[26] Hemodialysis staff must wear gloves, all sharp substances and needles must be disposed of properly after dialysis. The hemodialysis machine does not need to be separated. After dialysis, the outside of the machine should be cleaned with hypochlorite and the inside with formaldehyde. Patients who will receive dialysis treatment for the first time should be screened for HIV before starting treatment and HIV tests every six months. A training program on AIDS should be implemented for patients and healthcare professionals.[27]

CONCLUSION

Considering the relatively average HCV seroprevalence in the hemodialysis center of Selçuk University hospital, it is clear that the most important risk factors are the length of the hemodialysis. The data from this study encourage us to better apply the rules of asepsis and to use recombinant human erythropoietin. The correlation between the positivity of serological markers of HBV, HIV and HCV is explained by blood transfusions hence the importance of detecting these infections and to undertake as soon as possible a vaccination against viral hepatitis B and the application of barrier measures against HIV. As a matter of fact, all these measures should make it possible to prevent contamination in dialysis centers while waiting to find passive immunization with gamma globulins or active immunization against the hepatitis C virus.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval has been provided by the Ethics Committee from the Faculty of Medicine, Selçuk University (02/09/2020 – 2020/348).

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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JOURNAL OF
CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.764439
J Contemp Med 2021;11(4):456-461

Orjinal Araştırma / Original Article

Ultrasonographic Evaluation of Swallowing Disorder in Children with Cerebral Palsy: Preliminary study

Serebral Palsili Çocuklarda Yutma Bozukluğunun Ultrasonografik Değerlendirmesi: Ön çalışma

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Abstract

Aim: Swallowing is a process influenced by many phases and complex neuromuscular mechanisms. Swallowing disorders are common in children with cerebral palsy (CP). The aim of this study is the dynamic evaluation of oral and pharyngeal phase changes of swallowing by ultrasound (US) in healthy and children with CP with swallowing disorder.

Material and Method: Sixteen children with CP (9 boys, mean age 45±21 months) in the patient group and 20 healthy children (11 boys, mean age 60±26 months) in the control group enrolled study. CP group was selected from orally fed children. In both groups, the measurements were performed with the transducer was placed under the chin and anterior part of the neck. During swallowing and rest distances between mandible symphysis and hyoid bone (MH) and between hyoid bone and thyroid cartilage (HT); frame rate of displays to determine swallowing times at same levels, tongue thickness and shear wave elastography for measuring tongue stiffness determined.

Results: The significant differences were found between tongue thickness, elastogram and screen frame rates at HT level of the two groups (respectively p<0,002, p<0,002, p<0,003). No significant difference was found between the patient and control groups in terms of other measurements. Muscle tone change was observed during rest in patients with CP with dysphagia. This tonus was high in spastic CP cases. Active tone was slightly decreased. The high tongue elastographic values during rest was consistent with this information in the literature. The most important change detected in children with CP is the increase in image frame rate, which indicates a long swallowing time in HT level.

Conclusion: Prolonged swallowing time, thickness of the tongue and tonus of the tongue muscles can be used to evaluate dysphagia in patients with CP. We think that pre- and post-treatment comparisons can be used to evaluate treatment effectiveness.

Keywords: Cerebral palsy, dysphagia, ultrasound, elastography

Öz

Amaç: Yutma birçok fazdan ve karmaşık nöromüsküler mekanizmalardan etkilenen bir süreçtir. Serebral palsi (CP) olan hastalarda yutma bozuklukları yaygındır. Bu çalışmanın amacı, sağlıklı ve yutma bozukluğu gelişen CP'li çocuklarda ultrason (US) ile yutmanın oral ve faringeal faz değişikliklerinin dinamik olarak değerlendirilmesidir.

Gereç ve Yöntem: Hasta grubunda 16 CP'li (9 erkek, ortalama yaş 45 ± 21 ay) ve 20 sağlıklı çocuk (11 erkek, ortalama yaş 60 ± 26 ay) kontrol grubuna alındı. CP grubu oral yoldan beslenen çocuklardan seçildi. Her iki grupta da ölçümler dönüştürücü ile çene altına ve boynun ön kısmına yerleştirildi. Mandibula simfizi ile hyoid kemik (MH) arasındaki ve hyoid kemik ile tiroid kıkırdağı (HT) arasındaki yutma ve dinlenme mesafelerinde; aynı seviyelerde yutma sürelerini belirlemek için ekranların kare hızı, dil kalınlığı ve dil sertliğini ölçmek için kayma dalgası elastografisi belirlendi.

Bulgular: İki grubun HT düzeyinde dil kalınlığı, elastogram ve ekran kare hızları arasında anlamlı fark bulundu (sırasıyla p <0,002, p <0,002, p <0,003). Hasta ve kontrol grubu arasında diğer ölçümler açısından anlamlı fark bulunmadı. Disfajili CP çocuklarda istirahat sırasında kas tonusunun değiştiği görüldü. Spastik CP vakalarında bu tonus yüksekti. Aktivitede tonus biraz azaldı. Dinlenme sırasındaki yüksek dil elastografik değerleri literatürdeki bu bilgilerle tutarlıydı. CP'li çocuklarda tespit edilen en önemli değişiklik, HT düzeyinde uzun bir yutma süresine işaret eden görüntü kare hızındaki artıştır.

Sonuç: CP'li çocuklarda disfajiyi US ile değerlendirmek için uzamış yutma süresi, dil kalınlığı ve dil kaslarının tonusu kullanılabilir. Bu noninvaziv ve tekrarlanabilir yöntemin tedavinin etkinliğini değerlendirmek için kullanılabileceğini düşünüyoruz.

Anahtar kelimeler: Serebral palsi, disfaji, ultrason, elastografi.

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Received *(Geliş Tarihi)*: 05.07.2020 **Accepted *(Kabul Tarihi)*:** 10.04.2021

INTRODUCTION

The swallowing process depends on the integrity of a complex neuromotor mechanism. It involves a coordinated process that is divided into the following phases: oral preparatory, pharyngeal and esophageal.[1] Dysfunction is one of these three phases which can result in dysphagia. This is a term for difficulty swallowing. It corresponds to a set of symptoms characterized by difficulty in propelling liquid or solid food from the oral cavity through the esophagus.[2,3] During the deglutition, it is necessary to protect the airways in order to avoid aspiration pneumonia.

Cerebral palsy (CP) is a common cause of disability in childhood. Since different regions are affected during the development of the nervous system, clinical findings differ.[4] Children with CP commonly have feeding disorders and swallowing problems (dysphagia).[5] Dysphagia is associated with motor dysfunction in children with SP. Silent aspiration can be seen in CP cases. Aspiration is an important cause of developing acute and chronic lung diseases. Respiratory complications are important factors in increasing morbidity and mortality in CP.[6]

Videofluoroscopic Swallow Study (VF) has been the most reliable method in the investigation of deglutition disorders.[7] The primary method of imaging is barium passage radiographs. Ultrasound (US) can be used to assess more swallowing oral and pharyngeal phases.[8] High spatial and temporal resolution, multiplanar evaluation capability, low cost, easily accessible, portability, repeatable, not requiring contrast material and ionizing radiation are some of the superior aspects of US.[9] There are no definitive markers in the literature regarding the diagnostic value of US findings in assessment of dysphagia.

The examination by US has disadvantages compared with assessment by VF. The VF provides wide-field imaging with panoramic view, while US can perform low-range imaging. In US, transducer can compress tissues. It may be difficult to place and hold the transducer fixed. Therefore, the practitioner needs to be patient. Some structures in the study plan do not have anatomical markers. In our study, the transducer was placed in the midline of the neck without compression. The anatomical marker points we have identified have significant echo changes and they could easily be found in repeated studies.[3,7,8]

In cases where the neuromotor mechanism such as CP is disrupted, the tongue, which is an important component of the swallowing process, should be evaluated. A decrease in the thickness of the muscle structures of the tongue may be indicative of inadequate stimulation. The degree of stiffness in the muscle layer can be evaluated by elastographic examination. In the studies aimed to elucidate the causes of dysphagia, elastography has not been used before.

Our purpose of the study is the dynamic evaluation of oral and pharyngeal phase changes of swallowing by US in healthy children and children with CP who developed swallowing disorder. We thought that tongue thickness and tongue elastographic values should differ due to insufficiency of excitations in neuromotor pathologies and we compared this data in the two groups.

MATERIAL AND METHOD

The children included in the study had no history of oral, cervical and thoracic operations, additional craniofacial anomaly and upper respiratory tract infection during the study. The patient group with CP was selected from orally fed children. Thus, it was assured that the swallowing mechanism was not affected for other reasons.

All procedures performed in studies involving human participants were 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. Parents of all participants were informed about the study protocol and their written consents were obtained. The child participants in the control group were informed face to face and what was asked of them was explained. After gaining the confidence of all participants, US examination was started using gel at room temperature.

Height and body weight of all participants were obtained. Body mass index (BMI) used to assist homogenization among the participants was calculated using the BMI formula (BMI=weight/height^2).

In the patient group, information was obtained about the difficulty of swallowing by talking with the parents of the child. These participants had no swallowing problems apart from solid food intake.

The US examinations were performed by a single pediatric radiologist with fifteen years of experience. Participants were comfortably seated on the examination table. None of the children were sedated. All of the children were convinced to talk for US exams. Parents stayed with their children throughout the examinations. Children with CP, who cannot sit, sat down leaning on their parents. We acted slowly and gently so that all children could adapt to the study. The examination time was an average of 5 minutes for healthy participants and 10 minutes for children with CP. When an effective examination could not be made, the examination was repeated with a pause in the required time.

All scanning was performed with real time scanner (Toshiba Aplio 500, Canon Medical System Corporation, Tokyo, Japan) employing a 5 MHz transducer. The measurement of the examination was recorded in hardware of scanner. To evaluate the oral phase of swallowing, the linguistic examinations were performed under the base of the mouth in the submental area. Sonographically, the mandibula, hyoid bone and thyroid cartilage, which can be identified as echogenic in the midline of the neck, were determined as the reference points. The cervical region was divided into two parts on anteriorly: Mandible to hyoid bone and hyoid bone to thyroid cartilage. Thus, laryngeal motion during swallowing was evaluated.

Transducer was positioned under the patient submental area in a longitudinal plane, floor of mouth, at the level of the mental protuberance of mandible and hyoid bone (**Figure 1**). Firstly, we measured the distances between mandible

to hyoid bone (MH) via US exam in resting period (MHrest) and swallowing its own spit (MHsw) (**Figure 2**). After the transducer was placed under the chin and reached the fixed position, it was instructed to swallow it a second time. Due to aspiration risk, the participants did not drink or eat anything during exams. Then, transducer was moved distally, region between hyoid bone and thyroid cartilage (HT). We measured the same length measurements again during rest (HTrest) and swallowing phases (HTsw). This data were recorded. The frame rate of the display, which shows the number of frames or images per second, was obtained during swallowing period and recorded for both regions. Subjects with CP and control group participants' tongue thicknesses on base of tongue in longitudinal image were made and recorded (**Figure 2**). Distance and thickness measurements were also made electronically in display. All length measurements were performed in millimeters. Then, at the rest stage in the longitudinal plan, tongue stiffness was determined using shear wave elastography (SWE) from glossal muscle structures near the tongue root. When calculating the SWE value, at least three measurements were made in the imaging area where the parallel lines were obtained as much as possible and their averages were recorded. The SWE data were performed in kiloPascal (kPa). The entire procedure was completed in 4 to 10 minutes. The procedure was repeated in cases where it was difficult to cooperate after the child was relieved by talking.

Statistical analyses were performed using the SPSS 22.0 for Windows (SPSS, Chicago, IL, USA). The Shapiro-Wilk test was used for examining the continuous variables, with normal and without normal distributions. An independent samples T-test was used for the between-group comparisons of the continuous variables with normal distributions. The data are expressed as the mean + standard deviations (SD). The Mann–Whitney U test was done for variables with a non-normal distribution. The data are expressed as median and interquartile ranges. Categorical data was analysed by Pearson's chi-square test, and Fisher's exact test was done if the expected frequency was less than 5 in >20 % of all cells. Statistical significance was considered as $p<0.05$.

RESULTS

There were 16 children with CP (9 boys and 7 girls) in the patient group and 20 healthy children (11 boys and 9 girls) in the control group. The mean age was 45±21 months in the patient group and 60±26 months in the control group. Body mass indexes (BMI) of the participants were calculated to ensure that children have similar body structure. BMI was 19±5.9 kg/m^2 in the patient group and 18.2±4.5 kg/m^2 in the control group (**Table 1**).

Table 1. The table showing measurements and intergroup relationships in both groups

	CP group	Control group	p
Age (months)	45.0± 21.0	60.0±26.0	-
BMI (kg/m^2)	19.0±5.9	18.2±4.5	p>0.05
TT in rest (mm)	14.0±3.7	20.4±3.7	p<0.02
MHsw (mm)	9.8±3.5	11.0±1.7	p>0.035
MHrest (mm)	14±2.8	16±2.2	p>0.065
HTsw (mm)	6.6±2.2	6.8±1.5	p>0.05
HTrest(mm)	10±3.1	11±1.1	p>0.405
TSWE in rest (kPa)	11.4±4.9	6.5±1.7	p<0.02
MH frame rates (image/sc)	13.5±3.6	12.2±2.2	p>0.179
HT frame rates (image/sc)	11.8±4.6	8.2±1.4	p<0.03

BMI: Body mass index, TT in rest: Tongue thickness in rest, MHsw: Distance between mandible to hyoid bone in swallowing, MH rest: Distance between mandible to hyoid bone in rest, HTsw: Distance between hyoid bone to thyroid cartilage in swalloving, HTrest: Distance between hyoid bone to thyroid cartilage in rest, TSWE in rest: Tongue Shear Wave Elastogram in rest, MH frame rates: Frame rate in mandible to hyoid bone level, HT frame rates: Frame rate in hyoid bone to thyroid cartilage level

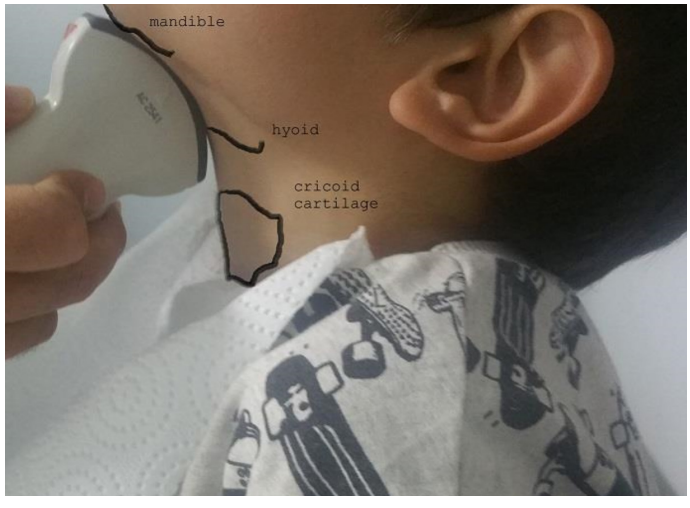

Figure 1. During the ultrasound (US) examination, the participant was in a sitting position. The anatomical landmaker relationship with the transducer placed under the chin is shown.

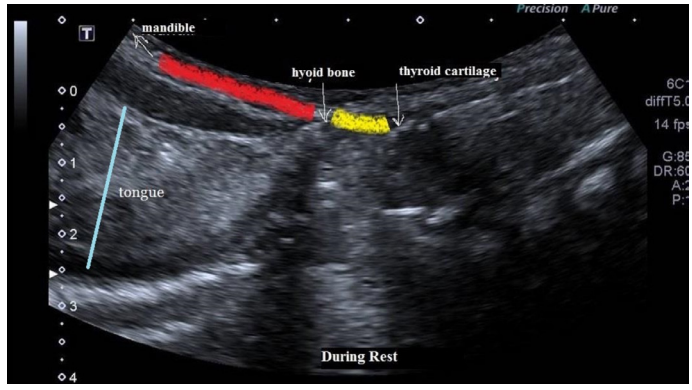

Figure 2. In healhty 7-year-old boy, US image shows distances between mandible and hyoid bone (red line), hyoid bone and thyroid cartilage (yellow line) during rest. In swallowing phase, the hyoid bone appears to move minimally upwards. Due to this, the distance between the hyoid bone and the mandible narrows. As the hyoid bone returns to its normal position, the distance between the hyoid and thyroid cartilage also narrows. Muscle thickness measurements taken from the area close to the root of the tongue were measured through longitudinal section (blue line). Anatomical control of the axial plane can be performed to confirm the measurement area (not shown).

In the CP group, the MH distance was 14±2.8 mm and the HT distance was 10±3.1 mm at rest. In the control group, these measurements were 16±2.2 mm and 11±1.1 mm, respectively. The MH and HT distance during swallowing were 9.8±3.5 mm and 6.6±2.2 in the CP group and 11±1.7mm and 6.8±1.5 mm in the control group, respectively. At rest, tongue thickness at the root level was 14±3.7 mm in the patient group and 20.4±3.7 mm in the control group (**Figure 3**). In the same stage, the tongue muscle stiffness obtained with SWE near the tongue root was 11.4 ± 4.9 kPa in children with CP and 6.5±1.7 kPa in the control group (**Figure 4**).

The screen frame rates throughout the swallowing action were calculated as 13.5±3.6 images/second in MH and 11.8±4.6 images/second in HT in children with CP. In the control group, these values were found to be 12.2±2.2 images/second in MH and 8.2±1.4 images/second in HT.

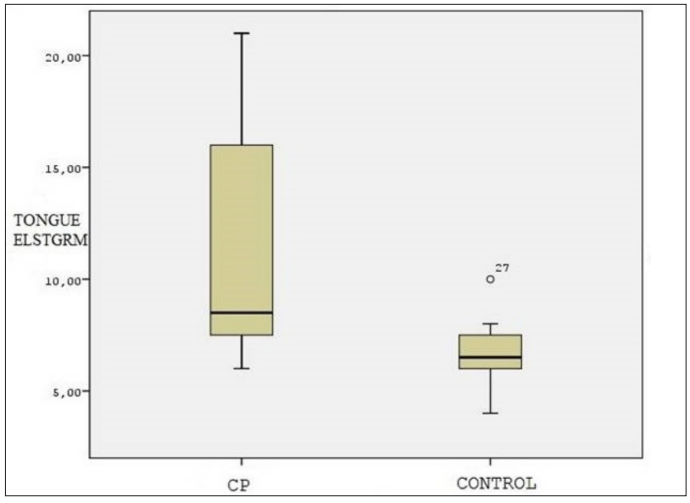

Figure 3. The graph shows that tongue thickness in children with CP is thinner than in the control group

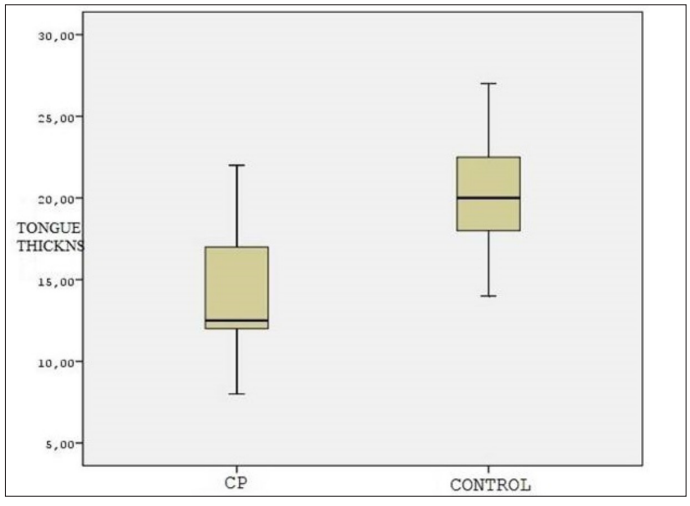

Figure 4. The graph shows that the tongue elastogram values during resting are higher in children with CP than in the control group. The graph shows that the tongue elastogram values during resting are higher in children with CP than in the control group

There was no significant difference between the CP and control groups in terms of MH and HT measurements at the resting and swallowing stages (p>0.005). The significant differences were found between tongue thickness, elastogram and screen frame rates at HT level of the two groups (respectively p<0.002, p<0.002, p<0.003) (**Table 1**). We calculated cut-off values of tongue elastogram, tongue thickness and frame rate at HT level for CP patients. The cut-off values, specificity and sensitivity ratios for these measurements are given in **Table 2**.

Table 2. In the table, diagnostic threshold values, sensitivity and specificity of screen frame rate in TT, TSWE and HT levels are given.

	Cut-off value	sensitiviy	spesivity
TT	16.5 mm	75%	85%
TSWE at rest	7.5 kPa	75%	75%
HT frame rate	8.5 image/second	75%	70%

TT: Tongue thickness, TSWE: Tongue elastogram values, HT level: Hyoid bone to thyroid cartilage distances

In both groups, no statistically significant difference was found between all measurements and gender (p>0.082-0.904 in children with CP and p>0.083-0,644 in control group).

DISCUSSION

Children with CP have commonly feeding disorders and swallowing problems (dysphagia) which are at risk in many instances for aspiration with oral feeding, with potential pulmonary consequences.[10] Pooled prevalence estimates determined by meta-analyses are as high as 50% for swallowing problems in patients with CP.[11] Oropharyngeal dysphagia may be characterized by problems in any or all phases of swallowing.[12] The types of oral and pharyngeal problems that children with CP have include reduced lip closure, poor tongue function, tongue thrust, exaggerated bite reflex, tactile hypersensitivity, delayed swallow initiation, reduced pharyngeal motility and drooling. Impaired oral sensorimotor function can result in drooling that in turn results in impaired hydration.[11,13] Fluid-related problems are common and are often associated with a timing gap at the onset of delayed pharyngeal swallowing. Children with CP frequently need more time to complete feeding tasks, but caution is urged as fatigue and may become a factor, as well as reduced attention to the task.[12] There is a risk of food aspiration and hypoxia during feeding. This risk in children with CP can decrease over time as developmental gains are made. The management of swallowing problems requires the investigation of the deglutition physiology by means of diagnostic imaging methods.[14] Barium lumen radiographs can be used to evaluate the passage, to reveal lumen compression, and to examine the peristalsis of the esophagus. Still VF is considered the gold standard, a suitable method for diagnosing swallowing dysfunctions. In this study, we tried to analyze the changes in the oropharyngeal swallowing movement of the USA in children with CP, using a noninvasive and easily repeatable method.

In the study by Kenny et al.[15] with a limited number of children with CP, tongue movement in the oral phase of swallowing was found to be insufficient in the posterior segment. In the same study, the movement of the hyoid bone during swallowing was found to be slow and inadequate. In another study, 20 children with spastic CP and 20 neurologically normal children were monitored by US imaging of the oral cavity during fluid and solid bolus tasks. In children with CP, the oral phase and total swallowing times for fluid bolus were longer than those of neurologically normal children. According to Casas et al.[16], prolonged swallowing time was found as a result of pharyngeal motor impairment in children with CP. Yang et al.[17] developed a descriptive scoring system for US observation of the oral stage of swallowing, as well as for items including tongue musculature bolus control, initiation, and coordination of tongue and hyoid movement. They significantly observed lower scores in 32 malnourished children with long-term neurological disability and severe feeding difficulties, when compared with 27 normal children. It indicated that US can detect impaired tongue movement in oropharyngeal dysphagia. In our study, instead of evaluating the movement of the tongue, muscle tone and muscle thickness of the tongue were examined. Tongue thickness decreased in children with CP with swallowing disorder compared to healthy children. SWE values of the tongue muscles were higher in children with CP. These findings may be related to an increase in overall muscle tone in CP group. According to another result we obtained, the longer frame rates at HT level in children with CP indicate longer swallowing time.

In a study to show the faringoglottal relationship in newborns, simultaneous pharyngoesophageal manometry, plethysmography, electromyography and glottal US were used.[17] According to this study, glottal adduction during deglutition occurs in any respiratory phase, thus ensuring airway protection before and during deglutition. It has been reported that the laryngeal glottic closure reflex prevents aspiration during deglutition. It is reported that the investigation of the pharyngoglottal relationship by using noninvasive methods may be more acceptable for patients and is applicable to all ages. In current study, we evaluated age group children who could perform swallowing command. Therefore, no supportive examination method other than US was used.

The application of US in assessing the pharyngeal phase of swallowing is less common compared with that of assessing the oral phase. Previous studies have used US for observing lateral pharyngeal wall motion, thyroid-hyoid bone approximation, and hyoid bone displacement.[9,19-21] Kuhl et al.[9] and Huang et al.[19] used US to measure hyoid bone-larynx approximation by using the result as a parameter to estimate larynx elevation. They found that the thyroid larynx approximation of the dysphagic stroke group was significantly less than that of the nondysphagic stroke group and the healthy group. They also reported similar measurement results between US and VF in 10 of the patients. Chi-Fishman.[8] and Sonies.[22] reported that hyoid bone movement can be observed in all stages of swallowing with US. These studies were conducted with adult participants with swallowing dysfunction due to neurological reasons. In this study, we measured the distances between mandible and hyoid bone, hyoid bone and thyroid cartilage to evaluate larynx movement in children with CP. We concluded that there was no statistically significant difference in hyoid bone movement between healthy and children with CP. We found that the laryngeal elevation deficiency, which was found in adults with dysphagia, was not in children with CP.

In the study of Yabunaka et al.[23] they used US to evaluate the movement of the hyoid bone in healthy adult patients and the changes caused by aging during deglutition. Their results were that as age increased, the average swallowing time increased and the movement of the hyoid bone decreased. In other words, as the age increased, the laryngeal phase of the swallowing deteriorated. In our study with a limited participant who could be considered as homogenous in the pediatric age group, we could not evaluate age-related changes. We did not find any gender related changes in healthy and CP children. In the presented study, the motion of the hyoid bone was interpreted with the same imaging method. According to our results, there was no significant difference between the two groups. Using parameters not included in Yabunaka's study, we showed an increase in swallowing time.

The muscle tonus is high in spastic CP group. Active tonus is normal or slightly decreased, primitive reflexes may be strong and persistent.[5] According to the result we have reached, in children with CP with dysphagia, muscle tone varied at rest. The high tongue elastographic values during rest is consistent with this information in the literature.

Although we have not reached similar results in studies with adult groups, our common finding is that swallowing disorders can be identified by US. This method is portable and can be used at the bedside. It is cost effective, noninvasive method and has no radiation. Another advantage of US examination is dynamic method. Finally, other abnormalities in the oral stage, such as inadequate bolus control, premature oral leakage, impaired tongue propulsion, and multiple swallowing, can be observed using US. The major disadvantage of US is that it is operator dependent.

This study had some limitations. First, there was a lack of gold standard measurement for US results. Second, the total sample size is small. The number of patients in both groups was low. In order to confirm the results of our study, studies with larger patient populations in each age group are needed. Thirdly, we could not provide liquid or semi-solid food to prevent the risk of aspiration during swallowing in patients with CP. The examination was performed when the patient swallowed his/her own saliva in both groups. A certain amount of liquid, semi-solid and solid food intake and swallowing dynamics could not be evaluated. Lastly, insufficient swallowing sometimes caused a repeated examination, which led to prolonged US examination.

CONCLUSION

Oral and pharyngeal phases of swallowing function can be evaluated with US, which is a noninvasive method, in children with CP with swallowing problems. Duration of swallow, tongue thickness and tonus of tongue muscles can be used to evaluate dysphagia in patients with CP. We think that, pre- and post-treatment comparisons can be used to evaluate treatment effectiveness. US can be used as a quantitative method to clinically evaluate the oral and laryngeal phases of swallowing. Defining thyroid cartilage, tongue movement and muscle structure; the motion of the hyoid bone can be measured accurately and reproducibly with US. In addition, US can be used as a rapid examination tool to screen high-risk patients and monitor swallowing function..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Local Ethics Commitee of Celal Bayar University medical School (permission granted: 28.03.2018, decision No: 20.478.486

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.

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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JOURNAL OF
CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.857806
J Contemp Med 2021;11(4):462-468

Orjinal Araştırma / Original Article

Can Hypoxia-Inducible Factor 1α be used as a Biomarker to Evaluate Disease Severity and Prognosis in COVID-19 Patients?

COVID-19 Hastalarında Hypoxia-Inducible Factor 1α Hastalık Şiddeti ve Prognozunu Belirlemede Bir Biyomarker Olabilir Mi?

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Abstract

Background: This study was aimed to answer the questions of whether the serum levels of Hypoxia-Inducible Factor 1α (HIF-1α), which is increased by up to 100 times in many tissues including pulmonary tissue in cases of acute lung injury, could be used as a parameter for monitoring the severity and prognosis in COVID-19 patients.

Material and Method: 40 patients, who were admitted to the hospital with COVID-19 clinical symptoms, and 20 healthy control subjects were included in the study. The diagnosis of 20 patients within the patient group were confirmed by the PCR test. The remaining 20 patients were regarded as COVID-19 suspect group. Clinical and laboratory data of patients on admission were recorded. Clinical laboratory tests and serum HIF-1α levels were measured from the blood samples of COVID-19 group on the day of admission and one week after hospitalization. COVID-19 group was divided into four subgroups according to disease severity and HIF-1α values of each group were compared.

Results: In this study, serum HIF-1α values of confirmed COVID-19 patient group were measured higher than healthy control group's serum HIF-1α values, however no significant difference was found for the COVID-19 suspect group. Within confirmed COVID-19 group, serum HIF-1α values on admission were higher than values after hospitalization, whereas Monocyte count, Platelet count and Ferritin values were lower. Among the confirmed COVID-19 cases, critically ill subgroup's serum HIF-1α levels of the first week were significantly lower than mild subgroup's serum HIF-1α levels of both the first week and the day of admission. HIF-1α values of COVID-19 group were strongly negative correlated with age, whereas weakly positive correlated with platelet counts.

Conclusions: HIF-1α, which are thought to prevent alveolar damage, increased in COVID-19 patients. Additionally, low levels of HIF-1α in COVID-19 patients might be considered as a factor responsible for the aggravation of the clinical severity.

Keywords: Biomarker, SARS-CoV-2, hypoxia-inducible factor 1α

Öz

Amaç: Bu çalışmada akut akciğer hasarı durumlarında birçok dokuda ve pulmoner dokuda düzeyleri 100 kat artan HIF -1α'nın serum düzeylerinin COVID-19 hastalarında hastalığın şiddeti ve prognozunu takipte etkili bir parametre olarak kullanılıp kullanılamayacağı sorularına yanıt aramak amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya COVID-19 klinik şikayetleri ile başvuran 40 hasta ve 20 sağlıklı kontrol bireyi dahil edildi. Hasta grubundan 20 hastanın PCR testi ile COVID-19 tanısı doğrulandı. Diğer 20 hasta ise COVID-19 şüpheli grup olarak kabul edildi. Hasta gruplarının başvuru klinik ve laboratuvar verileri kaydedildi. COVID-19 grubu hastaların başvuru günü ve başvuru sonrası 1. hafta kan örneklerinden laboratuvar testleri ve serum HIF-1α düzeyleri ölçüldü. COVID-19 grubu hastalık şiddetine göre dört alt gruba ayrılıp her grubun HIF-1α değerleri birbirleri ile karşılaştırıldı.

Bulgular: Bu çalışmada COVID-19 doğrulanmış hasta grubunda serum HIF-1α değerlerinin sağlıklı kontrol grup serum HIF-1α değerlerinden daha yüksek olduğu bulundu. Bununla birlikte COVID-19 şüpheli grup ile arasında anlamlı farklılık bulunamadı. COVID-19 doğrulanmış hasta grubunda hastane yatış günü serum HIF-1α değerlerinin yatış sonrası HIF-1α değerlerinden yüksek bulunurken, monosit, platelet ve ferritin değerleri ise düşüktü. COVID-19 doğrulanmış hasta grubunun kritik alt grubunun 1. hafta serum HIF-1α değerleri hafif alt grup 0. Gün ve 1. hafta değerlerinden anlamlı düzeyde düşüktü. COVID-19 grup HIF-1α değerleri hasta yaşı ile güçlü negatif korele bulunurken, platelet sayıları ile zayıf pozitif korele bulundu.

Sonuç: COVID-19 hastalarında alveolar hasarı engellediği düşünülen HIF-1α düzeyleri yükselmektedir. Bununla birlikte HIF-1α düşük seyreden COVID-19 hastalarında yeterli artış olmaması klinik tablonun ağırlaşmasından sorumlu bir faktör olarak da göz önünde bulundurulabilir.

Anahtar Kelimeler: Biyobelirteç, hypoxia-inducible factor 1α, SARS-CoV-2

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Received *(Geliş Tarihi)*: 10.01.2021 **Accepted *(Kabul Tarihi)*:** 02.04.2021

INTRODUCTION

In December 2019, a new coronavirus, previously called 2019-nCoV, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in Wuhan, China. SARS-CoV-2 caused a respiratory disease called Coronavirus 2019 (COVID-19), which was officially named by the World Health Organization (WHO), on February 11, 2020. Interpersonal transmission of coronaviruses mainly occurs through direct and indirect contact with saliva droplets or surfaces. COVID-19 caused serious diseases and deaths in China and other countries around the world.[1-5] Together with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), COVID-19 appears to cause a serious clinical features in humans, from mild fatigue to death due to sepsis or acute respiratory distress syndrome. The prognosis is worse in accompanying elderly patients. As of today, there is no specific therapy for COVID-19.[6-9] The mechanism of the SARS-CoV-2 infection has not yet understood. The key to human transmission is the virus's ability to bind to human cells: Coronaviruses use the spike proteins to bind to cells and SARS-CoV-2 uses the same angiotensin 2 enzyme (ACE2) receptor as the SARS-CoV.[5,7,10] Clinical features related to SARS-CoV-2 infection varies from mild fatigue to death from sepsis and / or ARDS.[6] The lack understanding of mechanism of the SARS-CoV-2 infection and this variety in clinical features are the leading reasons why a specific therapy has not yet been developed. There are not enough studies in the literature about the mechanism of this new viral infection.

HIF-1 is a heterodimeric receptor with a short half-life, that can be found throughout the body and has been shown to respond to hypoxic conditions. HIF-1 helps the metabolism adapt to and recovery from severe hypoxic conditions such as inflammation, sepsis, hypertension, hypervolemic shock, heart or lung diseases, and anemia. In these critical conditions, HIF-1α dimerizes with transcription factor HIF-1β to copy various hypoxia response genes. In early stages of acute lung injury / ARDS, damage to the alveolar membrane, alveolar epithelial cell apoptosis and pulmonary edema can easily lead to hypoxia and activation of HIF-1α.[11-14] Studies have shown that HIF-1α can control inflammation and alleviate acute lung damage by regulating glucose metabolism in alveolar epithelial cells. It has been reported that HIF-la expression increases after lung contusion, and this HIF-la expression stimulates the proliferation and expansion of type II alveolar epithelial cells to alleviate damage after acute lung injury.[12,15-17]

Acute pulmonary injury in COVID-19 has important clinical findings in both diagnosis and follow-up of the disease. The mechanisms that is effective in the development of this damage have not been elucidated yet. However, the formation of hypoxic conditions, inflammation and sepsis during the course of the infection are main factors that lead to multiple organ injuries. As a protective factor for such clinical conditions, increased expression of HIF-1α may play a role in the development of different clinical features. This study was aimed to answer the questions of whether the serum levels of HIF-1α, which is increased by up to 100 times in many tissues including pulmonary tissue in cases of acute lung injury, could be used as an effective parameter in monitoring the severity and prognosis of the disease in COVID-19 patients.

MATERIALS AND METHODS

Study Population

40 patients and 20 healthy control, who admitted to Tokat Gaziosmanpasa University Hospital between 6 April and 1 May 2020 with COVID-19 clinical symptoms, were included in the study. A suspect case for COVID-19 has been identified as someone who meets both of the following criteria: 1) fever with the presence of at least one these two condition; respiratory symptoms such as cough, sore throat or shortness of breath or radiographic evidence of pneumonia 2) history of contact with COVID-19 patient. A confirmed case was defined as a patient with positive results for the real-time reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 in the upper respiratory sample (nasopharyngeal and oropharyngeal swab) or in the lower respiratory sample (without sputum). 56 patients who admitted with COVID-19 clinical complaints, 20 of them formed the confirmed case group, another 20 patients formed the suspect case group. None of the patients in the suspect group developed COVID-19 during clinical and laboratory follow-ups. While forming the control group, individuals were chosen according to the criteria of not having any acute infection or chronic diseases, and having an age and gender distributions similar to other groups.

Clinical Classifications

All cases were divided into four groups according to their clinical symptoms such as severity of pneumonia, respiratory failure, shock, and other organ failures. (1) Mild type: mild clinical symptoms without pneumonia findings in imaging; (2) common type: fever, respiratory symptoms and pneumonia findings in imaging; (3) severe type: respiratory distress, respiratory rate ≥ 30 / min; oxygen saturation 93% at rest; PaO2 / FiO2 ≤ 300 mmHg; (4) critical type: respiratory failure requiring mechanical ventilation, shock and other organ failure requiring ICU monitoring and treatment.

Laboratory Assay

Clinical and laboratory data of COVID-19 group were evaluated at three different times: hospital admission day (day 0), one week after admission (week 1), and disease outcome. For the evaluation of the study parameter, Day 0 and Week 1 blood samples were collected, centrifuged and stored at -80°C. Laboratory evaluation of the patients and the control groups included inflammatory markers and disease-specific markers.

Procalcitonin, C-reactive protein (CRP), Ferritine and D-dimer which are known biochemical markers, were used to assess the disease activity. The HIF-1α serum levels were measured using an enzyme-linked immunosorbent assay commercially available kit (Bioassay Technology Laboratory Human Hypoxia-inducible Factor 1 Alpha ELISA Kit). Other laboratory data were obtained from the hospital information system.

Statistical analysis

The SPSS version 18.0 Windows software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis of the obtained data. Whether the variables show normal distribution or not was analyzed by the Test of Homogeneity of Variances. Since the variables did not show normal distribution, nonparametric tests, which were more suitable than statistical tests, were used. Mann–Whitney U test was used for non-homogenously distributed data and Student T test was used for homogeneously distributed data. Mann-Whitney U test was used in comparison of patients with healthy volunteers as well as in binary group comparisons. The categorical variables were compared using the chi-squared test. Kruskal-Wallis H test was used to compare more than two groups. Spearman correlation analysis was used to determine the relationship between numerical variables. Differences of $p<0.05$ were considered to be statistically significant.

Ethics approval

This research study was approved by Republic of Turkey Ministry of Health (KÖKSAL DEVECİ-2020-05-05T00_55_27) and the Tokat Gaziosmanpasa University clinical research ethics committee (15-KAEK-172) and it was planned and conducted in accordance with the provisions of the Helsinki Declaration.

RESULTS

The mean age of COVID-19 positive, COVID-19 suspect and control groups included in the study were 57.8±16.1, 60.7±19.2 and 61.2±11.9, respectively. 8 (40.0%) patients in the COVID-19 positive group, 10 (50.0%) patients in the COVID-19 suspect group and 7 (35.0%) individuals in the control group were over 65 years old. 35.0% of COVID-19 positive group was male, 65.0% was female, 35.0% male of COVID-19 suspect group was male, 65.0% female, 45.0% male of control group, 55.0% female (**Table 1**).

When the clinical symptoms of admission were evaluated, fever was the most common symptom in the COVID-19 positive group with 73.3%. In 20% of COVID-19 suspect group, fever was the symptom on admission ($p<0.05$). No significant difference was found between these two groups in terms of clinical presentations of dyspnea and cough ($p>0.05$). Chest tightness, sputum and fatigue could not be evaluated due to insufficient number of patients. When chronic disease of the patients were evaluated, it was found that these incidences were higher in the COVID-19 suspect group (60%) than the positive group (33.3%) ($p<0.05$) (**Table 1**).

When laboratory data of all three groups were compared, WBC, lymphocyte, monocyte and platelet counts of the COVID-19 positive group were significantly lower than the COVID-19 suspect group and the control group ($p<0.05$). AST values of COVID-19 positive group were significantly higher than AST values of COVID-19 suspect group and control group. COVID-19 positive group CRP, procalcitonin, ferritin and D-Dimer values were significantl"y higher than the values of COVID-19 suspect group and control group ($p<0.05$). Also, procalcitonin and ferritin values of COVID-19 suspect group were significantly higher than the control group ($p<0.05$) (**Table 1**).

The mean (range) of serum HIF-1α values of the COVID-19 positive, suspect and control groups were 2.27 (1.68-7.97), 2.69 (0.92-11.44) and 1.85 (0.58-2.73), respectively. No significant difference was found between serum HIF-1α values of COVID-19 positive group and COVID-19 suspect group ($p>0.05$). A significant difference was found between serum HIF-1α values of COVID-19 positive group, COVID-19 suspect group and control group ($p <0.05$) (**Table 1**).

In **Table 2**, laboratory results of 20 COVID-19 positive patients on admission (Day 0) and Week 1 after hospitalization were compared. The mean HIF-1α values (3.04±1.75) of Day 0 were significantly higher than the mean HIF-1α values (2.73±1.84) of Week 1 ($p<0.05$). Monocyte count, platelet count and ferritin values of COVID-19 positive patients in the first week after hospitalization were significantly higher than on admission values ($p<0.05$).

Table 3 shows the rates of disease severity of COVID-19 positive and COVID-19 suspect group on the day of admission (Day 0), on the first week after hospitalization and on the day of discharge (end of the disease). For COVID-19 positive group, the rate for mild severity was 15.0% on Day 0, it reached 50.0% in the 1st week and it was 85.0% at the end of the disease. The rate of cases with moderate severity on admission was 70.0%, which dropped to 35.0% in the first week and was 0.0% at the end of the disease. None of the cases were severe on admission to hospital and only 10.0% of cases were severe in the first week. 3 patients (15.0%) disease severity was critical on admission, their status did not change in the first week of the hospitalization and the disease resulted in death for 3 patients (15.0%). In COVID-19 suspect group, disease severity distributions were 12 cases (60.0%) of mild, 3 cases of moderate (15.0%), 5 cases of severe (25.0%) and no case of critical (0.0%).

Serum HIF-1α values of the COVID-19 positive and COVID-19 suspect groups were compared according to the disease severity. The 1st week serum HIF-1α levels of the COVID-19 positive critical/death cases (1.54 (1.14-1.94) was found to be significantly lower than serum levels of day 0 and week 1 of COVID-19 positive mild cases.[4.07 (2.14-6.01) and 3.43 (2.23-4.63), respectively] ($p<0.05$). For COVID-19 suspect group, no significant difference was found between serum HIF-1α values of the mild and severe cases ($p>0.05$) (**Table 4**).

Table 1. Comparison of demographic, clinical and laboratory data of study groups

	COVID-19 positive (n=20)	COVID-19 suspect (n=20)	Control (n=20)
Age (year)	57.8±16.1	60.7±19.2	61.2±11.9*
Gender (M/F)	7/13	7/13	9/11**
Clinical symptoms			
Fever	11 (73.3 %)[b]	3 (20.0 %)**	-
Dyspnea	5 (33.3 %)	7 (46.7 %)**	-
Coughing	11 (73.3 %)	9 (60.0 %)**	-
Chest tightness	0 (0.0 %)	3 (20.0 %)**	-
Sputum	0 (0.0 %)	4 (26.7 %)**	-
Fatigue	4 (26.7 %)	0 (0.0 %)**	-
Chronic Disease	5 (33.3 %)[b]	9 (60.0 %)**	-
Laboratory Tests			
WBC (×10³, cell/mL)	5.07 (3.15-6.50)[a,d]	9.22 (5.36-37.26)[d]	6.60 (3.58-10.09) ***
Lymphocyte (×10³, cell/mL)	1.13±0.53[b,d]	2.06±0.94	2.0±1.04 *
Monocyte (×10³, cell/mL)	0.30 (0.20-0.58)[b,d]	0.51 (0.19-1.71)	0.48 (0.20-1.40) ***
Platelet (×10³, cell/mL)	153.1±55.2[b,c]	233.8±82.1	242.9±63.0 *
AST (U/L)	37.6 (13.5-389.0) [b,d]	21.4 (13.0-43.4)	19.5 (10.0-179.0) ***
ALT (U/L)	24.0 (4.8-198.0)	23.0 (6.9-42.9)	15.0 (8.0-174.0) ***
Total Bilirubin (mg/dL)	0.60 (0.18-0.51)	0.38 (0.20-1.25)	0.50 (0.14-1.04) ***
Creatinine (mg/dL)	0.91±0.19	0.93±0.11	0.87±0.21 *
Na (mmol/L)	140.5±4.9	141.2±4.0	140.2±2.4 *
Cl (mmol/L)	103.7±5.3	103.8±3.6	104.2±2.9
CRP (mg/L)	43.15 (0.06-163.44)[a,c]	3.14 (0.22-159.97)	3.50 (0.54-67.0) ***
Procalcitonin (ng/mL)	0.087 (0.046-7.19)[b,c]	0.061 (0.034-0.179)[c]	<0.020*
Ferritin (ng/mL)	414.8 (96.35-1257.0)[b,c]	72.41 (9.93-227.0)[c]	38.10 (9.72-182.24) ***
D-dimer (mg/L)	0.34 (0.07-8.42)[b,c]	0.22 (0.05-0.97)	0.12 (0.06-0.14) ***
PT (sec.)	16.7±4.5	11.7±7.0	11.9±1.6 *
APTT (sec.)	28.7±5.2	28.6±5.5	32.4±3.6 *
Fibrinogen (mg/dL)	347.5 (113.0-620.0)	274.5 (241.0-308.0)	298.2 (185.0-380.4) ***
HIF-1α (ng/ml)	2.27(1.68-7.97)[c]	2.69 (0.92-11.44)[c]	1.85 (0.58-2.73) ***

* Student T test, ** Chi-squared test, *** Mann-Whitney U test, [a]P <0.001 significant difference from COVID-19 suspect group, [b]P <0.05 significant difference from COVID-19 suspect group, [c]P <0.001 significant difference from control group, [d]P <0.05 significant difference from control group

Table 2. Comparison of HIV-1 α and laboratory results of COVID-19 patients on admission and at the first week of hospitalization

	COVID-19 positive group (Day 0) (n=20)	COVID-19 positive group (Week 1) (n=20)	P value
HIF-1α (ng/ml)	3.04±1.75	2.73±1.84	<0.05*
WBC (×10³, cell/mL)	5.06±1.04	6.16±2.76	>0.05*
Lympochyte (×10³, cell/mL)	1.17±0.56	1.28±0.75	>0.05*
Monocyte (×10³, cell/mL)	0.34± 0.11	0.42±0.17	<0.05*
Platelet (×10³, cell/mL)	150.6±47.5	242.1±76.9	<0.05*
AST (U/L)	33.7 (13.5-119.4)	26.7 (14.4-148.2)	>0.05**
ALT (U/L)	21.9 (4.8-85.9)	35.25 (5.6-210.6)	>0.05**
Total Bilirubin (mg/dL)	0.59±0.39	0.63±0.36	>0.05*
Creatinine (mg/dL)	0.88±0.19	0.96±0.55	>0.05*
Na (mmol/L)	142.2±4.8	144.7±4.4	>0.05*
Cl (mmol/L)	103.9±5.5	106.4±5.7	>0.05*
CRP (mg/L)	30.53 (10.06-163.44)	24.83 (3.35-364.78)	>0.05**
Procalcitonin (ng/mL)	0.086 (0.055-0.544)	0.114 (0.045-17.43)	>0.05**
Ferritin (ng/mL)	391.3 (96.35-1063.0)	508.5 (107.9-1551.0)	<0.05**
D-dimer (mg/L)	0.52 (0.07-8.42)	0.66 (0.15-5.36)	>0.05**
PT (sec.)	17.05±4.9	16.37±2.7	>0.05*
APTT (sec.)	27.41±3.5	25.90±3.8	>0.05*
Fibrinogen (mg/dL)	324.1±96.4	379.2±107.6	<0.05*

* Student T test, ** Mann-Whitney U test

Table 3. Clinical classification of COVID-19 suspect group and COVID-19 positive group

	COVID-19 positive group (n=20)			COVID-19 suspect group (n=20)
	On Admission (Day 0)	In First Week (Week 1)	Hospital Discharge	On Admission (Day 0)
Mild Type	3 (15.0%)	10 (50.0%)	17 (85.0%)	12 (60.0%)
Common Type	12 (60.0%)	3 (15.0%)	0 (0.0%)	3 (15.0%)
Severe Type	2 (10.0%)	4 (20.0%)	0 (0.0%)	5 (25.0%)
Critical Type	3 (15.0%)	3 (15.0%)	3 (15.0%)	0 (0.0%)

Table 4. Comparison of serum HIF-1α levels according to the clinical classification of patient groups

	COVID-19 positive group (n=20)		COVID-19 suspect group (n=20)
Serum HIF-1α levels	On Admission (Day 0)	In First Week (Week 1)	On Admission (Day 0)
Mild Type	4.07 (2.14-6.01)	3.43 (2.23-4.63)	2.81 (0.92-11.44)
Common Type	2.28 (1.68 -7.97)	2.13 (1.20-8.22)	-
Severe Type	2.86 (2.06-4.04)	2.87 (2.05-3.69)	2.86 (2.06-4.04)
Critical Type	2.01 (1.94-2.09)*	1.54 (1.14-1.94)*	-

Mann-Whitney U test, *Significant difference from mild cases of COVID-19 positive group (p <0.05)

Table 5. Correlation analysis of HIF-1α results of patient groups

	COVID-19 positive group				COVID-19 suspect group		Control group	
	On Admission (Day 0) HIF-1α		In First Week (Week 1) HIF-1α		On Admission (Day 0) HIF-1α		HIF-1α	
	r	p	r	p	r	p	r	p
Age	-0.738	<0.001*	-0.579	0.024	0.232	0.405	-705	0.003*
Platelet count	0.594	0.042*	0.392	0.208	-0.271	0.328	262	346

Spearman corerelation analysis, * p<0.05

When the results of the correlation analysis of serum HIF-1α values in the study groups were evaluated, there was a strong negative correlation between the day 0 HIF-1α values and the patient age for COVID-19 positive group, whereas a weak positive correlation was found between the HIF-1α values and platelet count (r; - 0.738, p <0.001 and r; 0.594, p: 0.042, respectively). There was a weak negative correlation between HIF-1α values and the age of the patient only at week 1 (r; -0.579, p: 0.024). In COVID-19 suspected group, no relation was found between serum HIF-1α values and any of the study parameters. In the control group, there was a moderate negative correlation between HIF-1α values and the age (r; -0.705, p: 0.003). (**Table 5**).

DISCUSSION

In order to fight against COVID-19 pandemic, clinical and laboratory determinants of progression to severe and fatal forms need to be urgently identified. At the same time, many studies are needed to explain the mechanisms of the disease and to develop new treatment strategies. In this study, it was found that the serum HIF-1α values in COVID-19 confirmed patient group were higher than serum HIF-1α values of healthy control group. However, no significant difference was found for the COVID-19 suspect group.

On the day of hospitalization, serum HIF-1α values were higher than the HIF-1α values after hospitalization, whereas Monocyte, platelet and ferritin values were lower. Serum HIF-1α values of the critical cases subgroup of the COVID-19 confirmed patient group were lower than the mild cases subgroup's Day 0 and Week 1 values. Within COVID-19 group, HIF-1α values were strongly negative correlated with patient age, whereas platelet numbers were weakly positive correlated.

Clinically, patients with SARS had a triphasic disease pattern, such as fever, nonproductive cough, sore throat, and muscle pain.[18] In this study, COVID-19 patients had fever (73.3%), cough (73.3%), dyspnea (33.3%), and weakness (26.4%). The new coronavirus (COVID-19) pneumonia outbreaked at the end of 2019 is highly contagious, with a raw mortality rate of about 2.3%.[18] Approximately 80.9% of patients are mildly to moderately ill and have a better prognosis. However, the mortality rate increased significantly for patients who developed severe or critical levels and the raw mortality rate reached 49% in critical patients.[19] In this study, the cases 65% of the cases were mild and moderate, and 35% of them were severe or critical. The mortality rate for severe or critical patients was 42.8%. The main clinical signs of COVID-19indicate fever (90% or more), cough (about 75%) and dyspnea (up to 50%). A small but important subset has gastrointestinal symptoms..[7, 20-23]

The mechanism of the SARS-CoV-2 infection is not yet known. "Cytokine storm" or "cytokine cascade" are among the default mechanisms for organ damage. Various recent studies have linked some of biomarkers to a severe disease progression.[24] In this study, HIF-1α was evaluated both as its role in disease mechanism and as a biomarker. COVID-19 is a viral disease characterized by normal or low white blood cell count and decreased lymphocyte count. Among the hematological parameters, lymphopenia is clearly associated with disease severity. Patients who died from COVID-19have significantly lower lymphocyte counts than survivors.[25.26] In terms of laboratory tests, Zhang et al. found a decrease in WBC count in 38.66% of patients and a decrease in lymphocyte count in half of patients (48.45%). At the same time, CRP, ferritin, procalcitonin and D-dimer levels increased in a significant number of patients in relation to the severity of the disease.[25] It has been reported that especially in some patients with multiple organ failure, alanine aminotransferase, aspartate aminotransferase (liver failure), creatine kinase and lactate dehydrogenase, troponin (myocarditis), urea and creatinine (kidney failure) levels and cagulation parameters could increase. In severe cases, elevation in these parameters may be seen initially before multiorgan failure develops.[25,26]

In our study, WBC, lymphocyte, monocyte and platelet counts were lower in the COVID-19 positive group than in the COVID-19 suspect group and the control group. WBC values of the COVID-19 suspect group increased compared to the control group. AST, CRP, ferritin, procalcitonin and D-dimer levels, which were among other parameters, increased in the COVID-19 group compared to the suspect group and the control group. Suspect group procalcitonin and ferritin values also increased compared to the control group. These results support the studies that shows these parameters can be used to separate COVID-19 patients from the suspect group and the healthy group. However, when we evaluated the changes of these parameters after the first week of hospitalization of COVID-19 patients, a significant change was observed only in the monocyte, platalet counts and procalcitonin values. These findings led us to the conclusion that monocyte count, platalet count and procalcitonin levels could be more useful as follow-up tests for COVID-19 patients.

HIF-lα has been shown to regulate the expression of more than 100 downstream genes during acute hypoxia, protecting it from hypoxic stress in many ways, most of which affect the progression of inflammation.[12,17] In early stages of acute lung injury / ARDS, damage to the alveolar membrane, alveolar epithelial cell apoptosis and pulmonary edema can easily lead to hypoxia and activation of HIF-1α. Studies have shown that HIF-1α can control inflammation and alleviate acute lung damage by regulating glucose metabolism in alveolar epithelial cells.[12, 13] It has been reported that HIF-la expression increases after lung contusion, and this HIF-1α expression stimulates the proliferation and expansion of type II alveolar epithelial cells to alleviate damage after acute lung injury.[14, 27, 29] HIF-1 has also been found to be active in various epithelial tissues during trauma and infection. In their study, Sherman et al. investigated the responses of alveolar epithelial cells to lung contusions and they found an increase in expression of HIF-1α in the lungs in 48 hours in the lung and in 24 and 48 hours in the liver.[15] Matsuishi et al. in their study which they aimed to reconstruct acute lung injury by administering lipopolysaccharide in a rat model to examine early sepsis-related recovery, improvement and complications, reported that there was a significant levels of expression of HIF-1α mRNA in the untreated group compared to the group that treated with Lindiolol, a beta receptor blocker.[17]

Lung contusions are a risk factor and one of the causes of acute respiratory distress syndrome, in which fluid collects in the alveoli.[13] During acute respiratory distress syndrome, epithelial cells, especially alveolar type (AT) I cells, disappear, resulting in increased permeability. The fluid collection prevents gas exchange and can lead to both local and systemic hypoxia. Hypoxia is the driving force of inflammation. HIF-la is the key mediator of the inflammatory response following lung contusions, but can also be induced by inflammation that begins with hypoxia or other physiological disruptions. [30] ATII cells proliferate and get distributed over the decayed basement membrane to reseal the barrier. Repair of the alveolar epithelium is critical for clinical recovery. It is thought that the hypoxia-related factor (HIF) la supports the proliferation and spread of ATII cells during post-lung injury repair.[16]

In this study, an increase in serum HIF-1α levels was found in the COVID-19 positive group compared to the healthy control group. However, since this increase was also in the COVID-19 suspect group, there was no significant difference between the COVID-19 positive group and the COVID-19 suspect group. When we re-evaluated the samples of COVID-19 group after 1 week, a significant decrease was found in the values. When we compare HIF-1α levels according to the severity of these patients, we found that critical patients' HIF-1α levels were significantly lower than patients having mild disease course. At the same time, serum HIF-1α levels of COVID-19 patients were strongly negative correlated with patient age, whereas platelet counts were weakly correlated. These findings lead us to the conclusion that that there is an increase in HIF-1α levels in COVID-19 disease, but this increase is not a specific for COVID-19. Instead, the lack of adequate increase in HIF-1α levels in patients with critical condition may be determining factor in the course of the disease because, 3 critical COVID-19 patients, whose HIF-1α levels were low, didn't survive. An increase of HIF-1α in mild and moderate COVID-19 patients may prevent the progression of pulmonary damage, through stimulating the proliferation of type II alveolar cells. On the other hand, low HIF-1α levels in severe and critical patients can lead to the propagation of alveolar damage and multiple organ failure. The strong negative correlation between age and HIF-1α should be considered as another factor that may determine the severity of COVID-19 in elderly patients.

CONCLUSIONS

COVID-19 is a dangerous and severe disease, the mechanism of the emergence and progression is currently unclear, and therefore detailed study is required. In this study, monocyte, platelet and ferritin tests were illustrated that they are important biomarkers in disease follow-up. Serum levels of HIF-1α, which are thought to prevent alveolar damage, were increased in patients with COVID-19. However, low levels of serum HIF-1α should be considered as a factor responsible for alveolar damage in critically ill patients.

Limitations of study

The limitations of this study is that this study included a small number of patients from a single center. As more data are gathered from prospective studies with longer follow-ups, these findings should be reassessed continuously in upcoming months.

ETHICAL DECLARATIONS

Ethics Committee Approval: This research study was approved by Republic of Turkey Ministry of Health (KÖKSAL DEVECİ-2020-05-05T00_55_27) and the Tokat Gaziosmanpasa University clinical research ethics committee (15-KAEK-172) and it was planned and conducted in accordance with the provisions of the Helsinki Declaration.

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

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.

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.

Acknowledgment: The author thanks all the staff members of the Central Laboratuary in the Medical Faculty of Tokat GOP University, Turkey, for their technical assistance at all phases of the study.

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.881440
J Contemp Med 2021;11(4):469-473

Orjinal Araştırma / Original Article

Retrospective Evaluation of Laboratory, Radiological and Clinical Findings of COVID-19 Suspected Cases with a Public Health Perspective in Adiyaman Training and Research Hospital

Adıyaman Eğitim Araştırma Hastanesine Başvuran COVID-19 Şüpheli Vakaların Laboratuvar, Radyolojik ve Klinik Bulgularının Halk Sağlığı Bakışıyla Retrospektif Değerlendirilmesi

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Abstract

Aim: The purpose of this study is to evaluate SARS-CoV-2 cases based on clinical evidence from the perspective of public health.

Material and Method: This study is a retrospective study.The data of 354 people were analyzed which were among the patients admitted to the pandemic hospital in Adiyaman in the study.

Results: 70.6% of those admitted to the hospital with suspected COVID-19, 60% of those received inpatient treatment and 61.3% of those who were PCR-positive were male. The median age of those admitted to the hospital was 37 years. 90% were in a good general condition. The median length of hospitalization was 7 days. 14.8% PCR-positive patients required mechanical ventilation. Generally, D-dimer, CRP and WBC levels were poor, which were higher in those receiving intensive care ($p<0.05$). 19.5% of the cases were diagnosed with pneumonia as a result of the CT. COVID 19 was the most common diagnosis as a result of CT (11.0%).

Conclusion: The disease seems to be more common among men. CT abnormalities are common. D-Dimer, CRP and WBC levels are associated with severe disease.

Keywords: Communicable diseases, public health, COVID-19

Öz

Amaç: Bu çalışmanın amacı, SARS-CoV-2 vakalarını halk sağlığı perspektifinden klinik kanıtlara dayalı olarak değerlendirmektir.

Gereç ve Yöntem: Bu çalışma retrospektif tiptedir Araştırmada Adıyaman pandemi hastanesine başvuran hastalardan 354 kişinin verileri incelendi.

Bulgular: Hastaneye COVID-19 şüphesi ile başvuranların %70,6'sı, yatarak tedavi görenlerin %60'ı ve PCR pozitif olanların% 61,3'si erkekti. Hastaneye başvuranların ortanca yaşı 37 idi. % 90'ı genel olarak iyi durumdaydı. Ortanca hastanede kalış süresi 7 gündü. PCR pozitif hastaların% 14.8'i mekanik ventilasyona ihtiyaç duydu. Genel olarak D-dimer, CRP ve WBC seviyeleri zayıftı ve yoğun bakım alanlarda daha yüksekti ($p<0.05$) BT sonucunda vakaların% 19,5'i pnömoni tanısı aldı. BT sonucuna göre COVID 19 en yaygın tanıydı (% 11.0).

Sonuç: Hastalık erkekler arasında daha yaygın görünmektedir. BT anormallikleri yaygındır. D-Dimer, CRP ve WBC seviyeleri ciddi hastalıkla ilişkilidir.

Anahtar Kelimeler: Bulaşıcı hastalıklar, halk sağlığı, COVID-19

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Received *(Geliş Tarihi)*: 16.02.2021 **Accepted *(Kabul Tarihi)*:** 24.03.2021

INTRODUCTION

The COVID-19 outbreak emerged in late 2019 and has spread to all over the world very rapidly and has become a pandemic.[1] The infection has transmitted from human to human and spread from China to the continents of Asia, Europe and Africa infecting millions and killing tens of thousands of people. The 2019 n-CoV has impacted many countries and it presents a major public health issue. The index case in Turkey was identified on March 11, 2020 and the index case in the study region was identified on March 14, 2020. The average incubation period is 2 to 4 days.[2] In their study, Lauer et al.[3] found that less than 2.5% of infected people develop symptoms in 2.2 days while 97.5% in 11.5 days. The median incubation period was found to be 5.1 days

According to the joint report of WHO and China, the majority of the cases were between the ages of 30 and 69 and the median age was 51.[4] In terms of clinical course, the disease can cause as far as multi organ failure.[5] In severe disease, clinical signs such as fever, shortness of breath, tachypnea and hypoxia present. In addition to clinical signs, radiological signs also help support the diagnosis.[5] The study of Pan et al.[6] showed that 48% of the cases had mild disease, 29.9% moderate, 19.1% severe and 3% critical. 41.3% of the severe and critical cases was people over the age of 80.

Various immunological tests and Polymerase Chain Reaction (PCR) test, which targets specific genes, are performed to diagnose the infection. The most ideal diagnostic method for COVID-19 is quantitative real-time polymerase chain reaction (qRT-PCR) along with nasopharyngeal swab. Symptoms, risk factors, pneumonia findings and thorax CT images should also be taken into consideration when diagnosing the infection. Although PCR tests have high sensitivity, the fact that results are obtained 4 to 6 hours (reduced to 2-4 hours in recent kits) and experienced staff is required for application has led to the production of rapid antibody (immunoassay) tests. These tests can detect IgM and IgG antibodies, which are produced against SARS-CoV-2, in 15 minutes.[2] The purpose of this study is to evaluate SARS-CoV-2 cases based on clinical evidence from the perspective of public health. The purpose was to analyze cases admitted to the hospital and collect data on the COVID-19 infection, compile and interpret the data and contribute to the literature.

Pandemics affect men and women differently. The exposure risk and biological sensitivity may be different due to the other social factors as well as infections, social and economic results and the gender of an individual. Different sample groups or underreporting may be the reasons behind these differences

It is aimed to examine the suspected COVID-19 cases admitted to the Adıyaman Training and Research Hospital in terms of clinical, radiological and laboratory findings.

MATERIAL AND METHOD

Research type

This study is a retrospective study.

The universe and sample of the research

3064 individuals, who registered to Adiyaman Training and Research Hospital during the course of 3 months starting with the first case admitted on March 14, 2020, formed the universe of the study. The formula n=Nt2pq/d2(N-1)+t2pq was used to determine the sample size, which was calculated to be 354 with a confidence interval of 95%, prevalence of 50% and deviation of 5%. The stratified sampling method was made use of. Using the open epi program, random numbers were generated and the cases to be included in the study were identified. Averages were provided with standard deviation.

Data collection tools

The records of patients admitted to Adiyaman Training and Research Hospital with suspected COVID-19 were analyzed. During the analysis, demographic information laboratory, radiological and clinical findings were taken into consideration.

Data analysis

COVID-19-related laboratory (sedimentation, CRP, lymphocyte, white blood cell) and radiological findings and socio-demographic information (age, gender) of registered patients were made use of. The data obtained from the data collection form was performed using SPSS 22. Descriptive statistics were identified using figures and percentages. Relationship between categorical variables were analyzed using the Chi-square and Fischer's exact Chi-square test. Kruskall wallis and mann whitney u tests were used in comparing the averages. Correlation analysis was performed to determine the between some variables. The results were evaluated in a confidence interval of 95% and $p<0.05$ was considered significant.

Ethical aspect of the research

The ethical approval was received from the non-clinical research ethics committee of Adiyaman University (approval no: 2020/7-44).

RESULTS

70.6% of the cases in the study were male and their average age was 41.07±18.79. 60% of hospitalized patients were men which were significantly higher than women ($p<0.05$). The rate of those who were in an overall good condition was 90%. CT was performed on 30.8% of the cases. 19.5% of the cases were diagnosed with pneumonia as a result of the CT. COVID 19 was the most common diagnosis as a result of CT (11.0%).

The median age of the cases covered by the study was 37. The median age of PCR-positive patients was 44.5, and the median age of those receiving intensive care was 65. 61.3% of PCR-positive cases were male and 59% were inpatient (**Table 1, Table 2**).

The duration of hospital stay of PCR-positive patients was significantly higher for those diagnosed with pneumonia, those with poor general condition and those who are intubated (**Table 2**). The median hospital stay was 7 days, and the median hospital stay for intensive care patients was 8.5 days.

The mean values of CRP, WBC and D-dimer of the cases were 3.79±5.92, 9.47±4.92, 1084.96±1526.19, respectively (**Table 3**). A correlation was found between the duration of hospital stay and age, CRP, WBC, D-dimer and lymphocyte **(Table 4**).

Table 1. Examination of the first PCR result by some variables.

	PCR +		PCR -		Total	p
	n	%	n	%	n	
Gender						
Male	38	61.3	212	72.6	250	p>0.05 X²=3.154
Female	24	38.7	80	27.4	104	
Hospitalization						
Outpatient	8	12.9	246	84.2	254	p<0.01 X²=134.498
Ward patient	46	74.2	32	11	78	
Intensive care	8	12.9	14	4.8	22	
Age						
0-14 years	7	11.3	1	0.3	8	
15-49 years	29	46.8	202	69.2	231	p<0.01 X²=33.242
50-64 years	14	22.6	51	17.5	65	
65+	12	19.3	38	13	50	
CT						
N/Ab	15	24.2	230	78.8	245	
Covid	18	29.0	21	7.2	39	p<0.01 X²=73.608 fisher
Viral	10	16.1	10	3.4	20	
Normal	14	22.6	21	7.2	35	
Other	5	8.1	10	3.4	15	
Pneumonia						
Yes	31	50	38	13	69	p<0.01 X²=44.583
No	31	50	254	87	285	
Total	**62**		**292**			

[b]the reason for the difference

Table 2. Comparison of average duration of stay at the hospital of PCR-positive patients with certain conditions.

	Mean	p
Ward		
Outpatient	0±0	p<0.001 U:302 (outpatient were excluded)
Ward patient	9.24±6.40	
Intensive care	22±9,25	
Gender		
Male	10.55±9.65	U=411.500 p>0.05
Female	7.50±5.31	
According to CT		
Yes	12.48±9.74	U=411.500 p>0.05
No	7.07±3.87	
Pneumonia		
Yes	13.13±9.68	p<0.01 U=239.0
No	5.61±4.27	
General condition		
Good	6.90±4.62	p<0.001 X2=14.548 KW
Moderate	13.17±5.19	
Poor	26.17±13.92	
Intubation		
Yes	26.17±13.92	p<0.001 U: 50.0
No	7.57±5.03	
Age groups		
0-14	8.86±1.57	p>0.05 X2=4.411 KW
15-49	6.83±4.85	
50-64	12.79±13.33	
65 and over	11.83±8.65	

Table 3. Comparison of some laboratory averages with certain conditions.

	CRP	WBC	Lymphocyte	D-dimer
Gender				
Male	3.57±5.51	9.22±4.50	2.05±1.00	925.8±1360.40
Female	4.13±6.57	9.87±5.52	2.28±1.28	1354.78±8149.04
	p>0.05 U: 74.500	p>0.05 U: 4338.000	p>0.05 U: 4115.500	p>0.05 U: 2089.000
Type of treatment				
Outpatient	3.26±6.02c	10.68±4.92c	2.44±1.06b	1003.01±1744.71c
*Ward patient	2.99±3.67c	7.18±2.95b	1.98±1.16c	932.72±1246.81b
*Intensive care patient	9.57±9.15b	12.10±7.09c	1.31±0.69d	1957.94±1585.58c
	p<0.01 X2=19.744 KW	p<0.01 X2=34.078 KW	p<0.01 X2=29.936 KW	p<0.01 X2=16.294 KW
CT				
*CT not performed	3.04±5.99	10.73±5.15	2.61±1.25	1166.74±1852.88
*Consistent with COVID	3.99±4.34	6.90±2.68	1.66±0.63	1218.05±1714.23
*Consistent with viral	6.32±7.51	8.97±6.20	1.41±0.72	832.29±645.79
Normal	3.30±6.24	8.15±3.25	1.99±0.96	740.28±1015.89
Other (mix. bacterial. non-infectious)	5.38±5.92	11.59±5.72	1.77±0.73	1343.15±951.96
	p<0.01 X2=24.648 KW	p<0.01 X2=28.730 KW	p<0.01 X2=37.804 KW	p<0.05(0.01) X2=13.373 KW
General condition				
aGood	2.85±4.99 b	9.21±4.78	2.28±1.53 b	943.08±1498.43 b
Moderate	7.11±5.52 c	10.26±5.76	1.52±0.64 c	1631.25±1849.88 c
Poor	10.50±10.13 c	11.47±5.10	1.40±0.67 c	1711.30±1074.38 c
	p<0.01 X2:29.836 KW	p>0.05 X2:4.870 KW	p<0.01 X2:18.197 KW	p<0.01 X2:17.953 KW
Intubation				
Yes	10.50±10.13	12.25±5.78	1.36±0.68	1711.31±1074.39
No	3.29±5.19	9.26±4.80	2.21±1.31	1024.64±1522.46
	p<0.01 U: 493.000	p<0.05 U: 787.000	p<0.01 U: 587.000	p<0.01 U: 406.500
Total	**3.79±5.92**	**9.47±4.92**	**2.15±1.13**	**1084.96±1526.19**

* A significant difference was found according to Tamhane test.
aA significant difference was found using the Mann Whitney-U test.

Table 4. The examination of the correlation of hospitalization status with age and some laboratory findings

	r	p
Age	r=0.25	p<0.01
CRP	r=0.243	p<0.01
D-Dimer	r=0.141	p<0.01
WBC	r= -0.343	p<0.01
Lymphocyte	r= -0.323	p<0.01

DISCUSSION

In our study, 61.3% of the PCR-positive cases were men. It was found that 75% of COVID-19 patients to be men;[8] while another study stated the rate of men to be 49%.[9] Although these studies support our finding that COVID-19 is more common among men than women, another study found the number male and female cases to be similar.[10] In our study, the number of men receiving inpatient treatment was considerably higher than women (p<0.05). A study analyzed the rates of hospitalization and reported that men was affected disproportionally.[9] 58% of deaths were men. [10] Another study showed that death cases was increasing among men.[10] Although these studies support our finding that men require more hospital care, a study found the rate of hospitalized female patients to be higher than men.[11] Pandemics affect men and women differently. The exposure risk and biological sensitivity may be different due to the other social factors as well as infections, social and economic results and the gender of an individual.[10] Different sample groups or underreporting may be the reasons behind these differences.

In our study, 17.5% of patients admitted to the hospital with suspected COVID-19 tested positive with PCR. A study conducted with suspected COVID-19 cases, the rate of PCR-positivity was 35%.8 5.5% of COVID-19 patients required hospital care. 20% of the hospitalized patients required intensive care. 70% of intensive care patients required ventilation.

In our study, the median duration of hospital stay was 7 days. A study found the median value to be 21 days[9] while another study 13 days.[12] Another study found this to be 10 days.[13] In different studies, the duration of hospital stay varies. This duration depends on living conditions in countries, socio-demographic features and healthcare services.

The duration of hospital stay of PCR-positive patients was significantly higher for those diagnosed with pneumonia, those with poor general condition and those who are intubated. This is an expected outcome.[9]

In our study, 14.8% of inpatient PCR-positive patients required mechanical ventilation. In a study conducted at Chicago University, 28.4% of the patients were intubated.[10] A study found that approximately 10% of the patients required mechanical ventilation.[11] According to a study in Colombia University, 4.4% of the patients were intubated.[7] The same study noted that 2.3% of lab-confirmed cases were intubated.

In our study, 46.7% of PCR-positive patients had CT abnormalities, 62% of them which were found to be consistent with COVID-19. A study found that CT images of 65% of patients, who were being followed-up due to COVID-19, had abnormalities and multifocal ground glass opacities were observed in 74% of these patients.[14]

In our study, it was found that D-dimer and CRP averages of patients, who are intubated, have poor general condition and receive intensive care, were significantly higher (p<0.05). A study found high D-dimer to be a risk factor for hospital mortality.[15] Another study found a correlation between high D-dimer and disease severity.[16] A study found CRP levels of severe patients to be significantly higher and CRP levels to be associated with mortality.[17] A study found a correlation between mortality and D-dimer, WBC and CRP.[18] Another study found an association between high CRP and disease severity. This is an expected result as CRP is an acute phase reactant.[19] Another study found that lymphocyte was low while age, CRP, WBC and D-dimer were high in patients who lost their lives.[20]

In our study, it was found that WBC was significantly higher in those who were in poor general condition, received intensive care, and whose CT results were consistent with mixed infection (p<0.05). In a study, high WBC was found to be a risk factor in hospital mortality.[15] WBC and D-dimer were significantly higher in patients who lost their lives. In addition, lymphopenia was detected.[15]

Our study showed that the duration of stay at hospital increased with increasing age. Another study showed that the disease became more severe with increasing age.[17] With the increase in age, the severity of the disease also increases.[15]

A correlation was found between the duration of hospital stay and age, CRP, WBC, D-Dimer and lymphocyte. In various studies, mortality was found to be associated with advanced age, comorbidity, high D-Dimer and CRP and lymphopenia.[15]

This study has some limitations. The first limitation is that it was conducted in a single center. Another limitation is the study was conducted based on records.

ETHICAL DECLARATIONS

Ethics Committee Approval: The ethical approval was received from the non-clinical research ethics committee of Adıyaman University (approval no: 2020/7-44). Necessary permission was obtained from the Ministry of Health and Adiyaman Training and Research Hospital

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

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.

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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JOURNAL OF
CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.862955
J Contemp Med 2021;11(4):474-477

Orjinal Araştırma / Original Article

Determining the Relationship between Spiritual Well-Being and Organ Donation Attitude

Spiritüel İyi Oluşluk ile Organ Bağışı Tutumu Arasındaki İlişkinin Belirlenmesi

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Abstract

Aim: The aim of this descriptive study is to determine the relationship between the spiritual well-being and organ donation attitude among Turkish society.

Material and Method: The study sample is consisted of 569 adults who were above 18 years of age, actively use the internet and voluntarily accepted to participate in the study. The data were collected via internet using Three-Factor Spiritual Well-Being Scale and Organ Donation Attitude Scale between October 2020 and January 2021.

Results: In this study, 66.3% of the participants were female. The median age of the participants was 21 years. It was found that 92.4% of the participants had not signed an organ donor card. The mean score of the Spiritual Well-Being Scale and the sub-dimensions of the scale, transcendence, harmony with nature and anomie were determined as 112.9±18.6 - 61.1±13.6 - 29.3±6.0 and 22.4±7.0, respectively. The mean positive attitude towards organ donation score of participants is 46.0±23.7 and the mean negative attitude score is 73.6±26.3. Participants' total Three-Factor Spiritual Well-Being Scale scores showed significant positive correlations with negative attitudes towards organ donation (r:0.298 p:0.0001) and negative correlations with positive attitudes towards organ donation (r:-0.177 p:0.0001).

Conclusion: As the spiritual well-being levels of the participants increase, their voluntary attitude towards organ donation decreases. It is recommended to plan campaigns and training programs for different spiritual beliefs to encourage individuals to donate organs.

Keywords: Spiritual well-being, organ donation, attitude

Öz

Amaç: Bu tanımlayıcı çalışmanın amacı, Türk toplumunda spiritüel iyi oluşluk ve organ bağışı tutumu arasındaki ilişkiyi belirlemektir.

Gereç ve Yöntem: Araştırmanın örneklemi 18 yaşın üzerinde olan, aktif olarak internet kullanan ve çalışmaya katılmayı gönüllü olarak kabul eden 569 yetişkinden oluşturmaktadır. Veriler, Ekim 2020 - Ocak 2021 tarihleri arasında internet üzerinden Üç Faktörlü Spiritüel İyi Oluş Ölçeği ve Organ Bağışı Tutum Ölçeği kullanılarak toplandı.

Bulgular: Bu çalışmada, katılımcıların %66,3'ü kadındı. Katılımcıların ortanca yaşı 21 yıldı. Katılımcıların %92,4'ünün organ bağış kartı imzalamadığı tespit edildi. Spiritüel İyi Oluş Ölçeği ortalama puanı ve ölçeğin alt boyutları olan aşkınlık, doğa ile uyum ve anomi alt boyut puanları sırasıyla 112,9±18,6 - 61,1±13,6 - 29,3±6,0 ve 22,4±7,0 olarak belirlendi. Katılımcıların organ bağışına yönelik ortalama olumlu tutum puanları 46.0±23.7 ve ortalama negatif tutum puanı 73.6 ± 26.3'tür. Katılımcıların toplam Üç Faktörlü Spiritüel İyi Oluş Ölçeği puanları, organ bağışına yönelik olumsuz tutumlarla anlamlı pozitif korelasyon (r:0,298 p:0,0001) ve organ bağışına yönelik pozitif tutumla negatif korelasyon göstermiştir (r:-0,177 p:0,0001).

Sonuç: Katılımcıların spiritüel iyilik düzeyleri arttıkça organ bağışına yönelik gönüllü tutumları azalmaktadır. Bireyleri organ bağışına teşvik etmek için farklı manevi inançlar için kampanya ve eğitim programlarının planlanması önerilmektedir.

Anahtar Kelimeler: Spiritüel iyi oluş, organ bağışı, tutum

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Received *(Geliş Tarihi)*: 17.01.2021 **Accepted *(Kabul Tarihi)*:** 03.02.2021

INTRODUCTION

In parallel with the developments in technology and surgical techniques, developments in organ transplantation are progressing rapidly. However, the limited number of organ donations worldwide cause the number of patients on the waiting list to increase rapidly. Therefore, the gap between the number of patients awaiting organ transplantation and organ donation proceed to increase.[1,2] According to the Ministry of Health, 75.448 organ transplants (except bone marrow) have been carried out in Turkey since 2008. However, it is known that the number of patients awaiting transplantation is 292.031 in Turkey. In line with these data, it can be said that organ donation is limited and does not meet the demand.[3]

It is known that people's attitudes towards organ donation depend on many factors such as education, socioeconomic level, culture, and religious belief. One of the factors affecting the attitude towards organ donation is spirituality.[2] Spirituality is defined as a broad personal search for and acceptance for meaning, purpose, and value in life.[2,4] Spiritual well-being is the search for the meaning and purpose on which life is based, and the realization of a power greater than yourself. An individual who achieves spiritual well-being is a person with high life satisfaction and self-fulfillment.[5] The spiritual dimension comes to the prominence especially in crisis situations where the individual experiences life-threating illness, stress, fear of death, question the meaning of life and lose hope.[6]

It is stated that the sense of purpose in life is a key mechanism that enables the importance of voluntary activities to be associated with the well-being of the person.[2] Accordingly, it is expected that the spiritual well-being of individuals will affect their attitudes towards organ donation. For this reason, determining the relationship between individuals' spiritual well-being and their attitudes towards organ donation is very important in terms of guiding studies to increase organ donation. However, the effect of spirituel well-being on attitudes towards organ donation is lacking. For this reason, this study was conducted to determine the relationship between the spiritual well-being and organ donation attitude among Turkish society.

MATERIAL AND METHOD

Study design and aim: This study is a descriptive study conducted to determine the relationship between the spiritual well-being and organ donation attitude among Turkish society.

Study sample: The sample of the study consisted of 569 adults who voluntarily accepted to participate in the study and actively used the internet. In the study, priori power analysis was performed with the G-Power 3.1 statistical program based on the data in a similar study by Arisal and Atalar (2020).[7] While the power of the test was 0.95 and the type I error was 0.05, the minimum sample required in the study was determined as 510. After data collection, posthoc power analysis was also performed. Accordingly, the correlation coefficient is 0.177; the alpha value was 0.05 and the strength of the study was found to be at least 0.92.

Data collection: The data of the research were collected between October 2020 and January 2021. Data were collected over the internet due to the pandemic process. Accordingly, the researchers published an invitation letter on social networking sites. The aim and link of the study is included in the invitation letter. IP verifying is provided to ensure that each participant can fill out a single questionnaire. Data collection forms filled online were backed up daily by the researchers. It took approximately 8-10 minutes for the participants to fill in the form.

Data collection instruments: The data of the study were collected using the Data Collection Form. This form consists of 3 parts. In the first part of the form, there are questions aiming to determine the socio-demographic characteristics of the participants included in the study.

In the second part of the form, there is Three-Factor Spiritual Well-Being Scale (TFSWBS) which was developed by Ekşi and Kargaş (2017). The scale consists of 29 items and is a five-point Likert type. Seven questions in the scale are reverse coded. The score range to be obtained from the scale ranges from 29-145. As the score obtained from the scale increases, the level of spiritual well-being increases. The Cronbach alpha coefficient of the scale is 0.886.[5]

In the third part of the form, there is Organ Donation Attitude Scale. The scale was used to determine the participants' attitudes towards organ donation. The Turkish validity and reliability study of the Organ Donation Attitude Scale was conducted by Yazıcı Sayın (2015). The Turkish form of the scale consists of 40 items related to organ donation attitude. These items consist of 20 positive and 20 negative attitudes towards organ donation. The scores that can be obtained from positive attitudes are between 20 and 120, likewise, the total negative attitude score is between 20-120. High positive and low negative scores indicate strong voluntary attitudes towards organ donation. The scale is in a Likert format with six options for each item.[8]

Ethical considerations: This study was approved by the non-interventional clinical research ethics committee of a university (Approval number: 2020/09-63). Necessary information about the purpose and application of the research was given to the participants included in the study in the introduction part of the data collection form. In line with this information, "I agree to participate in the study" and "I do not agree to participate in the study" options were included in the introduction part of the data collection form. Accordingly, the participants who accepted to participate in the study were able to complete the data collection form. In order to apply the " Three-Factor Spiritual Well-being Scale" and "Organ Donation Attitude Scale" used in the study, written permission was obtained from the authors who made the Turkish validity and reliability of the scale via e-mail.

Data analysis: The data obtained from the study were analyzed using the Statistical Package for the Social Sciences (SPSS) for Windows version 20.0. Descriptive statistics (number, percentage, mean, standard deviation) were used to evaluate the data. Kolmogorov Smirnov test was used to determine whether the data showed normal distribution. The relationship between spiritual well-being and organ donation attitude was evaluated using Spearman Correlation Analysis. In all results, p value less than 0.05 was considered statistically significant ($p < 0.05$).

RESULTS

The median age of the participants included in the study was determined as 21 (min: 18, max: 102) years. The socio-demographic characteristics of the participants are shown in **Table 1**.

In this study, it was determined that 92.4% (n:526) of the participants had not signed an organ donor card. In addition, it was determined that 46.0% (n: 262) of the participants would consider donating the organs of any relative (mother, father, sibling, child, spouse, etc.) who had brain death in the future.

In this study, the mean score of the Spiritual Well-Being Scale of the participants was determined as 112.9±18.6 (min:57 max:144). The mean scores of the sub-dimensions of the scale, transcendence, harmony with nature and anomie, were found to be 61.1± 13.6 (min:15 max75), 29.3±6.0 (min:7 max:35) and 22.4±7.0 (min:7 max:35), respectively.

The mean positive attitude towards organ donation score of participants is 46.0±23.7 (min:20 max:120), the mean negative attitude score is 73.6±26.3 (min:20 max:120). It was determined that the mean scores of "fear of medical neglect" and "fear of physical injury" which are indicators of negative attitude were 37.3±13.8 (min:10 max:60) and 36.3±13.5 (min:10 max:60), respectively.

The correlation between participants' spiritual well-being and organ donation attitude scores are shown in **Table 2**. Participants' transcendence, harmony with nature, anomie and total TFSWBS scores showed significant positive correlations with negative attitudes towards organ donation and subscales of fear of medical neglect and fear of physical injury. Participants' harmony with nature, anomie and total TFSWBS scores showed significant negative correlations with positive attitudes towards organ donation (**Table 2**).

DISCUSSION

As it is known, the insufficient number of organ donations and transplants around the world causes many patients who have been receiving treatment for organ failure recently to die while waiting for an organ. In this study, it was found that participants have low positive and high fear of medical neglect and fear of physical injury scores which means participants showed negative attitudes towards organ donation. In studies conducted in Turkey the mean positive attitude scores vary between 90 and 95; fear of medical neglect scores vary between 25 and 27; and fear of physical injury vary between 25 and 32.[9-11] Our positive attitude scores were lower and negative scores were higher than similar studies. This difference is thought to be due to the sociocultural characteristics (such as younger age, tradition, civique, etc.) of the participants in the sample group.

It is known that there are many factors affecting organ donation attitudes. It is known that one of the most important factors affecting organ donation negatively is religious conceptualizations and beliefs. It is stated that this situation arises from the religious misconception of the individuals.[7,12,13] Spirituality can be considered as a component of religion, it is a concept which includes religious practices but it is comprehensive to be limited to religious beliefs and practices.[2,6] It is known that spirituel issues such as spiritual bond with the recipient, a spiritual concern about organ loss, subjective norms, bodily integrity, and traditional beliefs about death are significant factors affecting individuals' willingness to

Table 1. Distribution of the participants according to their socio-demographic characteristics

Socio-demographic Characteristics	Number	Percentage
Gender		
Male	192	33.7
Female	377	66.3
Marital status		
Married	142	25.0
Single	427	75.0
Education status		
Literate	8	1.4
Primary education	19	3.3
Secondary education	29	5.1
High school	199	35.0
Undergraduate	285	50.1
Graduate	29	5.1
Chronic disease		
Yes	90	15.8
No	479	84.2
Total	**569**	**100**

Table 2. Correlation between spiritual well-being and organ donation attitude scores

Spiritual Well-Being Scale Scores	Organ Donation Attitude Scale Scores			
	positive attitude towards organ donation	negative attitude towards organ donation	Fear of medical neglect	Fear of physical injury
Transcendence	r:-0.081 p:0.054	r:0.145 p:0.001	r:0.164 p:0.0001	r:0.115 p:0.006
Harmony with nature	r:-0.228 p:0.0001	r:0.313 p:0.0001	r:0.315 p:0.0001	r:0.285 p:0.0001
Anomie	r:-0.248 p:0.0001	r:0.158 p:0.0001	r:0.183 p:0.0001	r:0.111 p:0.008
Total SWBS	r:-0.177 p:0.0001	r:0.298 p:0.0001	r:0.323 p:0.0001	r:0.248 p:0.0001

become organ donors.[2,7,12,14] Bresnahan et al. (2007) stated that increased spiritual concerns are causing fears about organ donation which restrains participants willingness to donate organs.[14] In this study, a weak negative correlation was found between spiritual well-being and positive organ donation attitude. In other words, as the spiritual well-being levels of the participants increase, their voluntary attitude towards organ donation decreases. Nevertheless, there was a positive correlation between spiritual well-being and negative organ donation attitude. It can be said that individuals who are spiritually strong have a negative attitude towards organ donation. It is thought that the negative attitude of people who are spiritually strong to organ donation may be due to misconceptual religious and spiritual beliefs. At the same time, this result is thought to be due to the fact that people with high spiritual concerns are less willing to donate organs. Therefore, it can be said that studies examining the relationship between spiritual concerns and attitude to organ donation are needed.

Bortz et al. (2015) stated that willingness to donate organs correlated with low level of transcendental spirituality.[2] Similarly, in this study it was found that participants with high transcendental spirituality tend to have negative attitudes towards organ donation. It thought that transplantation nurses, who have an important place in the campaigns on organ donation, have responsibilities to determine the spiritual values of the society and to encourage the society to donate organs.

CONCLUSIONS

There was a negative correlation between spiritual well-being and positive organ donation attitudes. It is recommended that transplantation nurses, who provide a holistic care service, plan campaigns for different spiritual beliefs to encourage individuals to donate organs. In addition, it is recommended that training programs for individuals with varying levels of spiritual well-being should be conducted with multidisciplinary teams.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethiccal Issue: This study was approved by the non-interventional clinical research ethics committee of Izmir Bakircay University (Approval number: 2020/09-63).

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

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.

Financial Disclosure: The author(s) received no financial support for the research, authorship, and/or publication of this article.

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.892114
J Contemp Med 2021;11(4):478-482

Orjinal Araştırma / Original Article

New Markers in the Differentiation of Covid 19 Disease and Pneumonia: Neutrophil and Platelet Lymphocyte Ratio

Covid 19 Hastalığında, Pnömoninin Ayırt Edilmesinde Yeni Belirteçler: Nötrofil/Lenfosit ve Trombosit/Lenfosit Oranı

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Abstract

Background: COVID-19 is a disease that starts like a simple upper respiratory infection and causes pneumonia and severe respiratory failure. Due to cytokine storm and hyperinflamation, some hematological and biochemical findings appear in the course of the disease. Complete blood count (CBC) is a very simple and inexpensive test that can be used in many infectious diseases.

Material and Method: Eighty patients diagnosed with COVID-19 by RT-PCR were divided into two groups according to the presence of pneumonia in the thorax CT (CT + 40 patients and CT- 40 patients). Forty healthy patients who had no previous disease were selected as the control group. The demographic and laboratory characteristics of COVID-19 patients with and without pneumonia in all three groups and control group patients were compared retrospectively.

Results: While there was a significant difference between the COVID-19 group and the control group in terms of neutrophil lymphocyte ratio (NLR) and mean platelet volume (MPV), no differences were observed in COVID patients with and without pneumonia in terms of NLR and MPV. There was no significant difference between the COVID-19 group and the control group and the COVID pneumonia group in terms of Platelet lymphocyte ratio (PLR).

Conclusion: NLR and MPV can be used as diagnostics for the diagnosis of COVID-19 disease, while PLR cannot be used. However, NLR and MPV values are not significant in evaluating COVID pneumonia and disease severity.

Keywords: COVID-19, SARS-CoV-2, pneumonia, neutrophil lymphocyte ratio, platelet lymphocyte ratio, mean platelet volume, MPV, NLR, PLR

Öz

Arka Plan: COVID-19; Basit bir üst solunum yolu enfeksiyonu gibi başlayıp zatürreye ve ciddi solunum yetmezliğine neden olan pandemik bir hastalıktır. Hastalıkta sitokin fırtınası ve hiperinflamasyon nedeniyle bazı hematolojik ve biyokimyasal bulgular ortaya çıkar. Tam kan sayımı (CBC), birçok bulaşıcı hastalıkta kullanılabilen çok basit ve ucuz bir testtir.

Gereç ve Yöntem: RT-PCR ile COVID-19 tanısı alan 80 hasta toraks BT'de pnömoni varlığına göre iki gruba ayrıldı (CT + 40 hasta ve CT- 40 hasta). Kontrol grubu olarak daha önce hastalığı olmayan 40 sağlıklı gönüllü seçildi. Her üç gruptaki pnömonili ve pnömonisiz COVID-19 hastaları ile kontrol grubundakilerin demografik ve laboratuvar özellikleri retrospektif olarak karşılaştırıldı.

Bulgular: COVID-19 grubu ile kontrol grubu arasında nötrofil lenfosit oranı (NLO) ve ortalama trombosit hacmi (MPV) açısından anlamlı fark varken, pnömonili ve pnömonisiz COVID hastalarında NLO açısından farklılık gözlenmedi. Platelet lenfosit oranı (PLR) açısından COVID-19 grubu ile kontrol grubu ve COVID pnömoni grubu arasında anlamlı fark yoktu.

Sonuç: NLR ve MPV, COVID-19 hastalığının teşhisi için tanı olarak kullanılabilirken, PLR kullanılamaz. Bununla birlikte, NLR ve MPV değerleri COVID pnömonisi ve hastalık şiddetinin değerlendirilmesinde anlamlı değildir.

Anahtar Kelimeler: COVID-19, SARS-CoV-2, pnömoni, nötrofil lenfosit oranı, trombosit lenfosit oranı, NLR, PLR, MPV

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Received *(Geliş Tarihi)*: 06.03.2021 **Accepted *(Kabul Tarihi)*:** 06.04.2021

INTRODUCTION

COVID-19 disease is a serious infectious disease that started in Wuhan, China in December 2019 and influenced the whole world and was accepted as a pandemic by the World Health Organization (WHO) in March 2020, affecting both upper and lower respiratory tract.[1] Virus causes acute respiratory failure such as serious acute respiratory failure virus (SARS) in 2002-2003 and middle east respiratory syndrome virus (MERS) in 2012-2013. The incubation period of the disease is 2-14 days. Symptoms begin at the latest after this period. The most common symptoms are fever, cough, respiratory failure, loss of smell and taste, and recently increasing complaints of diarrhea.[2] As of July 2020, approximately 10,000,000 new cases and nearly 500,000 deaths have been reported.[3] Although the first transition of the disease was determined as animal-human, its fastest spread was in the form of human-human. The disease begins with the intake of aerosols from the respiratory tract. The virus, which is primarily located in the nasopharynx, descends to the lung in time. It causes accumulation of fluid in the alveoli in the lung, leading to the appearance of ground glass on tomography. Therefore, it leads to acute respiratory failure.[4,5]

In COVID-19 disease, diagnostic haematological parameters were determined. The most commonly defined parameters are lymphopenia, leukocytosis, neutrophilia, thrombocytopenia, D-Dimer height, C-Reactive protein (CRP) height, PT-INR height Troponin increase, Lactate Dehydrogenase height (LDH).[2,6–8] Complete blood count (CBC) is a fairly simple, practical and inexpensive test.

Neutrophil-lymphocyte ratio, Platelet lymphocyte ratio and mean platelet volume can be used in COVID-19 as well as in other diseases.[9,10] In our study, hematology parameters of PCR positive patients with and without COVID-19 will be compared.

MATERIAL AND METHOD

For this study, 80 patients diagnosed with COVID-19 and 40 healthy volunteers at our center between March 2020 and June 2020 were used. All patients were evaluated retrospectively. Patients with COVID-19 were divided into two groups as CT + and CT- according to the presence of pneumonia in Thorax CT. The patients were divided into three groups as control, PCR + CT- and PCR+ CT+

COVID-19 patients in the study consisted of patients diagnosed with Polymerase Chain Reaction (PCR) with the symptoms such as fever, weakness, myalgia, shortness of breath, cough, diarrhea, and loss of taste. Nasopharyngeal and throat swabs (combined swabs) were taken from the patients and evaluated by PCR. The diagnosis of PCR was made with Applied Biosystems GeneAmp® PCR System 9700 device (Thermo Fisher Scientific, USA). Thorax CT was also performed in patients diagnosed with COVID-19 by PCR, and the patients were called CT + and CT-. For the control group, 40 healthy volunteers were selected in our center for various reasons and without chronic or acute infectious diseases. Laboratory values of 40 patients in PCR + CT-, PCR + CT + and control group were evaluated retrospectively. Leukocyte (WBC), hemoglobin, hematocrit, mean platelet volume (MPV), neutrophil, lymphocyte count, C-reactive protein (CRP), sedim and procalcitonin values were calculated in the patients' complete blood count (CBC) and biochemistry tests. In addition, neutrophil lymphocyte ratio and platelet lymphocyte ratio were calculated according to these values. These values were compared for all three groups.

Covid-19 diagnosis and treatment for the Republic of Turkey Ministry of Health Science Board has benefited from Covidien-19 guidelines. Accordingly, patients with complaints such as fever, weakness, joint pain, headache, shortness of breath, cough, smell and taste disorder, diarrhea were taken by nasopharyngeal swab in the isolation rooms and PCR device was diagnosed and the patients who had SARS-CoV-2 virus were identified. Thorax CT was taken to evaluate the presence of PCR + lung pneumonia. CT examinations (MSCT, Philips Brilliance ICT 256; Philips Medical Systems, Netherlands) were performed with the device (512x512matrix, voltage 100 kV, current 150 mAs). Those with consolidation and ground-glass area in tomography were evaluated as pneumonia. In treatment, Hydroxychloroquine tablet 2 * 200 mg (5 days) and Enfluvir tablet (2 * 75 mg tablet 5 days) were given to all patients. Those with severe pneumonia and favipravir areas were excluded from the study.

In addition, these patients were evaluated in terms of age, gender, smoking, additional disease, and severity of disease. The degree of the disease; 1) Mild (no pneumonia or mild pneumonia), 2) Moderate (dyspnea, hypoxia or severe progression in lung findings within 24 hours), 3) Severe (Respiratory Failure, Shock, Multi-Organ Failure). Afyonkarahisar Health Sciences University for Non-Interventional Studies from the Clinical Research Ethics Committee (07.11.2020/2020-7) and the Commission for Scientific Research from the Ministry of Health of the Republic of Turkey (04/29/2020) has been allowed us to carry out the study. The study was carried out in accordance with the Declaration of Helsinki.

Statistical Analysis

All values are calculated as mean ± standard deviation. The data obtained were evaluated with descriptive statistics (Arithmetic mean, median, standard deviation, percentage distributions). When comparing the mean between groups, the normal distribution suitability was first evaluated by the Kolmogorov Smirnov and Shapiro Wilk tests. When comparing the percentage distributions of categorical data between groups, Chi Square test and one wow anova were used. SPSS 22.0 (IBM SPSS Statistics, Chicago, USA) was used for data analysis. $p<0.05$ was considered statistically significant.

RESULTS

Of the 120 people who participated in our study, 80 (66.66%) were PCR positive Covid 19 and 40 (33.33%) were healthy people with no chronic disease.

When the hemogram values of the participants in our study were evaluated, the WBC results of COVID-19 PCR + patients were 6.01 (2.72-12.46) 10^3/ul and 7.35 (4.73-15.35) 10^3/ul in the control group. and there was a statistically significant difference (p<0.001). Considering neutrophil values, COVID-19 PCR + was 1.52 (0.49-49.48) 10^3/ul in the control group and 2.00 (0.78-5.41) 10^3/ul in the control group (p<0.001) In terms of eritrocyte distribution volume ratios (RDW), COVID-19 was 18.80 (11.40-24.20)% in PCR + patients, while it was 13.15 (11.70-18.80) in the control group (p=0.011). When evaluated in terms of mean platelet Volume (MPV) values, COVID- 19 was 10.12 (8.10-13.40) in PCR + patients and 9.30 (8.00-10.90) in the control group (p<0.001). In terms of reactive protein (CRP) values, COVID-19 was 2.80 (0.00-195.40) mg/l in PCR + patients and 0.80 (0.00-59.30) mg/l in the control group. (p=0.049) (**Table 1** and **2**).

When neutrophil/lymphocyte ratio (NLR) and Platelet/ lymphocyte ratio (PLR) ratios were evaluated, there was no statistically significant difference in terms of PLR rates (p=0.334, p=0.026 respectively) (**Table 2**)

When the comparison of NLR and PLR ratios between two groups was evaluated in our study, there was a statistically significant difference between the group with PCR + thorax bt - and thorax bt and healthy individuals without disease clinic in terms of NLR rates. When CT positive and negative groups were compared, there was no significant difference in terms of both NLR and PLR (**Table 2**).

When 40 patients with positive PCR and thorax bt were evaluated, the most common 27 (67.5%) right lung lower lobe, 23 (57.5%) left lung lower lobe, 13 (32.5%) right lung middle lobe, 11 (27.5%) was the right upper lobe of the lungs, 9 (22.5%) was the left lung upper lobe and 8 (20%) was the left lung lingula, and it was observed that it was observed most commonly in the right lung lower lobe (**Picture 1**).

Table 1. Laboratory variables of patients and control group

Laboratory values	COVID-19 (N=80)	Control (N=40)	P value
WBC (10^3/ul)	6.01 (2.72-12.46)	7.35 (4.73-15.35)	P<0.01
Hemoglobin (g/dl)	13.84±1.57	13.80±1.72	0.905
RDW (%)	18.80 (11.40-24.20)	13.15 (11.70-18.80)	0.011
Platelet (10^3/ul)	258.02 (95.0-811.0)	249.50 (73.00-483.00)	0.286
MPV (Mean Platelet Volüme)	10.12 (8.10-13.40)	9.30 (8.00-10.90)	P<0.01
Prokalsitonin (ng/ml)	0.23 (0.12-0.68)	0.23 (0.00-0.37)	0.909
Hematocrit (%)	41.85 (32.80-409.00)	41.75 (23.60-50.10)	0.674
Neutrophil (10^3/ul)	3.26 (1.02-8.16)	4.57 (2.32-9.56)	P<0.01
Lymphocytes (10^3/ul)	2.15 (0.86-4.96)	2.47 (1.03-5.94)	0.090
CRP (mg/l)	2.80 (0.00-195.40)	0.80 (0.00-59.30)	0.049
Sedimentasyon	5.16±9.02	4.35±7.26	0.791
Neutrophil lymphocyte ratio (NLR)	1.52 (0.49-6.48)	2.00 (0.78-5.41)	0.026
Platelet lymphocyteratio (PLR)	105.11 (39.92-375.21)	106.89 (56.10-276.00)	0.347

Table 2. Descriptive and laboratory variables of all groups

Laboratory values	COVID 19 (PCR+, CT+) N:40	COVID 19 (PCR+, CT-) N:40	Control N:40	P value
Age	44.45±11.77	36.20±15.57	43.50±14.68	0.019
WBC (10^3/ul)	6.57 (2.95-12.46)	5.54 (2.72-10.68)	7.35 (4.73-15.35)	P<0.01
Hgb (g/dl)	13.74±1.61	13.94±1.53	13.80±1.72	0.848
RDW (%)	13.00 (11.40- 24.20)	12.75 (11.50-14.90)	13.15 (11.70-18.80)	0.011
Platelet (10^3/ul)	243.00 (95.00-811)	220.50 (151.00-454.00)	249.50 (73.00-483.00)	0.05
MPV	9.95 (8.20-13.40)	9.95 (8.10-12.70)	9.30 (8.00-10.90)	P<0.01
Prokalsitonin (ng/ml)	0.24 (0.12-0.68)	0.22 (0.16-0.43)	0.23 (0.00-0.37)	0.216
Hematocrit (%)	41.60 (32.80-398.00)	41.90 (34.50-409.00)	41.75 (23.60-50.10)	0.827
Neutrophil (10^3/ul)	3.58 (1.29-8.16)	2.82 (1.02-7.08)	4.57 (2.32-9.56)	P<0.01
Lymphocytes (10^3/ul)	2.24 (1.11-4.87)	2.02 (0.86-4.96)	2.47 (1.03-5.94)	0.05
CRP (mg/l)	4.55 (0.00-195.40)	1.55 (0.10-24.50)	0.80 (0.00-59.30)	0.001
Sedim	6.45±11.11	3.87±6.17	4.35±7.26	0.957
Neutrophil lymphocyte ratio (NLR)	1.52 (0.53-5.14)	1.53 (0.49-6.48)	2.00 (0.78-5.41)	0.068
Platelet lymphocyte ratio (PLR)	109.76 (46.82-315.56)	103.25 (39.92-375.21)	106.89 (56.10-276.00)	0.599

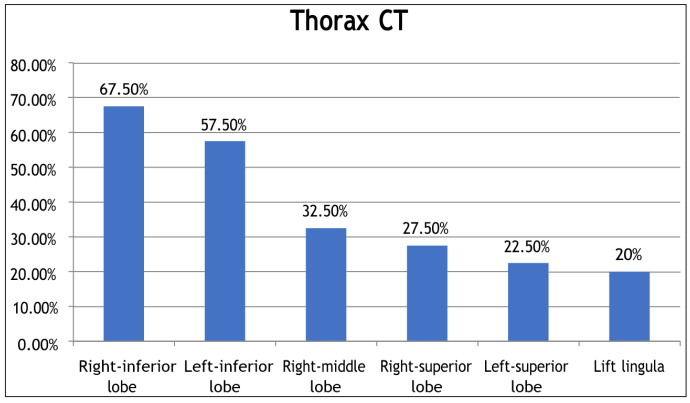

Figure 1. Frequency of lung lobe involvement in PCR + Thorax CT + patients

1. Hemogram is a simple and inexpensive test that can be easily applied anywhere.
2. NLR and MPV can be used in the diagnosis of Covid-19 disease, PLR has no diagnostic significance. While MPV increases in Covid-19 disease, NLR decreases.
3. In terms of NLR and MPV values, no significant difference was observed in patients with Covid-19 pneumonia compared to those who did not develop the disease.

DISCUSSION

COVID-19 disease is a viral infection disease caused by SARS-CoV-2 virus, which started in December 2019 in Wuhan, China, causing acute respiratory failure and coagulopathy in the organs, affecting the lung, which affected Europe and America in the first months of 2020. The disease begins as a simple upper respiratory tract infection by clinging to the respiratory tract via droplets. They descend to the lung in a short time and cause pneumonia. The disease forms ground-glass areas with Thorax CT. This image is typical for COVID-19 pneumonia. The disease then begins to cause diffuse alveolar damage. Disease diagnosis; The nasopharynx is placed by PCR by swab from the oropharynx or bronchoalveolar lavage. There is an increasing number of studies showing that CT is also diagnostic in PCR-patients.[4,11,12]

PCR gold is the standard in the diagnosis of COVID-19. Sensitivity and specificity of laboratory values are not very high. However, certain values may assist in prognosis and treatment in the diagnosis and follow-up of COVID-19. Certain hematological parameters in COVID-19 patients have also been diagnostic. he most common laboratory finding in these patients is lymphopenia.[6] The virus is thought to disrupt the immune response. In many studies, lymphopenia rates have been

defined between 35 and 75%. This rate increased as the severity of the disease increased. The rate of lymphopenia was very low in children with mild patients, in which the immune matter was less impaired.[7] In most studies, the lymphocyte count has been defined below<1.0 * 10^9/L.[8] In our study, the lymphocyte count was 2.15 10^9/L, which was above the values of COVID-19 patients in the literature. However, in our study, it may be related to the very low number of patients with severe COVID-19.

Similar to the information in the literature, hemoglobin values were evaluated as referenge range in our study. Leukocytosis is seen in the case of a bacterial infection or superinfection in COVID-19 disease. In a study in the literature, it was stated that leukocytosis was seen in 11.4% of severe patients.[7] In our study, although the leukocyte count was significantly lower than the control group, it was evaluated in the normal range. Although neutrophil count is expected to increase due to cytokine storm and hyperinflamation in infection, it remained in normal range in our study. However, their number has decreased significantly compared to the control group.

Reduced platelet counts (thrombocytopenia) is an expected condition in many viral diseases. A reduction in COVID-19 patients can also be expected. Both thrombocytopenia and mean platelet volume (MPV) have been used as a prognostic indicator in many diseases and sepsis.

Thrombocytopenia was used especially as a marker of hypoxemia.[13,14] In our study, platelet counts were monitored similarly to the control group, and MPV values were significantly increased compared to the control group. Platelet counts were significantly higher in CT- compared to CT +, and MPV values did not change in the presence of pneumonia.

In addition to hemogram findings, biochemical markers can also be used in the diagnosis and follow- up of COVID-19. The most important of these are values such as C-reactive protein (CRP), procalcitonin, LDH. CRP is produced in the liver and used as an acute phase reactant. Viral inflammation also increases.[15] In our study, it was found to be higher compared to the control group. Procalcitonin hormone is a prehormone with calcioma precursor and plays an important role in calcium metabolism. They show poor prognosis by increasing in sepsis and intense inflammation.[16] In our study, no significant difference was observed between the control group and tomography positivity.

Neutrophil lymphocyte ratios (NLR), platelet lymphocyte ratios (PLR) and MPV (mean platelet volume) are used in the diagnosis and follow-up of many diseases.[17,18] There are many studies related to these values in the literature.[19,20] In many diseases, its predictive and prognostic value is important. In our study, NLR decreased in patients with COVID-19 compared to the control group, but did not change significantly with the presence of pneumonia. In a China-based study, it was stated that NLR values can be used to assess the severity of COVID-19 disease.[21] Neutrophil lymphocyte values were

investigated in community-acquired pneumonias, and no relationship was observed between disease grade and values.[22,23] PLR did not differ significantly from the control group. Therefore, based on our conclusions, NLR of COVID-19 patients is important in diagnosis and follow-up. However, its relation with the development of pneumonia and disease degree could not be determined. PLR has been used in many

diseases in the literature, but according to our observation, it has been understood that it will not be suitable as a marker n COVID disease and COVID pneumonia.

CONCLUSION

Neutrophil lymphocyte ratios are important in the diagnosis of COVID-19, but the significance of NLR values was not found in the development of pneumonia. Platelet lymphocyte ratio (PLR) is no considered as usefulin the diagnosis of COVID-19.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was received from Afyonkarahisar Healty Science University Clinical Research Ethic Committee (2020/7).

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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JOURNAL OF
CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.886263
J Contemp Med 2021;11(4):483-488

Orjinal Araştırma / Original Article

Memory Complaints and Activities of Daily Living in Geriatric Depression: Is There A Difference between Early-and Late-Onset Depression?

Geriatrik Depresyonda Bellek Yakınmaları ve Günlük Yaşam Aktiviteleri: Erken ve Geç Başlangıçlı Depresyon Arasında Fark Var Mıdır?

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Abstract

Aim: To investigate the cognitive complaints and activities of daily living in patients with geriatric depression. Inter-group comparisons were performed by dividing geriatric depression patients into early- and late-onset subgroups.

Materials and Methods: Ninety-four patients with geriatric depression and 39 individuals as a control group were included. Thirty-three of the geriatric depression patients had late-onset depression, and 61 had early-onset depression. All participants completed sociodemographic data, the Mini Mental Test, the Clock-Drawing Test, the Katz Activities of Daily Living Scale, and the Subjective Memory Complaints Questionnaire. Geriatric Depression Scale-15 was used to measure the severity of patients' depression.

Results: Late-onset depression patients exhibited significantly poorer performance on the Clock Drawing Test than the control group. Significantly greater subjective memory complaints were determined in patients with early- and late-onset depression than in the control group. A negative relationship was found between the severity of depression and activities of daily living in patients with geriatric depression.

Conclusion: Geriatric depression may differ in terms of cognitive functions according to the age of onset.

Keywords: Geriatric depression, cognitive, functionality, elderly, memory

Öz

Amaç: Bu çalışmada geriatrik depresyon hastalarının kognitif belirtileri ve işlevsellik düzeyleri araştırılacaktır. Geriatrik depresyon hastaları erken ve geç başlangıçlı depresyon alt gruplarına ayrılarak gruplar arasında karşılaştırmalar yapılacaktır.

Gereç ve Yöntem: Çalışmaya toplam 94 geriatrik depresyon hastası (33 geç başlangıçlı depresyon, 61 erken başlangıçlı depresyon) ve kontrol grubu olarak da 39 kişi dahil edilmiştir. Katılımcıların hepsi için sosyodemografik veri formu, Saat Çizme Testi, Katz Günlük Yaşam Aktiviteleri Ölçeği ve Öznel Bellek Yakınmaları Anketi doldurulmuştur. Geriatrik depresyon hastalarının depresyon şiddetinin ölçülmesinde Geriatrik Depresyon Ölçeği-15 kullanılmıştır.

Bulgular: Saat Çizme Testinde geç başlangıçlı depresyon hastaları kontrol grubuna göre daha kötü bir performans sergilemiştir. Erken başlangıçlı ve geç başlangıçlı depresyon hastalarında kontrol grubuna göre daha fazla öznel bellek yakınmalarının olduğu tespit edilmiştir. Geriatrik depresyon hastalarında depresyon şiddeti ile günlük yaşam aktiviteleri arasında negatif yönde bir ilişki bulunmuştur.

Sonuç: Geriatrik depresyon; başlangıç yaşına göre kognitif işlevler açısından farklılıklar gösterebilmektedir.

Anahtar Kelimeler: Geriatrik depresyon, bilişsel, fonksiyonellik, yaşlılık, bellek

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Received *(Geliş Tarihi)*: 25.02.2021 **Accepted *(Kabul Tarihi)*:** 07.04.2021

INTRODUCTION

The geriatric period refers to the age over 65 years. An increase in the proportion of individuals in this group compared to the general population is predicted in future years.[1] The prevalence of major depressive disorder at geriatric age has been reported at 1-5% in large sample studies. However, when subthreshold symptoms or other depressive disorders are included, this may rise to as high as 15%.[2] The frequency of depression may also vary depending on the place of residence.[3]

Geriatric depression is a term used to refer to depressive attacks seen after the age of 65. There is no difference in diagnostic criteria with depressive disorders seen at earlier ages in diagnostic classification systems. Although there is no difference between geriatric depression and depressive disorders seen at younger ages in terms of diagnostic criteria, differences may occur in symptom variation.[4] For example, geriatric depression patients have been observed to express their symptoms with somatic complaints rather than emotionally.[5] Geriatric depression is divided into two categories based on age at the time of the first attack – early-onset depression (EOD) and late-onset depression (LOD). However, there is no consensus regarding the age at which this distinction applies, and different ages may be employed in the literature, from 50 to 65. In addition to age at onset, there may also be differences between these two groups in terms of the disease's course and its clinical features.[6]

Cognitive complaints associated with both age and accompanying medical diseases may appear in the geriatric period. The relationship between cognitive complaints and depression may be a two-way one. Cognitive complaints may be identified in various ways – subjective complaints reported by the patient or relatives, and objective complaints identified by a physician through examination. Subjective and objective memory complaints in geriatric depression patients may differ. Greater subjective memory complaints but similar levels of objective memory complaints have been observed in the geriatric period compared to a control group.[7] However, subjective memory complaints have been determined in a third of the healthy elderly individuals.[8] The prevalence of subjective memory complaints rises with age, and can reach as high as 60%.[9] A relationship has been determined between subjective memory complaints and anxiety and depression levels in the geriatric population with no cognitive disease.[10] The significance of subjective memory complaints may be related to the risk of future dementia development.[11] Objective impairments may also occur in several cognitive areas in geriatric depression.[12] In a study performed using the clock drawing test, LOD patients exhibited poorer performances than EOD patients and a control group.[13]

One criterion employed in the diagnosis of depression is a decrease in functionality.[14] Activities of daily living represent one area of functionality. A two-way relationship exists between activities of daily living and geriatric depression. Activities of daily living improve following treatment in geriatric depression.[15] However, a reduction in activities of daily living has been linked to depressive symptoms in a study group consisting of healthy elderly individuals.[16] Longitudinal observational studies have also determined a relationship between a decline in activities of daily living and the development of depressive symptoms.[17] Decreased activities of daily living in geriatric depression have been shown to be potentially linked to white matter lesions[18] and inflammation levels.[19]

The present study compared the activities of daily living and cognitive functions of individuals with geriatric depression and a control group. Patients were also divided into early and late-onset subgroups and compared in terms of these variables. Relations between the variables in the geriatric depression group were also subjected to correlation analysis. The research hypothesis was that cognitive effects and impairment of daily activities would be greater in the geriatric depression group. We also hypothesized that cognitive functions would be poorer in the LOD group compared to the EOD group.

MATERIAL AND METHOD

The study group was selected from patients aged 65 or over admitted to the Samsun Ondokuz Mayıs University Psychiatric Clinic, Turkey, diagnosed with a major depressive disorder based on DSM 5,[14] and treated on an outpatient basis. Ninety-four patients with geriatric depression and 39 controls were included. Patients were divided into early-onset depression (age <65 at first attack) and late-onset depression (age ≥65 at first attack) groups based on age at first depressive attack. Thirty-three cases were assessed as LOD and 61 as EOD. Individuals with neurocognitive disorders (delirium or dementia), unable to complete the study scales, unable to cooperate sufficiently to complete the scales, or refusing to participate were excluded from the study. Clinical examination and a standardized Mini Mental State Examination (MMST) were used to exclude neurocognitive disorder. A score of 24 or higher on the MMST[20] was adopted as an inclusion criterion. Information concerning patients' age, sex, marital status, and psychiatric diseases was collected using a data form. Information concerning the marital status and education level were deficient for 10 patients (five from the LOD and EOD groups). The Structured Clinical Interview for DSM 5 (SCID-5) was employed to diagnose major depressive disorder. All patients diagnosed with major depressive disorder and included in the study completed the Geriatric Depression Scale (GDS-15), the Clock-Drawing Test (CDT), the Katz Activities of Daily Living Scale (KADLS), and the Subjective Memory Complaints Questionnaire (SMCQ).

Individuals aged over 65, with no cognitive disease, and agreeing to participate were included in the study. The control group was selected from individuals who applied to the psychiatry outpatient clinic for various reasons, and did not have an active psychiatric disease. The control group completed the CDT, SMCQ, and KADLS. This group also underwent clinical examination and the MMST for the assessment of cognitive disorders.

Ethical approval for the study was granted by the Ondokuz Mayıs University Clinical Research Ethical Committee (no: 2019/534). Written consent was also obtained from all participants.

Data Collection Tools:

Standardized Mini Mental State Examination

The standardized MMST consists of orientation, memory, attention, language, and visual-spatial skills sections, assessed out of 30, and providing information about the individual's cognitive state. It was developed by Folstein et al.[21] The optimal cut-off values for discriminating between dementia and control groups in the Turkish-language reliability and validity study were found as 23/24.[20]

Geriatric Depression Scale-15

The initial GDS consisted of 30 questions. Shorter forms were later developed. The 15-question form was developed by Burke et al.[22] The scale is short, easy to apply, and completed by the participant. A cut-off point of five was determined in the Turkish-language reliability and validity study.[23]

Clock Drawing Test

The CDT is a simple cognitive screening test for cognitive areas such as abstract thinking, planning, and motor skills. It exhibits a high correlation with other tests measuring cognitive functions. Therefore, it has been described as a test capable of use for all cognitive functions, similarly to the MMST.[24] Different evaluation methods are available for calculating the test results. The Shulman scoring system was employed in the present study. When applied using Shulman scoring, the patient is given a circle and asked to fill in the numbers and to draw a time of 11:10. In this method, a score between 0 and 5 is awarded depending on the organization of the response.[25] Higher scores indicate better cognitive functions.

Katz Activities of Daily Living Scale

The KADLS consists of six questions investigating activities in the individual's daily life, such as bathing, dressing, toilet, transferring, feeding, and fecal and urinary continence. Each question is scored either 0 or 1, with total possible scores ranging from 0 to 6. Higher scores indicate a higher degree of independence. The Turkish-language reliability and validity of the scale were researched by Arık et al.[26]

Subjective Memory Complaints Questionnaire

The SMCQ consisting of 14 Yes/No questions was developed by Youn et al.[27] It can be used to evaluate the level of cognitive symptoms in neurocognitive disorders, and also in the assessment of cognitive complaints with depression and anxiety or various personality characteristics.[28] The reliability and validity of the Turkish-language version were investigated by Özel Kızıl et al.[29] Higher scores indicate greater complaints associated with memory.

Statistical Analysis

Statistical analysis was performed on SPSS 15.0 software. Normality of distribution of the study data was assessed using the Kolmogorov-Smirnov test. The Chi-Square Test was used to evaluate relationships between categorical variables. The Kruskal-Wallis Test was applied in three-way comparisons (between the EOD, LOD, and control groups) of the non-normally distributed variables of age, CDT, SMCQ, and KADLS. The Mann-Whitney U Test with post-hoc Bonferroni correction was applied to identify the groups between which differences emerged in variables with significant differences. Relations between GDS-15, CDT, SMCQ, and KADLS scores in the geriatric depression group were evaluated using Spearman's Rank Correlation Coefficient. P<(0.05/3)=0.016 was regarded as statistically significant in the Bonferroni-corrected Mann-Whitney U Test, and p <0.05 for all other comparisons.

RESULTS

Mean ages were 70.4±5.3 years in the control group and 73.0±7.8 and 71.8±6.5 in the LOD and EOD groups, respectively. Eight members of the control group, 27 of the EOD group, and 13 of the LOD group had been educated for longer than eight years. No differences were determined between the study groups in terms of age, sex, medical status, or education level (**Table 1**).

Table 1. Sociodemographic data of the groups and their comparison.

Variables		Patients with geriatric depression (n: 94)		Controls (n: 39)	p value
		LOD (n: 33)	EOD (n: 61)		
Age, mean(±SS)		73.0±7.8	71.8±6.5	70.4±5.3	0.459
Sex, n	Male	15 (45.5%)	20 (32.8%)	18 (46.2%)	0.309
	Female	18 (54.5%)	41 (67.2%)	21 (53.8%)	
Marital status, n	Married	23 (82.1%)	42 (75%)	32 (82.1%)	0.631
	Single/ others	5 (17.9%)	14 (25%)	7 (17.9%)	
Educational level	0-8 years	15 (53.6%)	29 (51.8%)	14 (35.9%)	0.231
	>8 years	13 (46.4%)	27 (48.2%)	25 (64.1%)	

EOD: Early-Onset Depression, LOD: Late-Onset Depression. The marital status and education levels of five patients could not be reached in both late-onset and early-onset depression groups. n: number of participants.

Significant differences were observed between the three study groups (LOD, EOD, and control) in terms of CDT (χ^2: 16.140, p: <0.001) and SMCQ (χ^2: 19.853, p: 0.001). Post hoc analyses revealed that these derived from higher scores in the control group compared to the LOD group for CDT (Z: -3,198, p: 0.001), and to higher scores in the EOD (Z: -4,138, p: <0.001) and LOD (Z: -3,549, p: <0.001) groups compared to the control group for SMCQ. No difference was determined between the groups in terms of KADLS (χ^2: 0.603, p: 0.740). Comparisons in GDS-15 revealed higher scores in the LOD group than the EOD group (Z: -2.632, p: 0.008) (**Table 2**).

Table 2. Comparison of the groups in terms of GDS-15, CDT, SMCQ, and KADLS.

Variables	Patients with geriatric depression (n: 94)		Controls (n: 39)	U/χ^2	p value
	LOD (n: 33)	EOD (n: 61)			
GDS-15	57.52	42.08		676.00	0.008
CDT	47.73	69.06	80.09	16.140	<0.001*
SMCQ	78.70	75.08	44.46	19.853	<0.001**
KADLS	63.55	68.84	67.05	0.603	0.740

The Mann-Whitney U Test with post-hoc Bonferroni correction was applied to identify the groups between which differences emerged in variables with significant differences. GDS-15: Geriatric Depression Scale, CDT: Clock-Drawing Test, SMCQ: Subjective Memory Complaints Questionnaire, KADLS: Katz Activities of Daily Living Scale. *: Control> LOD, **: EOD=LOD> Control, EOD: Early-Onset Depression, LOD: Late-Onset Depression. n: number of participants. U value is given for GDS-15 and χ^2 value for others.

The correlation analysis results between variables in patients with geriatric depression are shown in **Table 3.** This revealed a low degree of significant negative correlation between GDS-15 and KADLS scores (r: -0.450, p: <0,01.).

Table 3. Correlation levels of GDS-15, CDT, SMCQ, and KADLS scores in patients with geriatric depression.

VARIABLES	1	2	3
GDS-15 (1)	1.000		
CDT (2)	0.084	1.000	
SMCQ (3)	0.192	0.000	1.000
KADLS (4)	-0.450*	0.125	-0.198

Spearman Rank Correlation Coefficients are given. GDS-15: Geriatric Depression Scale, CDT: Clock-Drawing Test, SMCQ: Subjective Memory Complaints Questionnaire, KADLS: Katz Activities of Daily Living Scale. * p<0,01.

DISCUSSION

CDT scores were lower, and SMCQ scores were higher in the LOD group compared to the control group in the present study, while SMCQ scores were higher in the EOD group than in the control group. No significant difference was determined between the two geriatric depression subgroups, EOD and LOD, apart from greater severity of depression in the LOD group. These findings are discussed below.

Cognitive complaints frequently accompany affective symptoms in patients with geriatric depression. Variation may therefore occur between EOD and LOD patients. Cognitive functions of patients with LOD have been found to be more impaired compared to in healthy controls.[30] This impairment in cognitive functions has been shown to be at a similar level to that in patients with mild cognitive disorder.[31] Impairment in initial cognitive functions may not be reversed after treatment.[32] Şenel et al.[33] reported increased subjective memory complaints in geriatric depression compared to a control group, but observed no significant difference between the groups in terms of CDT. A study comparing a control group with EOD and LOD patients reported lower CDT scores in the LOD group than in the other two groups.[13] However, cognitive complaints predominate in the clinical manifestation of executive dysfunction syndrome, the first of the possible hypotheses in geriatric depression.[34] The difference in the CDT in the LOD group in the present study is therefore consistent with the previous literature as a finding that may indicate objective impairment in cognitive functions. Some studies in this area have found no difference between geriatric depression, making no distinction between EOD and LOD, and control groups. LOD may therefore be regarded as a subtype of geriatric depression involving greater cognitive effects.

One of the DSM-5 diagnostic criteria for depressive disorders is difficulty in such cognitive functions as thinking and concentration. These symptoms have been reported to be expected to improve after treatment, with this manifestation being referred to as 'pseudodementia' to avoid cognitive dysfunction in dementia.[14] Higher subjective memory complaints have been observed in patients with geriatric depression compared to a control group.[7] Subjective memory complaints have been observed in more than half of geriatric depression patients in remission, with these being associated with other cognitive functions.[35] Zandi[36] determined more severe depressive symptoms in individuals with subjective memory complaints compared to those with no such complaints. One double-blind, randomized placebo-controlled study reported that subjective memory complaints responded better to a combination of escitalopram and memantine than to a combination of escitalopram and placebo.[37] A higher rate of the APO-E4 allele, known to be linked to Alzheimer's disease, was found in individuals with subjective memory complaints in a community-based study. This elevation was higher in the presence of depressive symptoms. On the other hand, in the regression analysis, it was found that depression was not a predictor of subjective memory complaints.[38] In the light of these findings, the greater subjective memory complaints in patients with geriatric depression (in both the EOD and LOD groups) as an expected result.

There may be various reasons for the fact that no difference in activities of daily living was observed between the groups in this study. One may be the fact that the case group in this study consisted of outpatients. Another reason may be the content of the scale used to evaluated activities of daily living (KADLS). This scale investigates such activities as bathing, dressing, toilet, transferring, feeding, fecal and urinary continence. Although the level of depression in the geriatric period is correlated with levels of activities of daily living,[39] impairment in these domains is expected in severe depressive disorder.[14] In geriatric depression, impairment is first expected in instrumental activities of daily living.[40] Accordingly, impairment in basic activities of daily living may not be observed in mild and moderate depressive disorders treated on an outpatient basis. However, in line with expectations, the negative correlation between the severity of depression in geriatric depression and KADLS scores is a finding compatible with the previous literature.[41]

One reason for the absence of variation between the EOD and LOD subgroups in terms of CDT, SMCQ, and KADLS may be that depressive symptoms were more severe in the LOD group. One study comparing two such groups in terms of CDT results reported greater impairment in the LOD group's CDT results. However, the mean age of the LOD group was

higher in that age, and MMST scores were lower.[13] In contrast, there was no difference in age between the two groups in the present study. One previous study reported greater cognitive effects in a LOD group.[42] CDT was employed for cognitive assessment of the patients in the present study. CDT may have been unable to account for the differences in cognitive findings between the groups.

One limitation of the present study is that only patients treated on an outpatient basis were included. The study findings cannot, therefore, be generalized to all geriatric depression patients. Our study has other limitations that it was single-centered, containing a small number of cognitive scales, some of the scales were self-report, it's cross-sectional nature, was not controlled the effects of accompanying diseases or drugs used.

CONCLUSION

In cognitive functions evaluated by the clock drawing test, lower scores were obtained in the LOD group than the control group. Subjective memory complaints are more common in geriatric depression than controls. A negative relationship was found between the severity of depression and activities of daily living in geriatric patients with depression. However, further studies employing different tests to better evaluate cognitive functions may shed further light on this subject. In addition, using scales that evaluate more complex functions while evaluating daily living activities can give more accurate results.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval for the study was granted by the Ondokuz Mayıs University Clinical Research Ethical Committee (no: 2019/534)

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.

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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JOURNAL OF
CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.902207
J Contemp Med 2021;11(4):489-493

Orjinal Araştırma / Original Article

Chest CT Features of SARS-CoV-2 Pneumonia

SARS-CoV-2 Pnömonisinin Toraks BT Özellikleri

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Abstract

Aim: CT has an important place in diagnosing SARS-CoV-2 due to the RT-PCR test's high false-negative rate and the faster evaluation of CT, although the RT-PCR test is the gold standard. This study aims to understand chest CT features and distributions in patients with SARS-CoV-2 proven by RT-PCR.

Material and Method: This study is retrospective and includes one hundred adult patients with confirmed SARS-CoV-2 infection who admitted to the hospital. The Chest CT findings of these patients were retrospectively recorded. Radiological Society of North America reporting guidelines for SARS-CoV-2 pneumonia was referenced to classify chest CT findings.

Results: In SARS-CoV-2 patients confirmed by RT-PCR, the mean age of 79 pneumonia patients (54.02±16.99) was higher than age of patients without pneumonia (42.47±17.78). Prevalences of ground-glass opacity, consolidation, posterior dominance, bilaterality, peripheral distribution, multifocality, vascular enlargement, pleural effusion, lymphadenopathy, tree-in-bud pattern, halo sign and reverse halo sign were 74.68%, 3.79%, 17.72%, 43.03%, 70.88%, 84.81%, 84.81%, 12.65%, 2.53%, 1.26%, 2.53%, 8.86%, and 3.79%, respectively.

Conclusion: This study's findings indicate that common chest CT findings in SARS-CoV-2 pneumonia are ground glass opacities with multifocal, multilobar, peripheral and bilateral involvement. No significant result was shown in favor of posterior or lower lobe dominance.

Keywords: SARS-CoV-2, coronavirus disease-19, chest computed tomography, pneumonia

Öz

Amaç: SARS-CoV-2'nin tanısında; altın standartın RT-PCR testi olmasına ragmen, RT-PCR testinin yüksek yalancı negatiflik oranı ve toraks BT'nin daha hızlı sonuç vermesi nedeniyle, BT de önemli bir yere sahiptir. Bu çalışmanın amacı RT-PCR ile kanıtlanmış SARS-CoV-2 hastalarında toraks BT özelliklerinin ve dağılımının değerlendirilmesidir.

Gereç ve Yöntem: Bu çalışmaya hastaneye başvuran, SARS-CoV-2 tanısı RT-PCR ile doğrulanan, 100 yetişkin hasta dahil edilmiştir. Bu hastaların toraks BT bulguları retrospektif olarak kaydedilmiştir. BT bulguları, Kuzey Amerika Radyoloji Topluluğu tarafından SARS-CoV-2 için yayınlanan klavuza göre değerlendirilmiştir.

Bulgular: RT-PCR ile doğrulanan 100 SARS-CoV-2 hastasının, 79'unda pnömoni mevcut olup yaş ortalaması (54,02±16,99) iken pnömoni bulgusu olmayan 21 hastanın yaş ortalaması (42,47±17,78) olarak bulunmuştur. Buzlu cam opasitesi, konsolidasyon, posterior ağırlıklı tutulum, bilateral tutulum, periferik dağılım, multifokalite, vasküler genişleme, plevral efüzyon, lenfadenopati, tomurcuk ağaç paterni, halo işareti ve ters halo işareti prevalansları sırasıyla %74,68, %3,79, %17,72, %43,03, %70,88, %84,81, %84,81, %12,65, %2,53, %1,26, %2,53, %8,86 ve %3,79 olarak bulundu.

Sonuç: SARS-CoV-2 pnömonisinde sık görülen göğüs BT bulguları multifokal, multilobar, periferik ve bilateral tutulumlu buzlu cam opasiteleridir. Posterior ya da alt lob hakimiyeti lehine anlamlı sonuç gösterilememiştir.

Anahtar Kelimeler: SARS-CoV-2, koronavirüs-19, toraks bilgisayarlı tomografisi, pnömoni

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Received *(Geliş Tarihi)*: 06.04.2021 **Accepted *(Kabul Tarihi)*:** 21.04.2021

INTRODUCTION

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was the first notice in December 2019 in Wuhan, China. After that, the disease spread worldwide and was named the coronavirus disease 2019 (COVID-19).[1,2] World Health Organization declared this disease as a pandemic.[1,3] Clinical findings of COVID-19 are a spectrum that can range from the common cold to acute respiratory distress syndrome.[4]

The common symptoms of COVID-19 are dry cough, fever, dyspnea, and fatigue. The incubation period is 1-14 days (average five days).[5] The disease is diagnosed by clinical findings, chest computed tomography (CT), and the-real-time-reverse transcription-polymerase chain reaction (RT-PCR).[6] RT-PCR test is the gold standard with specificity is 95%.[7] However, false-negative RT-PCR results were reported even these patients can have abnormal chest CT findings.[8,9] The sensitivity of RT-PCR varies between 42% and 71%, and false-negative results are more common of the disease because the sensitivity of the sampling kit, the timing of the sample collection, and the sample collection method affect the sensitivity of the test.[4,10] What makes chest CT important is that it results faster, and its sensitivity is higher.[4] Some studies have shown that CT has higher sensitivity (86-98%) and a lower false-negative rate than RT-PCR.[10] But the specificity (25%) of CT findings for COVID-19, in contrast to sensitivity, is not high.[11]

The common and typical CT findings of the SARS-CoV-2 disease are ground-glass opacities (GGOs) with peripheral, subpleural, bilateral, multilobar, and basal distribution. Consolidation, crazy-paving pattern, and fibrotic bands are also common. Besides, the halo sign, reverse halo sign, vascular enlargement, and bubble sign are characteristic features of this disease. There are also atypical chest CT findings such as pleural effusion, pleural thickening, bronchiectasis, mediastinal lymphadenopathy (LAP), cavitation, pneumothorax.[12] SARS-CoV-2 CT findings are similar to imaging features of various other disease processes, including drug reaction, inhalation exposure, and other infections.[10] So CT's specificity is not as high as sensitivity in the diagnosis of SARS-CoV-2.[11]

Society of Thoracic Radiology, the American College of Radiology, and the Radiological Society of North America (RSNA) published an expert consensus statement for standardization on reporting chest CT findings related to COVID-19 (SARS-CoV-2) pneumonia. Cases were classified as typical, indeterminate, atypical, or negative for SARS-CoV-2 pneumonia according to the RSNA guidelines.[10]

CT findings for SARS-CoV-2 are essential for early isolating and identifying the patient because the RT-PCR test resulting is slower, and its sensitivity is lower than the chest CT. This study aimed to assess chest CT features and distributions of patients with SARS-CoV-2.

MATERIALS AND METHODS

This study is a retrospective and conducted in a state hospital in Turkey. A hundred patients (n=100) admitted to the hospital and diagnosed SARS-CoV-2 with RT-PCR between 1st-30st June were enrolled in the study. Age under eighteen years and patients with chronic lung disease was the exclusion criteria. Researchers recorded the demographic characteristics and CT findings from the hospital registry system retrospectively. All patients were diagnosed with SARS-CoV-2 using RT-PCR test in the state hospital's microbiology laboratory. The Local Ethics Committee approved the study.

Radiologic Assessment

Two expert radiologists blindly evaluated all CT images and later matched their findings, using the state hospital's local radiology Picture Archiving and Communication Systems (PACS). This study referenced RSNA expert consensus for SARS-CoV-2 to classify CT findings as typical, indeterminate, atypical, or negative. Typical, indeterminate, atypical, or negative CT findings are described in detail in **Table 1**. All CT images were analyzed and recorded in this context. The present study's findings are shown in **Table 2**. Chest CT examinations were conducted with a 16-slice spiral CT scanner (Alexion 16, Toshiba, Japan).

Table 1. Radiological Society of North America Chest CT Classification System for Reporting Covid-19 Pneumonia.[25]

COVID-19 Pneumonia Imaging Classification	CT Findings
Typical appearance	Peripheral, bilateral GGO with or without consolidation or visible intralobular lines (crazy-paving). Multifocal GGO of rounded morphology with or without consolidation or visible intralobular lines (crazy-paving). Reverse halo sign or other findings organizing pneumonia (seen later in disease).
Indeterminate appearance	Absence of typical features and presence of: multifocal, diffuse, perihilar, or unilateral GGO with or without consolidation lacking a specific distribution and are nonrounded or nonperipheral. Few very small GGOs with a nonrounded and nonperipheral distribution.
Atypical appearance	Absence of typical or indeterminate features and presence of: Isolated lobar or segmental consolidation without GGOs. Discrete small nodules (centrilobular, tree-in-bud). Lung cavitation. Smooth interlobular septal thickening with pleural effusion
Negative for pneumonia	No CT features to suggest pneumonia

GGO: Ground glass opacity, CT: Computed tomography

The CT findings were recorded as GGO, consolidation, multifocal, multilobar, bilateral distribution, location of consolidation or GGO, reverse halo sign, halo sign, vascular enlargement (≥3 mm), air-bubble sign, subpleural line, tree-in-bud pattern, air bronchogram, reticular pattern, LAP (defined as lymph node with short-axis >10 mm), pleural and, pericardial effusion, presence of lung cavitation, bronchiectasis.

Statistical Analyses

Data were analyzed with statistical software (SPSS statistical package, version 20.0; IBM Corp.). Categorical variables were displayed as counts and percentages, and continuous variables were shown as mean±standard deviation. The groups were tested with Kolmogorov-Smirnov to test the normality. One Way ANOVA and Tukey tests were used for numeric data. $p<0.05$ was considered statistically significant.

Table 2. SARS-CoV-2 Pneumonia Chest Computed Tomography findings.

Chest CT findings	n	%
Bilateral	56	70.88
Unilateral	23	29.11
Peripheral	67	84.81
Central	2	2.53
Lower	43	54.43
Upper	4	5.06
Posterior	34	43.03
Anterior	7	8.86
Multilobar	59	74.68
Multifocal	67	84.81
Consolidation	3	3.79
GGO + Consolidation	14	17.72
GGO	59	74.68
Vascular Enlargement	10	12.65
Crazy Paving	11	13.92
Subpleural Line	9	11.39
Halo	7	8.86
Reticular Pattern	7	8.86
Air Bronchogram	6	7.59
Reverse Halo	3	3.79
Air Bubble	2	2.53
Pleural Effusion	2	2.53
Tree-in-Bud	2	2.53
Bronchectasis	1	1.26
LAP	1	1.26
Pericardial Effusion	0	0
Cavitation	0	0

GGO: Ground glass opacity, LAP: Lymphadenopathy

RESULTS

Of the 100 patients participating in the study, 43 (43%) were male, and 57 (57%) were female, and the mean age was 51.60±17.71 years. 21 (%21) of the patients had no signs of pneumonia in CT, and 79 (%79) patients had positive CT findings. The mean age of 21 patients without pneumonia was 42.47±17.78 and the mean age of 79 patients with pneumonia was 54.02±16.99. These findings show that age and pneumonia rate positively correlates (p: 0.007).

54 (68.35%) of the 79 patients with pneumonia had typical (**Figure 1** and **2**), 18 (22.78%) had indeterminate (**Figure 3**), and 7 (8.80%) had atypical (**Figure 4**) CT findings for SARS-CoV-2 pneumonia. 59 (74.68%) patients had GGO (**Figure 1, 2** and **3**), 3 (3.79%) patients had consolidation, and 14 (17.72%) patients had GGO + consolidation (**Figure 1**) on chest CT . Fifty-six patients (70.88%) had bilateral lung lesions, and 23 patients (29.11%) had unilateral lung lesions. Lower lobe involvement was more prominent in 43 patients (54.43%) and upper lobe involvement in 4 patients (5.06%). 67 (84.81%) of CT findings of the patients with pneumonia have peripherally, 2 (2.53%) centrally distributed, and the remaining 10 patients had peripheral and central distribution. 34 (43.03%) of CT findings of the patients with pneumonia has posterior dominance, 7 (8.86%) anterior dominance and 38 (48%) patients had no anterior/posterior dominancy. Only one patient had LAP, two patients had pleural effusion, and two patients had the tree-in-bud pattern (**Figure 4**). Pericardial effusion or lung cavitation was not observed in any patient. The features of CT findings and rates are given in **Table 2**.

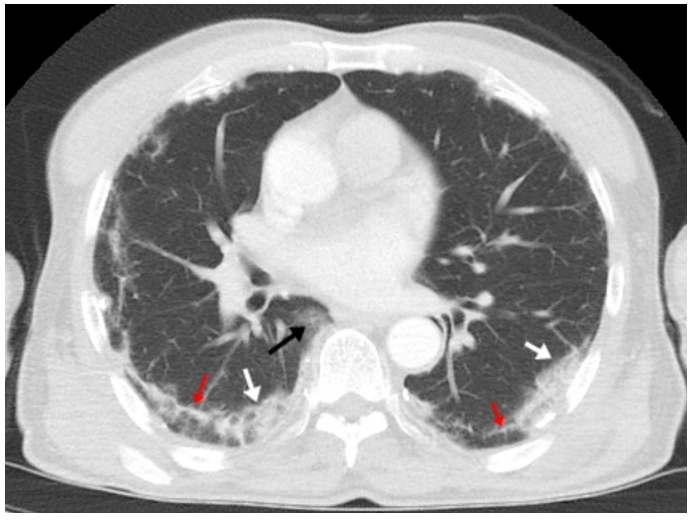

Figure 1. Axial chest CT image shows subpleural line (red arrow), multifocal-peripheral ground-glass opacities (black arrow), and consolidation (white arrow)-typical appearance for SARS-COV-2.

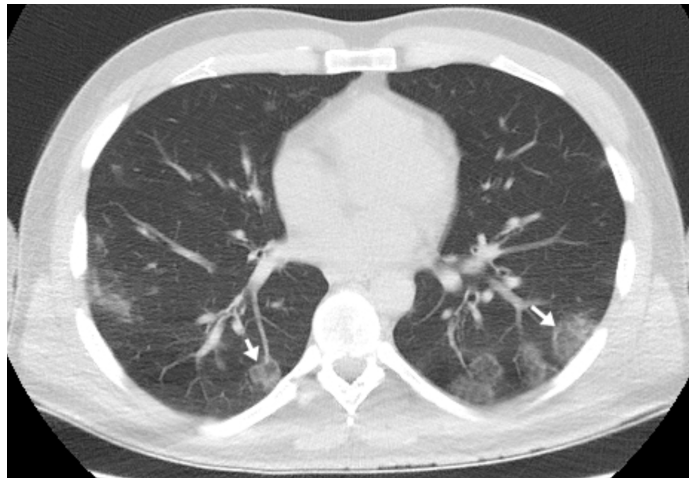

Figure 2. Axial CT image shows peripheral ground-glass opacities with the reverse-halo sign (white arrow). Typical appearance for SARS-COV-2.

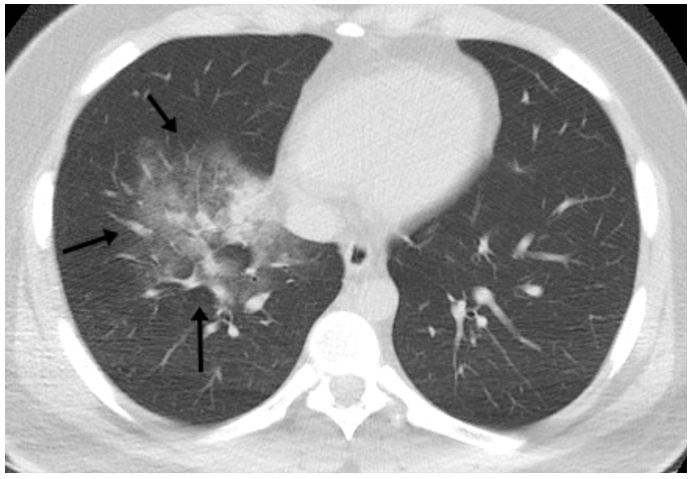

Figure 3. Axial CT image shows central-unilobar ground-glass opacities (black arrow). Indeterminate appearance for SARS-COV-2.

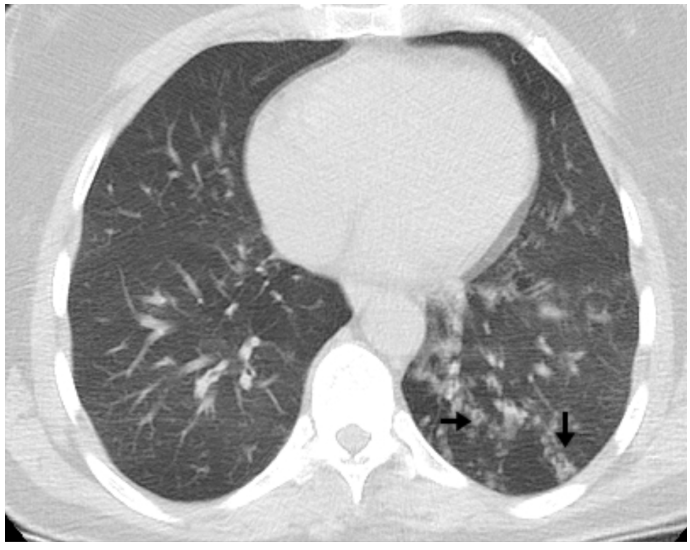

Figure 4. Axial chest CT image shows tree-in-bud pattern (black arrow)-atypical appearance for SARS-COV-2

DISCUSSION

This study evaluating the chest CT features and distribution of patients with SARS-CoV-2 shows that the pneumonia formation of SARS-CoV-2 increases with age. The average age of patients with pneumonia (54.02±16.99 years) was higher than the average age of patients without pneumonia (42.47±17.78), which shows that the rate of SARS-CoV-2 developing pneumonia increases as the patient's age increases ($p< 0.05$). In this study, the higher rate of female patients (57%) and the higher average age of patients with pneumonia (54.02±16.99) were similar to the studies in the literature. In the study of Çinkooğlu et al.[1] the proportion of female patients was 53%, and the mean age of patients with pneumonia was 51.0±15.8. Melendi et al. also found that the average age of patients with pneumonia was higher than the average age of patients without pneumonia (34 vs. 50).[13] On the other hand, lung involvement percentage was just 4% in the early-stage (0–3 days).[14] In this study, we do not know whether this mean age difference is real or related to the early stage of the disease, since the patients were not followed up and the stage of disease during CT scan was not known. This is one of the limitations of our study.

Chest CT has demonstrated about 56–98% sensitivity in detecting SARS-CoV-2 at initial presentation, although RT-PCR has a sensitivity as low as 42–71% for helping detect SARS-CoV-2.[10,15] Although its high sensitivity for the diagnosis of SARS-CoV-2, the specificity of chest CT is low (25%), as noted in a report of 1014 patients in the screening population.[11,16] However, for infectious disease control, sensitivity was more critical than specificity.[8] On the other hand, radiologists in the United States and China distinguished SARS-CoV-2 from other viral pneumonia at chest CT in recent studies.[15] Although GGO was more frequent in patients with SARS-CoV-2, consolidations were more frequent in patients with non-COVID-19 viral pneumonia; both infections were usually bilaterally involving multiple lobes.[17] SARS-CoV-2 pneumonia's CT features like GGO, peripheral distribution, reverse halo sign, vascular enlargement, and reticular opacity were more common than non-COVID-19 viral pneumonia.[15] In non-COVID-19 viral pneumonia, the involvement pattern was peripheral and central, while in SARS-CoV-2, mainly peripheral and posterior, was involved.[17]

This study indicates that GGOs with multifocal, multilobar, peripheral, and bilateral involvement are common chest CT findings in SARS-CoV-2 pneumonia. There was just 54.43% lower lobe dominance and 43.03%posterior dominance in this study. Adams et al. prepared a meta-analysis from 28 publications (a total of 3466 patients) and calculated pooled prevalence about SARS-CoV-2 chest CT findings. Normal chest CT imaging findings prevalence was 10.6% in COVID-19. Prevalences of posterior dominance, GGO, bilateral abnormalities, vascular enlargement, multifocality, peripheral distribution, pleural effusion, LAP, tree-in-bud pattern, central lesion distribution and cavitation were 90.0%, 81.0%, 75.8% , 72.9%, 63.2%, 59%, 5.2%, 5.1%, 4.1%, 3.6% and 0.7%, respectively.[9] In the other studies at literature; the major chest CT abnormalities for SARS-CoV-2 observed were consolidation 2-69%, GGO 34-98%, multifocal 42-63%, peripheral 50-87%, bilateral 75-90%, reticulation 1-59%, crazy-paving 14-34% and 17-56% negative CT findings.[6,11,18-24]

Current studies about CT findings of SARS-CoV-2 in the presence of secondary diseases such as superinfections and aspiration are limited. But recent research shows that more than 20% of patients with SARS-CoV-2 may have co-infections. In this study, the rate of patients with atypical CT findings was 7%, and we do not know if SARS-CoV-2 or other infections caused these findings.[25]

The present study had several limitations. Main limitations are that the research did not include patients with false-negative RT-PCR results, and there was no clinical information about the patients. The disease stage of the patients in the during of CT examination was unknown and their follow-up could not be done. Other limitations are that it is a retrospective study, and the number of patients is low.

CONCLUSION

SARS-CoV-2 is an infection seen with multiple peripheral GGO or GGO+ consolidation, regardless of anterior/posterior dominance and lower lobe/upper lobe dominance in CT.

ETHICAL DECLARATIONS

Ethics Committee Approval: Tokat Gaziosmanpaşa University Ethics Committee approved the study with the number 20-KAEK-225 in 27.08.2020.

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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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.907284
J Contemp Med 2021;11(4):494-499

Orjinal Araştırma / Original Article

Evaluation of IL-1β, IL-18 and Caspase-1 Levels in Familial Mediterranean Fever Patients with Attack and Remission Period

Ailesel Akdeniz Ateşi Hastalarında Atak ve Remisyon Döneminde Serum IL-1β, IL-18 ve Kaspaz-1 Düzeylerinin Değerlendirilmesi

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Abstract

Background: In the pathogenesis of the Familial Mediterranean Fever (FMF) disease, cytokines play important roles in the inflammation of the serous membranes. In this study, we aimed to investigate the relationship of IL-1β, IL-18 and caspase-1 with disease severity scores and acute-phase reactants (APR) in FMF

Material and Method: Sixty patients diagnosed with FMF according to Tel-Hashomer criteria were divided into two groups as attack and attack-free period. Serum cytokines and caspase-1 levels were examined by the ELISA method in 60 patients and 30 healthy volunteers, and the relationship between APR and disease activity was investigated.

Results: FMF attack patient's levels of IL-1β (p=0.001), IL-18 (p=0.043) and caspase-1 (p=0.021) were increased as compared to healthy individuals. There was also a positive relation between IL-1β levels and disease severity as well as acute-phase reactants of attack patients. In FMF remission patients, while a trend towards increased serum IL-1β (p=0.075) and IL-18 (p=0.516) levels were noted, it did not reach statistical significance. However, a borderline difference was observed in the caspase-1 (p=0.049) levels of remission as compared to healthy individuals. In addition, we found no relationship between IL-1β, IL-18 and caspase-1 levels and clinical parameters in remission patients.

Conclusion: The correlation of IL-1β with disease severity supports inhibition of IL-1β activity would provide a therapeutic benefit to patients with FMF. It further suggests that the caspase-1 can serve as a useful marker not only during the attack but also in the remission period, and provides a useful clue for the diagnosis and treatment of the disease.

Keywords: Autoinflammatory diseases, Familial Mediterranean fever, pro-inflammatory cytokines, caspase-1

Öz

Giriş: FMF hastalığının patogenezinde sitokinler, seröz membranların iltihaplanmasında önemli rol oynarlar. Bu çalışmanın amacı, atak ve remisyon döneminde olan FMF hastalarında, serum IL–1β, IL-18 ve kaspaz-1 serum düzeylerinin hastalık şiddeti ve akut faz cevabı ile ilişkisini araştırmaktır.

Gereç ve Yöntem: Tel-Hashomer kriterlerine göre FMF tanısı almış 60 hasta atak ve remisyon dönemi olarak iki gruba ayrıldı. 60 FMF hastasının ve 30 sağlıklı bireyin serum sitokin düzeyleri ELISA yöntemi ile incelendi ve akut faz reaktanları ve hastalık şiddeti ile ilişkisi araştırıldı.

Bulgular: FMF atak hastalarının IL-1β (p=0.001), IL-18 (p=0.043) ve kaspaz-1 (p=0.021) düzeyleri, sağlıklı bireylere göre artış gösterdi. FMF atağı olan hastaların IL-1β seviyeleri ile hastalık şiddeti ve akut-faz cevabı arasında pozitif bir ilişki olduğu gözlemlendi. Remisyon dönemi hastalarının serum IL-1β (p=0.075) ve IL-18 (p=0.516) seviyelerinde artışa doğru bir eğilim kaydedilirken, sadece kaspaz-1 (p=0,049) düzeylerinde bir farklılık gözlemlendi. Bununla birlikte, FMF remisyon hastalarında IL-1β, IL-18 ve kaspaz-1 seviyeleri ile klinik parametreler arasında bir ilişki bulunamadı.

Sonuç: Bu çalışmada, IL-1β ile hastalık şiddeti arasındaki korelasyonun, IL-1β'nin inhibisyonun FMF'li hastalara terapötik bir fayda sağladığını desteklemektedir. Ayrıca, kaspaz-1'in sadece atak döneminde değil, ataklar arası dönemde de yararlı bir biyobelirteç olarak hizmet edebileceğini, hastalığın tanı ve tedavisi için yararlı bir ipucu sağlayabileceğini göstermektedir.

Anahtar Kelimeler: Otoinflamatuar hastalıklar, Ailevi Akdeniz ateşi, pro-inflamator sitokinler, kazpaz-1

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Received *(Geliş Tarihi)*: 31.03.2021 **Accepted *(Kabul Tarihi)*:** 29.04.2021

INTRODUCTION

Familial Mediterranean fever (FMF) is the most common autoinflammatory disease with autosomal recessive inheritance.[1] FMF is caused by mutations of the Mediterranean Fever (MEFV) gene, coding a protein named pyrin. It is expressed mainly in myeloid cells, is implicated in inflammation by the activation of caspase-1, which is responsible for the maturation of IL-1β and IL-18.[2] The deficiency in the amount or activity of pyrin results in an inability to suppress and/or inhibit the inflammatory processes.[3] In the pathogenesis of the FMF disease, cytokines play important roles in the inflammation of the serous membranes. The cytokines that are produced throughout and took part in the inflammatory procedure are the principal stimulators of the manufacture of acute-phase proteins such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum amyloid A (SAA) and fibrinogen in FMF.[4]

IL-1β and IL-18 are members of the interleukin (IL) -1 family and have long been recognized as a potent inflammatory mediator.[5] IL-1β is one of the key cytokines in the mediation of inflammation in autoinflammatory diseases.[6] IL-1β mainly functions to stimulate leukocyte activation and induces fever and acute-phase proteins at high levels which trigger the systemic inflammatory responses. IL-1β activation is triggered by an intracellular sensor that activates the inflammasome to cleave pro-IL-1β into its active form by caspase-1.[7,8] The IL-1β levels are known to be increased in Familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and neonatal-onset multisystem inflammatory disease (NOMID).[9] Several studies also report that increased IL-1β levels in FMF attack patients.[10,11] The results of these studies suggest that IL-1β values seem to correlate with CRP levels and IL-1β could be used in the diagnosis of an acute attack and monitoring the response to the treatment.[10]

In a similar manner of IL-1β, IL-18 is produced as a pro-peptide that needs to be cleaved by caspase-1 after activation of the inflammasome.[12] IL-18 precursor is present and constitutively expressed in monocytes, macrophages and proximal tubular epithelial cells.[13] The IL-18 levels are known to be increased in various pathologic conditions, such as inflammatory arthritis, inflammatory bowel disease, and systemic lupus erythematosus.[14] Serum IL-18 concentrations can discriminate patients with FMF from healthy controls. However, IL-18 has been distinctly evaluated for its potential to discriminate disease activity in FMF. Interestingly, while several studies showed that disease severity increases with IL-18 in the pathogenesis of FMF disease, others have not observed a relationship between IL-18 and disease activity.[15-17]

Caspase-1 is a member of a family of nine cysteine proteases and mediates programmed cell death by promoting the cleavage of critical intracellular proteins upon apoptotic activation.[18] Caspase-1, however, seems to be uniquely involved in participating in the inflammatory response by cleaving the precursors of IL-1 beta, IL-18 and IL-33.[5] Pyrin is expressed mainly in neutrophils, eosinophils, monocytes, dendritic cells, and synovial and peritoneal fibroblasts (mostly in the innate immune system cells) and regulates caspase-1 activation.[1,19,20] These studies indicate that inhibition of the interaction between pyrin and caspase-1 leads to an increase in caspase-1 activity and a subsequent increase in IL-1β secretion in FMF disease.[21]

Furthermore, several studies have been reported the activation of cytokine networks during FMF attacks. However, information on the regulation of inflammation by cytokines in FMF is limited and contradictory especially during the FMF attack and remission period. Therefore, the present study was performed to determine the IL–1β, IL-18, caspase-1 as indicators of FMF.

MATERIAL AND METHOD

Study Populations

In this study, whole blood and serum samples were obtained from FMF patients who came to the physical therapy and rehabilitation and emergency department of Tokat Gaziosmanpasa University Hospital. Sixty FMF patients were divided into two groups, FMF remission and attack. Twelve male and eighteen female patients, aged 20-57 years, were evaluated only during a remission period (defined as being free of attacks for at least 2 weeks based on clinical (fever, abdominal pain, and arthritis) and laboratory findings [high sensitive C-reactive protein (hs-CRP), fibrinogen, and white blood cell (WBC) count). Fifteen male and 15 female attack period patients, aged 19-56 years, were determined based on clinical (fever, abdominal pain, arthritis) and laboratory findings (high levels of fibrinogen, white blood cell (WBC) counts and erythrocyte sedimentation rate (ESR)). Eight male and twenty-two female healthy individuals, aged 20-56 years were included as a control group.

Clinical Classifications

FMF patients were diagnosed according to the Tel-Hashomer diagnostic criteria, requiring the presence of at least 1 of 4 major criteria, 2 of 5 minor criteria, or 1 minor criterion plus 5 of all 10 supportive criteria for definite FMF diagnosis.[22] All patients were being treated with colchicine (1–2 mg/day), were identified. Epidemiologic data (including sex, consanguinity of parents, familial history, and age of onset of inflammation signs) and main clinical data (including fever; thoracic, abdominal and articular; duration; the presence of amyloidosis; and response to colchicine) were recorded.

Laboratory Assay

A sample of 8 ml fasting venous blood was taken in the morning from all participants. The serum was obtained by centrifugation of blood samples at 3000 rpm for 15 min at 4°C. Afterward, serum samples were stored at -80°C until further analyzed.

Hs-CRP, fibrinogen, and WBC counts were measured within less than 1 hr after the sampling. Hs-CRP levels were determined by the nephelometric method (Beckman Array 360 Protein System, Minnesota, Brea). Fibrinogen levels were measured by the clotting time method (Beckman Coulter, Inc., Fullerton, CA), and leukocytes were determined with an automatic hematology analyzer (Beckman Coulter, Inc., Fullerton, CA).

The enzyme-linked immunosorbent assay (ELISA) technique was applied to determine the serum concentrations of IL-1β, IL-18 and caspase in 60 patients and 30 controls. The optical density was determined using an enzyme-linked immunoassay kit according to the manufacturer protocol (BT Lab., CHINA) The spectrophotometric reading was performed by a Multiskan GO Microplate Spectrophotometer (Thermo Scientific, USA).

Statistical Analysis

The Shapiro-Wilk test was used to check the normal distribution of the data. Skewed variables were expressed as median with interquartile range. Since the variables did not show normal distribution, nonparametric tests, which were more suitable than statistical tests, were used. Mann–Whitney U test was used for nonhomogenous distributed data. Mann-Whitney U test was used in a comparison of patients with healthy volunteers as well as in binary group comparisons. Spearman's rank correlation coefficient test was used to explore the correlations between the cytokines and clinical characteristics. All statistical analyses were performed by SPSS 23.0 software (SPSS Inc., Chicago, IL, USA) and graphs were generated using GraphPad Prism version 8.3.0 (GraphPad Software, Inc., CA, USA). A two-tailed P-values in the figures and tables are indicated as follows: (*: p≤0.05; **: p≤0.01, ***: p≤0.001).

Ethics approval

This research study was approved by Tokat Gaziosmanpasa University clinical research ethics committee (#19-KAEK-164) and it was planned and conducted by the provisions of the Helsinki Declaration. All participants gave informed written consent to participate in the study.

RESULTS

The baseline clinical characteristics of FMF attack and remission patients were summarized in **Table 1**. Among FMF attack patients, 20.0% (6/30) were heterozygotes, 36.6% (11/30) were homozygotes, 30.0% (9/30) were compound heterozygotes and no mutation was found in 13.3% (4/30). In FMF remission patients, there were 36.6% (11/30) heterozygotes, 13.3% (4/30) homozygotes, 33.3% (10/30) compound heterozygotes and no mutation was found in 16.6% (5/30). The mean age at diagnosis of FMF attack (19.0±9.3) and remission (28.6±13.2), (p=0.002). Disease severity calculated by defined Pras et al.[23] and the pras score of FMF attack patients was significantly higher than FMF remission (p=0.009).

Table 1. Baseline characteristics of patients with FMF.

	FMF (during attack) (n=30)	FMF (attack free) (n=30)
Age at diagnosis (years)	19.0±9.3*	28.6±13.2
Duration of illness (years)	12.2±9.0	10.7±6.8
BMI	24.2±4.5*	27.1±3.9
Pras score	7.8±2.5*	6.8±2.1
Dose of colchicine (mg/day)	2.8±0.6	2.9±0.6
Family history of FMF, n (%)	16 (53.3)	11 (36.6)
Fever, n (%)	22 (73.3)*	16 (53.3)
Abdominal pain, n (%)	26 (86.6)	23 (76.6)
Chest Pain, n (%)	14 (46.6)	10 (33.3)
Joint pain, n (%)	18 (60)	20 (66.6)
Arthritis/arthralgia, n (%)	13 (43.3)	9 (30)
Myalgia, n (%)	9 (33.3)	10 (33.3)
Splenomegali	1 (3.3)	0
Type of mutation		
Heterozygote, n (%)	6 (20.0)	11 (36.6)
Homozygote, n (%)	11 (36.6)	4 (13.3)
Compound heterozygote, n (%)	9 (30)	10 (33.3)
Wild type, n (%)	4 (13.3)	5 (16.6)

Data are presented as the mean±SD for continuous variables. P values were obtained using a Mann-Whitney U test. (*: p≤0.05) : significance between attack and remission in FMF patients.

In addition, the baseline laboratory characteristics of FMF attack, remission patient groups and healthy individuals were presented in **Table 2**. Accordingly our results, WBC, neutrophil, CRP and fibrinogen measurements were significantly higher in FMF attack compared to healthy individuals (p<0.0001, p<0.0001, p<0.0001, p=0.026, resp.). There was also a significant differences in WBC, neutrophil, CRP and fibrinogen levels between FMF attack and remission (p<0.0001, p<0.0001, p<0.0001, p=0.036, resp.). However, the NLR ratio was higher in both FMF attack and remission than in healthy individuals (p<0.0001, p<0.0001, resp.). When we compared the clinical parameters of remission and control groups, we also found that ESR (p=0.0216) was significantly higher in remission patients..

In FMF attack patients serum concentrations of IL-1β (p=0.001), was significantly higher than the control group. And also, FMF attack patient's levels of IL-18 (p=0.043), caspase-1 (p=0.021) were statistically altered compared to healthy individuals (**Figure 1**). The results suggest that serum levels of IL-1β and caspase-1 are correlating together in FMF attack. In FMF remission patients, while a trend towards increased serum IL-1β (p=0.075) and IL-18 (p=0.516) levels were noted, it did not reach statistical significance. However, a borderline difference was observed in the caspase-1 (p=0.049) levels of remission according to control (**Figure 1**).

In addition, we performed a Spearman correlation analysis to evaluate the relationship of these cytokines among themselves and patients clinical findings. There was a correlation between IL-1β and acute phase reactant ESR (r=0.710, p=0.01), CRP (r=0.550, p=0.05, resp.) in FMF attack patients. We also observed a significant correlation between IL-1β, lymphocyte and pras score (r=-0.500, p=0.008, r=0.570, p=0.004) in FMF attack patients (**Table 3**). There was no relationship between IL-1β, IL-18 and caspase-1 with clinical parameters of FMF remission patients.

Table 2. Comparison of parameters among patients and healthy controls.

Comparison of parameters	Attack (n=30)	Remission (n=30)	Control (n=30)
WBC 10^3/mL	10.8 (5.2-26.9)***†††	7.3 (4.3-11.9)	6.8 (4.3-11.3)
Lymphocyte	1.9 (0.9-4.8)	2.1 (0.9-3.1)	2.2 (1.2-5.0)
Neutrophil	8.2 (3.0-24.5)***†††	4.5 (1.6-9.8)	3.9 (2.0-6.5)
NLR, %	3.8 (1.1-26.9)***†††	0.5 (0.09-1.3)***	1.4 (1.0-4.8)
ESR, mm/h	14.5 (9.0-65.0)	13.0 (5.0-43.0)*	11.0 (2.0-49.0)
CRP, mg/L	25.4 (0.1-199.3)***†††	2.2 (0.2-42.1)	1.8 (0.1-12.0)
Fibrinogen	328.0 (233.0-463.0)*†	258.3 (171.4-464.0)	272.0 (183.0-399.0)
IL-1β, pg/mL	11750.0 (3178-25054.0)***	4063.0 (1210.0-18029.0)	2117.0 (1254.0-4180.0)
IL-18, ng/mL	13.6 (2.4-140.9)*	4.2 (2.6-139.9)	5.3 (0.1-14.64)
Caspase-1, ng/mL	3.8 (1.0-60.6)*	1.9 (1.1-50.8)*	1.1 (0.7-4.7)

Median (interquartile range) or minimum-maximum levels are shown. *: p≤0.05; **: p≤0.01, ***: p≤0.001 significance between FMF patients and healthy controls. NLR: neutrophil to lymphocyte ratio; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Table 3. Correlation of IL-1β, IL-18 and Caspase-1 serum levels with continuous variables in FMF patients and healthy controls.

Continuous Variables	Attack						Remisson						Control					
	IL-1β		IL-18		Caspase-1		IL-1β		IL-18		Caspase-1		IL-1β		IL-18		Caspase-1	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
WBC	0.12	0.69	0.20	0.58	0.36	0.22	-0.07	0.86	0.43	0.21	0.14	0.71	0,07	0,87	-0,41	0,25	0,19	0,61
Lymphocyte	-0.50	0.08*	-0.02	0.97	-0.05	0.87	0.21	0.55	0.34	0.33	0.05	0.90	-0,33	0,35	-0,28	0,43	0,22	0,53
Neutrophil	0.21	0.49	-0.02	0.97	0.30	0.31	-0.17	0.65	0.21	0.56	0.04	0.92	0,14	0,71	0,04	0,92	-0,08	0,84
NLR	0.43	0.15	0.09	0.81	0.05	0.87	0.14	0.70	0.12	0.75	-0.05	0.90	0,49	0,15	0,32	0,37	-0,24	0,51
ESR	0.71	0.01**	0.17	0.64	0.15	0.65	0.16	0.68	0.07	0.86	0.08	0.83	0,02	0,95	-0,71	0,03*	-0,20	0,58
CRP	0.55	0.05*	0.09	0.81	-0.07	0.81	-0.55	0.10	-0.38	0.28	-0.52	0.12	0,59	0,08*	-0,04	0,92	0,08	0,84
Pras Score	0.57	0.04*	0.17	0.63	0.43	0.14	-0.43	0.21	-0.26	0.46	-0.33	0.35						

Statistically significant; a Spearman's correlation between variables, *: p≤0.05; **: p≤0.01.

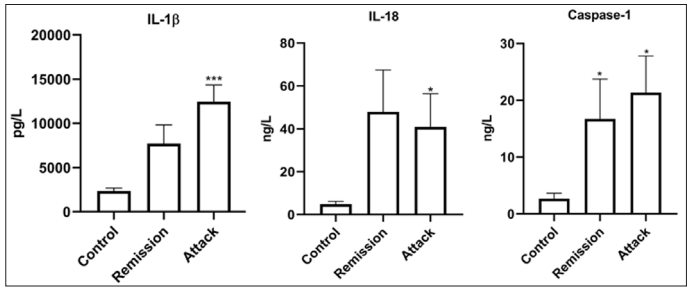

Figure 1. Comparison of serum IL-1β, IL-18 and Caspase-1 in FMF attack/remission patients and control group. Graphed data with error bars denoting standard error of the mean (SEM). Statistical significance was calculated using SPSS-Mann-Whitney U test. (*: p≤0.05; **: p≤0.01, ***: p≤0.001).

DISCUSSION

In the present study, FMF attack patient's disease severity was higher than the remission group (**Table 1**). In addition, WBC, neutrophil, CRP and fibrinogen measurements were increased in FMF attack compared with remission and control group. However, the NLR ratio was higher in both FMF attack and remission than in control (**Table 2**). And also, FMF attack patient's levels of IL-1β, IL-18 and caspase-1 were increased compared to healthy individuals (**Figure 1**). We also found a positive correlation between IL-1β and disease severity, neutrophil, ESR and CRP levels in FMF attack patients (**Table 3**). In FMF remission patients NLR and ESR measurements were higher compared to control. Furthermore, an increase was observed in remission patients IL-1β, IL-18 and caspase-1 levels compared to control, a significant difference was observed only caspase-1 level. We did not observe a relationship between IL-1β, IL-18 and caspase-1 levels and inflammatory markers including CRP, ESR in FMF remission patients.

In the literature, Notarnicola et al.[24] have investigated the transcriptional cytokine expression levels of TNF-α, IL-1β, IL-6 and IL-8 and found higher cytokine expression in FMF remission than control. Yildirim et al.[10] also found higher serum IL-1β levels in patients with FMF than control subjects. Experimental and clinical evidence support the prominent role of IL-1β in the pathogenesis of FMF. Evidence for the role of IL-1β arises from clinical recovery after IL-1β blockade in FMF pathogenesis.[25,26] However, parameters that trigger attacks are still under investigation. Here, we showed that the association of IL-1β with disease severity and acute-phase proteins during the attack period. It is known that acute-phase reactants such as CRP and ESR may increase in many diseases,[27] so they are not sufficient to evaluate FMF disease. Therefore, there is a need for new pathways that can increase or contribute to the reduction of disease severity of FMF attack. In our study, increased IL-1β level in FMF attack patients was positively correlated with disease severity, neutrophil, ESR and CRP (**Table 3**). It was reported that increased levels of inflammatory mediators such as ESR, CRP, and SAA in FMF attacks.[18] Korkmaz et al.[4] reported high APR in 34% of the remission intervals. These findings support that neutrophils were the source of IL-1β in the blood which acts the disease progression and increasing CRP and ESR levels mediate this progress.[26] The correlation of IL-1β with disease severity supports inhibition of IL-1β activity would provide a therapeutic benefit to patients with FMF.

Herein, we also observed an increase in IL-18 level during the attack period of FMF disease, we did not observe any relationship between IL-18 and disease severity or acute-phase response both attack and remission. Only a few studies have investigated serum IL-18 levels in patients with FMF, the results of which have demonstrated higher IL-18 levels in FMF patients compared to healthy controls.[13,28] The studies by Haznedaroglu et al.[15] and Simsek et al.[16] compared IL-18 levels and disease activity, found no relationship with IL-18. However, of these, Gohar et al.[17] observed the correlation with clinical disease activity and IL-18 in patients with FMF attack and remission. These results show that IL-18 plays a distinct role in the disease progression of FMF patients. Although longer-term prospective studies are needed to confirm this.

Finally, there was an increase in caspase-level in FMF attack and remission patients, but we did not observe a correlation with clinical parameters. Some studies demonstrated that pyrin itself can either inhibit or accentuate caspase-1 activity through the interaction of its N-terminal death-fold with ASC, a key molecule in the inflammasome.[12,29] Yu et al.[30] demonstrated that activated pyrin interacts with ASC and activates caspase-1 and subsequently leads to active IL-1β secretion. Neutrophils from patients with FMF secreted IL-1β and showed increased caspase-1 activity in vitro.[31,32] Consequently, overproduction of IL-1β by caspase-1 is the main cause of episodic fever and inflammatory findings in FMF.[33] Our results suggest that the elevation of caspase-1 levels may be important in monitoring subclinical inflammation of remission period in FMF patients. These findings may also contribute to the evaluation of FMF and IL-1β and caspase-1 cytokine levels together in the diagnosis of the disease.

CONCLUSION

In summary, our results support the importance of IL-1β, IL-18 and caspase-1 as a disease activity marker and show that longitudinal examination of pro-inflammatory cytokines may contribute to better follow-up of FMF patients.

Limitations of study

The results of this study are subjected to some limitations. First, this study was not based on longitudinal observations but was conducted with a cross-sectional design. Second, it is a single-center study with a relatively small sample size, which might underestimate or overestimate the relationship between biomarkers and renal involvement due to FMF.

ETHICAL DECLARATIONS

Ethics Committee Approval: The present study was approved by the ethical review committee of the Tokat Gaziosmanpasa University clinical research ethics committee date 2018 numbered 19-KAEK-164.

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.

Financial Disclosure: This study was supported by Gaziosmanpasa University Research Fund (Project Number: 2019/84).

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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CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.823844
J Contemp Med 2021;11(4):500-505

Orjinal Araştırma / Original Article

Role of NLR and MLR in Differentiating Childhood Tuberculosis From Community Acquired Pneumonia

Çocukluk Çağı Tüberkülozunu Toplum Kaynaklı Pnömoniden Ayırmada Yeni Parametreler Arayışı - Mümkün mü?

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Abstract

Background: The neutrophil-lymphocyte ratio (NLR) and monocyte-lymphocyte ratio (MLR) are useful biomarkers of inflammation used in many diseases to evaluate bacteremia, disease activity, recurrence rate, surveillance and prognosis.

Objective: Aim of this study was to evaluate NLR and MLR in the differential diagnosis of children with pulmonary tuberculosis disease from community acquired pneumonia (CAP).

Material and Method: I reviewed hospital-records of 50 children with pulmonary tuberculosis disease in the Pediatric Infectious Disease Ward between June 2016 and December 2018, and compared; NLR and MLR with 50 CAP and 50 healthy children. Also; erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were compared between the tuberculosis and CAP group.

Results: When 3 groups were compared there was significant difference among NLR and MLR values between 3 groups. In pairwise-comparisons, there was significant difference among NLR and MLR values between tuberculosis versus healthy controls, and CAP versus healthy controls. However, there was no significant difference among NLR, MLR values between tuberculosis versus CAP groups.

Conclusion: This study is unique that evluates NLR and MLR in tuberculosis differentiation. Although NLR and MLR values are useful biomarkers of inflammation in both pulmonary tuberculosis and CAP seperately, they're not as useful as expected in differentiating tuberculosis from CAP in children.

Keywords: Tuberculosis, community acquired, pneumonia, child, neutrophil to lymphocyte ratio, monocyte to lymphocyte ratio

Öz

Giriş: Nötrofil-lenfosit oranı (NLO) ve monosit-lenfosit oranı (MLO), bakteriyemi, hastalık aktivitesi, nüks oranı, sürveyans ve prognozu değerlendirmek için birçok hastalıkta kullanılan yararlı inflamasyon biyobelirteçleridir.

Amaç: Bu çalışmanın amacı akciğer tüberkülozu olan çocukların TKP'den ayırıcı tanısında NLO ve MLO' nı değerlendirmektir.

Gereç ve Yöntem: Haziran 2016 ile Aralık 2018 tarihleri arasında Çocuk Enfeksiyon Hastalıkları Servisi'nde akciğer tüberkülozu olan 50 çocuğun hastane kayıtlarını incelenerek NLO ve MLO değerleri 50 TKP ve 50 sağlıklı çocuk ile karşılaştırıldı. Ayrıca; tüberküloz ve TKP grubu arasında eritrosit sedimantasyon hızı (ESR) ve C-reaktif protein değerleri (CRP) karşılaştırıldı.

Bulgular: 3 grup karşılaştırıldığında, 3 grup arasında NLO ve MLO değerleri arasında anlamlı fark vardı. İkili karşılaştırmalarda, sağlıklı kontrollere karşı tüberküloz ve TKP ile sağlıklı kontroller arasında NLO ve MLO değerleri arasında anlamlı fark vardı. Ancak tüberküloz ve TKP grupları arasında NLO, MLO değerleri arasında anlamlı bir fark yoktu.

Sonuç: Bu çalışma, çocukluk çağı tüberküloz ayırıcı tanısında NLO ve MLO'nı değerlendiren ilk çalışmadır. NLO ve MLO değerleri, hem akciğer tüberkülozu hem de TKP'de ayrı ayrı iyi birer inflamasyon biyobelirteci olmasına rağmen, çocuklarda tüberkülozu TKP'den ayırmada beklendiği kadar yararlı değildir.

Anahtar Kelimeler: Tüberküloz, toplum kaynaklı pnömoni, çocuk, notrofil lenfosit oranı, monosit lenfosit oranı

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Received *(Geliş Tarihi)*: 10.11.2020 **Accepted *(Kabul Tarihi)*:** 26.04.2021

INTRODUCTION

Diagnosis of tuberculosis disease in children is still a very difficult problem for pediatricians all over the world. Children with pulmonary tuberculosis present various clinical symptoms; such as prolonged cough, fever, fatigue, sweating and anorexia but none of these symptoms are specific to tuberculosis. The gold standard test for the diagnosis of tuberculosis is culture, however the bacteriological confirmation rate is <30% for all pediatric tuberculosis cases.[1] Currently, tuberculosis disease diagnosis relies on clinical and radiological features, history of household exposure to Mycobacterium tuberculosis and the tuberculin skin testing (TST) in children. Interferon Gamma Release Assays (IGRAs) were evaluated for diagnosing tuberculosis disease; however their usage was expensive. The results were sometimes confusing; especially in children <5 years. Also like the TST, IGRAs did not differentiate TB disease from infection and had poor sensitivity among immunocompromised children with severe tuberculosis disease. Recently, mycobacteria specific antigen-induced and unstimulated cytokines IP10, IL5, IL13, IFN–γ, IL18 are evaluated as biomarkers to discriminate between tuberculosis disease and tuberculosis infection. These studies need funding and a long time through to be proven useful.[2,3]

Most of all childhood pulmonary tuberculosis cases are hospitalized as pneumonia at first and some of them are given pneumonia treatment during the diagnostic stage. Delays in the diagnosis can both lead to the worsening in the patient's clinical and nosocomial transmission of the bacilli to other patients and healthcare workers.[4]

While searching for a new, inexpensive and easily accessible marker contributing to the differential diagnosis of childhood pulmonary tuberculosis from CAP, we decided to evaluate the neutrophil to lymphocyte ratio (NLR), and monocyte to lymphocyte ratio (MLR) in tuberculosis patients and CAP groups. There are many studies investigating the hematological parameters NLR and MLR as markers of inflammation in several rheumatologic, cancer and/or infectious diseases.[5-8] While many studies supported the usefulness of these parameters, some studies did not.[9-12] In this study, we compared the NLR and MLR values of our pulmonary tuberculosis patients with CAP patients and healthy children to determine their usability in the differential diagnosis of childhood pulmonary tuberculosis on admission. Also, the well known inflammation markers ESR and CRP were compared between the tuberculosis and CAP groups. Healthy controls did not have any ESR or CRP values studied, so they weren't included in the comparison of ESR and CRP.

MATERIAL AND METHOD

The medical records of patients who were diagnosed and treated for pulmonary tuberculosis disease and community acquired pneumonia in the pediatric infection ward between June 2017 and December 2019 were evaluated. A total of 50 children with pulmonary tuberculosis; group T and 50 children with community acquired pneumonia; group P and 50 age- and gender-matched healthy control children; group C were enrolled in the study.

The diagnosis of tuberculosis disease was established according to the first 3 diagnostic categories of NIH criteria.[13] The first category included confirmed tuberculosis cases with positive smear of sputum or early morning gastric aspirate and/ or positive culture for M.tuberculosis. The second category included highly probable cases having clinical symptoms and radiological signs of tuberculosis disease with an active or recently treated family member with tuberculosis disease. The third category included possible cases with positive TST or IGRAs and not responding to standard pneumonia treatment, with/or without an active or recently treated family member with tuberculosis disease. Of the tuberculosis group 17 (34%) patients were in category 1, 31 (62 %) patients were in category 2, 2 (4%) patients were in category 3. All children in the third category fully recovered with antituberculosis treatment.

The community acquired pneumonia diagnosis was established according to the physical examination, laboratory findings, and chest X-ray findings of children.[14,15] Children admitted with cough, fever and/or localized chest pain, having moderate to severe respiratory distress, focal auscultatory findings, elevated acute phase reactants and radigraphic features of alveolar infiltrates, segmental/ lobar consolidation, with/without pleural effusion/empyema were diagnosed as pneumonia.[14-16] CAP group consisted of these children whose hospital records were available.

Healthy children were selected through children who applied to hospital for routine check-up, or vaccination status screening or for preoperative evaluation of minor elective surgery (for example: hernia repair). Children with any sign of infection or systemic illness were excluded from the control group.

Hematological parameters including white blood cell (WBC) count, hemoglobin (Hb), neutrophil count, lymphocyte count, platelet count (PLT), monocyte count and mean platelet volume (MPV) were recorded for all groups. NLR, MLR and platelet to lymphocyte ratio (PLR) were calculated as the ratio of neutrophils to lymphocytes, monocytes to lymphocytes and platelets to lymphocytes, respectively. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) of all tuberculosis and CAP patients were recorded if available. Comparison between the three groups were performed with regards to WBC, neutrophil count, lymphocyte count, monocyte count, platelet count, MPV, NLR and PLR. White blood cell, Hb, neutrophil count, lymphocyte count, PLT, MPV, NLR, MLR and PLR values. CRP and ESR were compared between the tuberculosis and CAP groups.

The blood cell counts were performed in the Sysmex XN-350 and C-reactive protein measures were determined on the BN Prospec (Dade Behring, Siemens) Nephelometer.

The Non-Interventional Clinical Ethics Committee of Yüksek İhtisas Education and Research Hospital approved the article with number 2019/01-26.

Statistical Analysis

The normality of data distribution was determined using the Kolmogorov-Smirnov test. Normally distributed numerical variables were expressed in mean plus/minus standard deviation. Normally distributed numerical variables were compared using the Student's t-test or One-way ANOVA test. Tukey test was used for Post Hoc Tests. Data corresponding to an abnormal distribution were expressed in median (minimum-maximum). Abnormally distrubuted numerical data were compared using the non-parametric Mann–Whitney U-test or Kruskal-Wallis test. The Chi-square test was used to compare categorical variables between the groups. P-values of less than 0.05 were considered statistically significant. The data were analyzed using Statistical Package for Social Sciences (SPSS) version 22.0 program for Windows.

RESULTS

The median age of the tuberculosis group was 132 months (15-202 months) and 56% (n=28) were male. The median age of the CAP group was 87.5 months (3-201 months) and 58% (n=29) were male. The median age of the control group was 89 months (16-194 months) and 60% (n=30) were male. There were no significant difference among the median ages (p=0.061) and gender distribution (p=0.686) between the three groups (**Table 1**).

Table 1. Demographic features of tuberculosis, CAP and healthy control group

Demographic features	Tuberculosis Group	CAP Group	Healthy Control Group	p value
Age (months) Median (min-max)	123 (15-202)	87,5 (3-201)	89 (16-194)	0.061
Gender (Male/Female) N (%)	28/22 (56 /44)	29/21 (58/42)	30/20 (60/40)	0.686

The most common symptoms in tuberculosis group at admission were cough (92%), persistent cough (88% with cough longer than 3 weeks, 72% with sputum), night sweating (72%), anorexia (72%), weakness (64%), fever (52%), hemoptysis (26%) and chest pain (8%). The CAP group was admitted with cough (92%, 24% with sputum), fever (92%), chest pain (24%) anorexia (20%), and weakness (18%). Only 4 (8%) of CAP patients had prolonged cough longer than 3 weeks and all of them were diagnosed with empyema. There was significant difference among the frequencies of persistent cough, cough with sputum, night sweating, anorexia, weakness, fever, and chest pain between the tuberculosis and CAP groups (all were p<0.001) (**Table 2**). Peripheral lymphadenitis was found in 14%, hepatomegaly and/or splenomegaly in 10%, abdominal pain in 6% and erythema nodosum in 4% in the tuberculosis group. Abdominal pain was found in 6%, hepatomegaly and/or splenomegaly in 4% in the CAP group. There was no significant difference among the frequencies of abdominal pain (p=0.42) and hepatomegaly and/or splenomegaly (p=0.26).

Tuberculin skin test (TST) of ≥15mm was found in 60% (BCG vaccination is a part of routine childhood vaccination program applied at age 2 months in Turkey), ≥10 mm was found in 66% while the anergy rate was 20% in the tuberculosis group. TST was applied to 12 (24%) of the CAP patients and none of them had positive tuberculin skin test ≥15 mm (**Table 2**). Four of these cases were diagnosed with empyema and 8 other cases had mild to moderate parapneumonic effusion fully recovering with pneumonia treatment.

Table 2. Symptoms, clinical signs and TST results of tuberculosis and CAP patients

Symptoms and clinical signs	Tuberculosis Group (n=50; %)	CAP Group (n=50; %)	p value
Cough	45; 96%	46; 92%	1
Persistent Cough*	44; 88%	4; 8%	<0.001
(cough with sputum)	36; 72%	12; 24%	<0.001
Night sweating	36; 72%	2; 4%	<0.001
Anorexia	36; 72%	10; 20%	<0.001
Weakness	32; 64%	9; 18%	<0.001
Fever	26; 52%	46; 92%	<0.001
Hemoptysis	13; 26%	-	
Peripheral lymphadenitis	7; 14%	-	
Chest pain	4; 8%	12; 24%	0.055
Abdominal pain	5; 10%	3; 6%	0.425
Hepatomegaly±Splenomegaly	5; 10%	2; 4%	0.264
Erythema nodosum	2; 4%	-	
TST result	**(n; %)**	**(n; %)**	
0 mm	10; 20%	3; 6%	
<10 mm	7; 14%	7; 14%	
10-14 mm	3; 6%	2; 4%	
≥15 mm	30; 60%	-	

*Cough longer than 3 weeks

Of the tuberculosis patients 17 (34%) had microbiological diagnosis [M. tuberculosis recovered from either sputum or early morning gastric aspirate (GA) or another body fluid (pleural fluid)], 3 (6%) patients had also histopathological diagnosis simultaneously with microbiological diagnosis; 33 (66%) patients had clinical and radiological diagnosis.

There was statistically significant difference among WBC, hemoglobin, neutrophil count, lymphocyte count, monocyte count, NLR, MLR and PLR values between the three groups (p<0.05). There was no statistically significant difference among platelet count and MPV between the three groups (p>0.05) (**Table 3**). In pairwise-comparisons, there was significant difference among WBC, hemoglobin, neutrophil count, lymphocyte count, monocyte count, NLR, MLR and PLR values between tuberculosis group versus healthy controls, and also CAP group versus healthy controls. However, although there was significant difference among WBC, neutrophil count and monocyte count between tuberculosis group and CAP groups, there was no difference among NLR, MLR and PLR values between tuberculosis and CAP groups (**Table 3**).

There was no significant difference among ESR values between the tuberculosis and CAP group (p<0.589), while median CRP value of CAP group significantly higher than tuberculosis group (p<0.017) (**Table 3**).

Table 3. Total comparison and pairwise-comparison of the laboratory findings of tuberculosis (T), CAP (P) and healthy control (C) groups

Parameter	Tuberculosis group (T)	CAP group (P)	Healthy Control group (C)	p1	p2	p3	p4
WBC (µL) Median (min-max)	8055 (4100-26920)	11460 (3060-41140)	6665 (4000-11820)	<0.001	0.006	0.002	<0.001
Hemoglobin (g/dL) Mean ± SD	12.3±1.89	12.2±1.73	13.2±1.18	<0.05	0.963	0.017	0.008
Neutrophil count (µL) Median (min-max)	5120 (1900-25120)	6985 (970-37120)	3060 (890-6600)	<0.001	0.018	<0.001	<0.001
Monocyte count (µL) Median (min-max)	570 (270-1420)	695 (220-2420)	435 (260-1150)	<0.001	0.005	<0.001	<0.001
NLR Median (min-max)	2.09 (0.43-30.43)	3.3 (0.14-25.34)	0.93 (0.28-2.75)	<0.001	0.479	0.001	<0.001
MLR Median (min-max)	0.25 (0.09-1.91)	0.35 (0.04-2.2)	0.14 (0.03-0.32)	<0.001	0.345	<0.001	<0.001
PLR Median (min-max)	158.3 (53.7-647.1)	141.9 (26.2-365.8)	105.8 (57-203)	<0.001	0.329	<0.001	0.002
ESR (mm/h) Median (min-max)	19 (2-101)	26 (3-100)			0.589		
CRP (mg/dL) Median (min-max)	3.36 (0.10-202)	26.3 (1.60-294)			0.017		

WBC: white blood cell; NLR: neutrophil/ lymphocyte ratio; MLR: monocyte/ lymphocyte ratio; PLR: platelet/ lymphocyte ratio; CRP: C reactive protein, ESR: erythrocyte sedimentation rate; p1: comparison of T&P&C; p2:comparison of T&P; p3: comparison of T&C; p4: comparison of P&C

DISCUSSION

Differentiating children with pulmonary tuberculosis from CAP based only on history, physical examination, and radiological findings is difficult, since they mostly develop paucibacillary disease and cannot easily generate sputum.

In this study, I found that the frequency of persistent cough with sputum (cough longer than 3 weeks), anorexia, night sweating, weakness and hemoptizis were higher in the tuberculosis group. There was statistically significant difference in all these symptoms (p>0.001) .On the other hand, fever and chest pain frequency were higher in the CAP group. There was statistically significant difference in fever frequency (p<0.001) despite chest pain (p=0.055). In the study by Yoon et al.[17] adult tuberculosis cases were compared with CAP cases. In the study cough (p=0.030), night sweating (p=0.021), weight loss (p<0.001), symptom duration >2 weeks (p<0.001) and hemoptizis (p=0.024) were higher in tuberculosis group than CAP cases. Also, similar to this study, fever was statistically significantly higher in CAP group than tuberculosis group (p<0.001).

Many children with pulmonary tuberculosis are hospitalized with the initial diagnosis of pneumonia and some of them are given antibiotic treatment during the diagnostic stage. In some tuberculosis cases treatment failure or relapsing after standard pneumonia treatment gives us clues about tuberculosis especially when the families do not give appropriate information. Delay in the isolation and early treatment with anti-TB agents can cause worsening in the patient's clinical, higher mortality and morbidity and nosocomial transmission of the bacilli to other patients and healthcare workers.[4,18] Therefore, a rapid and readily available test to distinguish pulmonary TB from CAP is becoming essential.

White blood cell populations play an important role in the systemic inflammatory response to infection.[19,20] In some studies the value of NLR in infectious lung diseases is evaluated. In a study by Abakay et al.[21] NLR was reported to be significantly higher in patients with advanced pulmonary TB as opposed to patients with mild to moderate pulmonary TB. In the study by Yoon et al.[17] they stated that NLR could be used for the discrimination of tuberculosis and community acquired pneumonia in the adults. Myeloid-specific cells have been known to serve as host cells for M. tuberculosis growth and lymphoid cells are thought to be the major effector cells in TB immunity. Given the central role of monocytes and lymphocytes in the induction of immune responses, their levels in peripheral blood might be expected to reflect the state of an individual's immunity to tuberculosis. In a recent clinical analysis from a cohort of South African infants the relative ratio of monocytes to lymphocytes at the start of monitoring was shown to predict risk of developing tuberculosis disease during follow-up.[22] In a study by Ozdemir et al.[23] NLR and PLR were found not useful in differentiating tuberculous lymphadenitis from sarcoidosis in adults. In this study, I evaluated NLR and MLR values of children with pulmonary tuberculosis, CAP and compared with healthy children. I found NLR and MLR values were elevated in both groups of children either with tuberculosis or CAP. The results showed that NLR and MLR are useful inflammatory indicators of either tuberculosis or CAP in children when compared to healthy children. However, when these parameters are compared for differential diagnosis of TB from CAP, NLR and MLR are not as useful as expected. To describe all, NLR and MLR are not promising parameters for differential diagnosis of childhood pulmonary tuberculosis from CAP. Our results differed from the studies of adult studies above mentioned. I did not classify TB patients having moderate or advanced radiological disease in the study. Moreover, I did not perform statistical comparisons between subgroups of TB patients according to NIH categories and CAP patients. The pneumonia patients were also not classified as moderate or complicated pneumonia (with parapneumonic effusion or amphyema). It can be argued, however the number of study participants are in small numbers.

CRP is a well known inflammation marker, levels of which is related to tuberculosis disease severity.[24,25] I n a study by Schleicher et al.[26] levels of CRP were found to be higher in patients with HIV-positive CAP than in those with pulmonary TB disease. In a study by Kang et al.[27] CRP was found helpful in discriminating pulmonary tuberculosis from CAP ($p<0.001$). In the study CRP levels of CAP patients were found higher than pulmonary TB patients. Similar to these studies, CRP was high in 44% of tuberculosis group and 86% of CAP group. CRP levels of CAP patients in this study were higher than TB patients and the results were helpful in making differential diagnosis ($p=0.017$).

The retrospective nature of this study is the major limiting factor. Also, the study population is consisted of limited number of patients. However, as far as I know, there is no other study evaluating the NLR and MLR in childhood tuberculosis. As well, all the patients in the CAP were hospitalized patients with severe symptoms and complication of pneumonia. Some of them were also investigated thoroughly for tuberculosis exclusion. I speculate that the number of study population should be increased to reach a clearer conclusion about the diagnostic value of NLR and MLR in differential diagnosis of tuberculosis and CAP in children. Further prospective studies are needed to compare the results and make a final decision.

CONCLUSION

This study shows that tuberculosis diagnosis still depends on clear evaluation of signs and symptoms, history of contact to an adult with tuberculosis disease, radiologic evidence and PPD test results. CRP can be a useful marker in differentiating pulmonary TB from CAP. However, NLR and MLR values are not as useful as expected..

ETHICAL DECLARATIONS

Ethics Committee Approval: The Non-Interventional Clinical Ethics Committee of Yüksek İhtisas Education and Research Hospital approved the article with number 2019/01-26.

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.

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.

Acknowledgment: I have many thanks to Dr. Hümeyra Aslaner for her precious statistical analysis in this article.

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.803436
J Contemp Med 2021;11(4):506-509

Orjinal Araştırma / Original Article

The Effect of Needle Sizes for Sample Adequacy in Thyroid Nodule Fine-Needle Biopsies

Tiroid Nodül İnce İğne Biyopsinde Yeterli Tanısal Numune Almaya İğne Boyutunun Etkisi

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Abstract

Aim: The aim of this study was to compare the diagnostic adequacy of thyroid samples obtained with 22-Gauge and 27-Gauge needles.

Material and Method: From January 2019 to December 2019, 860 patients with thyroid nodules who underwent ultrasound-guided fine-needle biopsies were included in this retrospective study. The results of the samples taken were classified cytologically according to the Bethesda 2017classification. Sample adequacy rates were calculated for each group and compared using chi-square tests.

Results: Our cytological results were reported as 157 (18.3%) inadequate materials (Bethesda1). There were no statistically significant differences among the adequacy rates achieved with 22- and 27-gauge needles (80.4% and 83.2%, respectively; P>0.05). There was no significant or permanent complication.

Conclusion: There was no difference between 22 and 27-Gauge needle sizes in diagnostic adequate sample. Prospective randomized controlled studies are needed to examine the relationships between nodule, needle, and patient dependent variables.

Keywords: Fine-needle aspiration biopsy, thyroid nodule, adequacy, needle size

Öz

Amaç: Bu çalışmanın amacı 22 ve 27-Gauge boyutlu iğneler ile yapılan tiroid biyopsilerinde alınan sitolojik örneklerin patolojik olarak tanı verme yeterliliğini karşılaştırmaktır.

Gereç ve Yöntem: Bu retrospektif çalışmaya Ocak 2019-Aralık 2019 tarihleri arasında 860 hastaya ultrason kılavuzluğunda yapılan tiroid ince iğne biyopsileri dahil edilmiştir. Alınan örneklerin sonuçları sitolojik olarak Bethesda 2017 sınıflamasına göre sınıflandırılmıştır. Örneklerin tanı yeterlilikleri her grup için ki-kare testi ile analiz edilmiştir.

Bulgular: Toplamda 157 (%18,3) tanısal olmayan mateyeral patoloji sonucu olarak rapor edildi (Bethesda 1). Araştırmamızda 22 ve 27-Gauge boyutlu iğneler ile elde edilen örneklerin tanısal yeterlilik oranları arasında istatistiksel olarak anlamlı bir farklılık yoktu (sırasıyla; %80,4 ve %83,2, P>0,05). Kalıcı veya ciddi bir komplikasyon görülmedi.

Sonuç: İnce iğne biyopsisinin yeterli numune vermesi açısından 22 ve 27 Gauge iğne boyutları arasında fark görülmemektedir. İğneye, nodülün özelliğine ve hastaya bağlı değişkenler arasındaki ilişkileri incelemek için prospektif randomize kontrollü çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: İnce iğne aspirasyon biyopsisi, tiroid nodülü, yeterlilik, iğne boyutu

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Received *(Geliş Tarihi)*: 06.10.2020 **Accepted *(Kabul Tarihi)*:** 11.04.2021

INTRODUCTION

Fine needle aspiration biopsy (FNAB) of thyroid is a minimal invasive diagnostic method used to distinguish malignancy from benign nodules. After the use of ultrasound guidance for FNAB which has high sensitivity and specificity, the rate of non-diagnostic pathological results has been significantly reduced.[1,2] FNAB was described in 1930 by Martin et al.[3] Today FNAB is commonly performed under ultrasound (US) guidance. The complication rates of FNAB under the guidance of US are low because needle, nodule, and surrounding tissues can be seen in real-time during the procedure. The most important problem with FNAB is non-diagnostic samples which reach up to 25%.[4] Needle size used during FNAB varies from 21 gauge to 27 gauge.[5] 25-27 gauge needles are mostly used in western countries such as Europe and America, while 21-22 gauge needles are used more frequently in Japan.[6] Thick needles increase the contamination rate of the sample taken, while thinner needles make it difficult to direct the needle during the procedure. Liquid-based cytological examinations are suggested to reduce non-diagnostic biopsy.[7] There are few articles on whether the needle size affects the pathological diagnosis.[4,8,11] In none of these articles, direct microscopic examination and liquid-based cytological examination were performed together. US-guided FNABs carried out in our unit are both evaluated conventionally by spreading the samples on glass slides and by liquid-based cytological examination. In this study, we aim to compare the pathological diagnostic ability of 22 gauge and 27 gauge needles.

MATERIAL AND METHOD

For our study, approval was obtained from the ethics committee of our institution and the Helsinki Declaration was followed during the study. 860 US-guided FNAB performed between January 2019 and December 2019 were evaluated retrospectively. Biopsies were performed by two interventional radiologists who have at least five years of experience in FNAB. One of our interventional radiologists who performed biopsy preferred the 22G needle and the other preferred the 27G needle.

The exclusion criteria were that biopsy was not performed under ultrasound guidance, or 22 Gauge or 27 Gauge needles were used during the biopsy. In addition, biopsies performed by physicians with less than 5 years of experience were also excluded. While performing biopsies, it was used with BK 1202 (BK Ultrasound, Herlev, Denmark) US device and 6-18 MHz linear probe as a guide. The procedures were performed while the patient was in supine position and neck in extension. First, skin sterilization was achieved with Povidone İodine solution. After the sterile sheath was put on to the probe, biopsy was performed. Some of the sample taken was spread on the slide and some were put in a liquid-based biopsy solution. Only 2 procedures were performed under general anesthesia due to anxiety. Anesthesia was not used in other procedures.

Biopsy results were evaluated cytologically by a single pathologist according to the Bethesda 2017 classification.[13] Bethesda classification and general clinical approach according to classification are shown in **Table 1**. We will compare the pathological diagnostic ability of 22 gauge and 27 gauge needles according to Bethesda 2017 classification.

Table 1: The 2017 Bethesda system for reporting thyroid cytopathology

Diagnostic Category	Usual Management
1- Non-diagnostic or unsatisfactory	Repeat FNAB
2- Benign	Clinical and sonographic follow-up
3- Atypia of undetermined significance or follicular lesion of undetermined significance	Repeat FNAB, molecular testing, or lobectomy
4- Follicular neoplasm or suspicious for a follicular neoplasm	Molecular testing, or lobectomy
5- Suspicious for malignancy	Near-total thyroidectomy or lobectomy
6- Malignant	Near-total thyroidectomy or lobectomy

FNAB: Fine needle aspiration biopsy

SPSS 22.0 package program was used for statistical analysis of the data. Continuous variables are expressed as mean±standard deviation, categorical variables as numbers and percentages. The differences between categorical variables were examined by chi-square analysis. In all analyses, $p<0.05$ was accepted statistically significant.

RESULTS

Among 860 patients we included in our study, 679 were female (% 79) and 181(% 21) were male. The average age of our patients was 53, and our youngest patient was 9 years old, and our oldest patient was 89 years old. The results of 157 patients (18.3%) came as non-diagnostic pathology. This rate was calculated as 17% in females and 22.6% in male patients. The majority of the diagnostic sample results according to the Bethesda classification are shown in **Table 2**. 22G needle was used in 438 patients whereas 27G needle was used in 422. 86 of 438 (19.6%) samples taken with a 22-gauge needle and 71 of (16,8%) samples taken with a 27-gauge needle were pathologically non-diagnostic. According to the statistical analysis, there was no difference between needle size and non-diagnostic results of pathologic samples (P=0.286)

The most common complication was temporary local pain. 9 patients (1.04%) had intrathyroidal bleeding and 2 patients had hematoma adjacent to the carotid artery. These complications regressed during follow-up. Dizziness was observed in some of our patients due to anxiety. Since the number of complications is very low, no statistical analysis could be performed to show that that is related to needle size.

Table 2. Our pathological diagnoses according to the 2017 Bethesda reporting system

Diagnosis	n	Percent (%)
1	157	18.3
2	663	77.1
3	10	1.2
4	1	0.1
5	17	2
6	12	1.4

DISCUSSION

US-guided FNAB is an effective and low-cost method for evaluating thyroid nodules and has a significantly low morbidity rate.[11,14] The most important problem encountered in the procedures for the search for the optimal needle size to be used during FNAB is the non-diagnostic pathology results due to the insufficient sample, which can be seen in up to 25%.

In our study, although the diagnostic pathological result rate (83.2%) of the samples taken with a 27- gauge needle was slightly higher than that of a 22-gauge needle (80.4%), the effect of the biopsy needle diameter on diagnostic result rate was not statistically significant (p=0.286). In the study conducted by Tangpricha et al., 21-gauge and 25-gauge needles were compared, and as a result of the study, it was stated that more cells appeared in biopsies taken with 25-gauge needles, but the rate of diagnosis was not changed. Despite the fact that more cells are present in this study, the authors attributed the rate of diagnosis not to be affected by blood contamination.[11]

In many research articles about the effect of needle size on diagnostic adequacy, needle size was found to be unrelated to non-diagnostic samples similar to our study.[4,6,9-12,14] The only study showing the higher diagnostic rate with smaller size needles is the research by Degirmenci et al.[8]

FNAB is a well-tolerated procedure that has only minor temporary complications and does not require local anesthesia.[6] In our procedures, no complications requiring intervention were observed. It was said that the degree of pain after FNAB could be related to needle size, the number of needle penetration, length of aspiration time, location of nodules, operator experience, and patient-related factors.[15] In biopsies with thinner needles, the pain may decrease due to the needle size on the other hand the pain may increase as the duration of the needle being in tissue may increase. In studies conducted until now, it hasn't been shown statistically that the pain is related to the size of the biopsy needle.[8,12,16] And also, the experience of the operator performing the procedure wasn't found to be related to the degree of pain.[17] Hemorrhage may occur in intranodular, parenchymal, subcapsular, or parathyroid tissues. It usually heals without any interventions. Anticoagulant antithrombotic drugs should be discontinued 3-10 days before FNAB, due to the increased risk of hemorrhagic complications.[18]

It has been reported that on-site evaluation of the FNAB specimens by a cytopathologist decrease the biopsy repetition rates and false-negative results and increase the biopsy success.[4,19] Stacul et al. found that on-site cytopathological evaluation reduced the diagnostic failure rates from 14% to 4%.[20] The on-site cytopathological evaluation may prolong the biopsy period on the day of the procedure but can reduce the coming back to the hospital and feeling psychologically uncomfortable.[4] In fact, it was reported that the cytotechnician and cytopathological were not different in terms of diagnostic adequacy in the on-site evaluation of FNAB samples.[21] In our study, on-site cytopathological evaluation was not performed. However, if possible, we think that it is important to evaluate the pathology at the processing site in order to protect the patient from repeated biopsies.

There were some limitations in our study. First of all, since the study was conducted retrospectively, the information presided from patient file records could be analyzed. In our study, only 22-gauge and 27-gauge needles could be compared. However, we think that it is necessary to evaluate the needles in intermediate size such as 25-gauge. In addition, we think that needle preference may vary depending on the structure of the nodule because of the possibility of the fine needle's bending and inability to enter the nodules with high calcification. Therefore, we suggest that the structure of the nodule should be taken into consideration in future prospective studies.

CONCLUSION

As a result, in our study, the adequacy of thyroid biopsy samples obtained with different sizes of needles (22 and 27-gauge) was compared and no significant difference was found between them. To reduce the risk of non-diagnostic samples, specimens are recommended to be evaluated by the cytopathologist at the processing site. Prospective randomized controlled studies are needed to examine to relationships between nodules, needles, and patient dependent variables.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol was approved by the Medical Ethics Committee of Pamukkale University (Permission granted: 25.06.2020, Decision no: 2020/37894).

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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JOURNAL OF
CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.876825
J Contemp Med 2021;11(4):510-514

Orjinal Araştırma / Original Article

Comparison of Appendicitis Scoring Systems in Pediatric Patients

Çocuk Hastalarda Apandisit Puanlama Sistemlerinin Karşılaştırılması

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Abstract

Background: Appendicitis is one of the most common causes of emergency department (ED) admission among pediatric patients, and the most common cause of abdominal pain requiring surgical intervention. The present study aimed to measure the success of three different appendicitis scoring systems in patients who were operated due to appendicitis upon presenting at the pediatric ED with acute abdominal pain.

Material and Method: The study included a total of 226 patients who were admitted to Pediatric Emergency Department and who underwent an appendectomy between December 2018 and May 2019. Through a retrospective review of patient files; age, gender, clinical findings, laboratory results, Pediatric Appendicitis Score (PAS), Lintula score, Acute Inflammatory Response (AIR) score, ultrasonography (USG) findings and pathology results of the patients operated due to appendicitis were recorded.

Results: A total of 226 patients were included in the study, with a mean age of 11.6±3.66 (1-17) years, and 57.1% (n=129) of the patients were female and 42.9% (n=97) were male. The pathology results were evaluated under three categories: suppurative (phlegmonous) appendicitis, 74.3%; perforated appendix, 9.7%; and reactive lymphoid hyperplasia, 15.9%. The cut-off values >3 for AIR, >7 for PAS and >15 for Lintula were found statistically significant. Among the three scoring systems, Lintula had the highest sensitivity (91.5%) and PAS had the highest specificity (69.4%).

Conclusion: Although scoring systems are used to diagnose appendicitis , the selected cut-off values for the scoring systems have an effect on the results. Patients with a PAS score of ≥7 were found to have more significant appendicitis results. We believe that PAS is likely to be a preferred scoring system in pediatric patients, especially under busy ED conditions; however, further studies with larger populations are needed to develop scoring systems that will guide physicians to establish a final diagnosis.

Keywords: Appendicitis, scoring systems, pediatric patients

Öz

Amaç: Çocuklarda acile en sık başvuru nedenlerinden olan ve en sık acil cerrahi girişim gerektiren karın ağrısı nedeni akut apandisittir. Çocuk acil servisine akut karın ağrısı ile başvuran hastalarda apandisit şiddetini değerlendirmek ve üç farklı skorlama sisteminin başarısını ölçmek amaçlanmıştır.

Gereç ve Yöntem: Bu çalışmada Aralık 2018- Mayıs 2019 tarihleri arasında Adana Şehir Eğitim ve Araştırma Hastanesi Çocuk Acil servisine başvuran ve apendektomi yapılan hastalar değerlendirildi. Çalışma için Adana Şehir Eğitim ve Araştırma Hastanesi etik kurul onayı alındı. Çalışmaya 226 hasta dahil edildi. Apandisit için ameliyat edilen hastaların PAS, Lintula, AİRS skorları, ultrasonografi bulguları (usg) ve Patoloji sonuçları kaydedildi. Apandisit cerrahi ve patoloji sonuçları dayanarak doğrulandı. Apandisit dışındaki nedenler için tesadüfi apendektomi yapılan, diğer hastalıklar nedeni ile hastanede yatış sırasında apandisit teşhisi konan veya tıbbi kayıtları eksik olan hastalar çalışma dışı bırakıldı.

Bulgular: Bu çalışmaya toplam 226 hasta dahil edildi. Hastaların yaş ortalaması 11,6±3,66 (1-17 yıl) yıldı. Hastaların %57,1 (129) 'si kadın, %42,9 (97)'u erkekti. Hastaların %17,3 (39)'ünde usg yapılamamıştır. USG yapılan 187 hastanın %67,3' ünde apendiks lümen çapı 7 mm ve üzerinde, %15,5'inde ise 6mm ve altında idi. Patoloji sonuçları üç grupta değerlendirildi. Hastaların %74,3'ü süpüratif, flegmenöz apandisit, %9,7' si ise perfore apandisit, %15,9'u reaktif lenfoid hiperplazi idi. AİR, Lintula, PAS skor grupları düşük ihtimal, orta ihtimal ve yüksek ihtimal akut apandisit olarak gruplara ayrıldı.

Sonuç: Apandisit tanısını koymada skorlama sistemlerinden faydalanılmakla birlikte skorlamaların seçilen cut off değerleri sonuçları etkilemektedir. Çalışmamızda skorlamalar arasında PAS 7 ve üzerinde olan hastalarda daha anlamlı sonuçlar ortaya çıkmıştır ve özellikle yoğun acil şartlarda PAS ın çocuklarda öncelikli kullanılabilir skorlama olabileceğini düşünmekle birlikte kesin tanıya hekimi yönlendirebilecek geniş populasyonlarda skorlama sistem çalışmalarının yapılması gerektiğini düşünmekteyiz.

Anahtar kelimeler: Apandisit, teşhis skoru, çocuk

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Received *(Geliş Tarihi)*: 08.02.2021 **Accepted *(Kabul Tarihi)*:** 24.03.2021

INTRODUCTION

Appendicitis is one of the most common causes of emergency department (ED) admission among pediatric patients, and is the most common cause of abdominal pain requiring surgical intervention.[1] The clinical manifestation of appendicitis is variable, from a simple inflamation to a wide range of pathologies, including perforation, within 24-36 hours after the onset of complaints. It is difficult, however, to determine the course of symptoms in an agitated and irritable child, due especially to the fact that the symptoms of appendicitis – such as abdominal pain, vomiting and uneasiness – may also indicate a number of other diseases. Furthermore, children may be unable to effectively express their complaints, appendicitis is associated with high morbidity and mortality when not diagnosed and treated in the early stage.[2] This has made various scoring systems, which have been developed to support or exclude the diagnosis of eppendicitis, become more important in recent years.

The objective of the present studies to evaluate the pediatric appendicitis score (PAS), Lintula score and acute inflammatory response (AIR) score of for appendicitis – one of the most common causes of surgery in pediatric patients, and is also associated with high mortality when not early diagnosed–and to determine whether there is a preferred scoring system for establishing the diagnosis.[3-7]

MATERIALS AND METHOD

We retrospectively assessed 226 patientswho presented and had appendectomy at the Adana City Training and Research Hospital Pediatric Emergency Department between December 2018 and May 2019. The patient files were used to obtain data regarding the age, gender, disease symptoms, physical examination and laboratory findings (WBC and neutrophil counts, CRP levels), USG findings and pathology results of the patients operated due to appendicitis along with the PAS, Lintula and AIR scores .The same clinician made the scoring assessment of all cases.

Appendicitis diagnoses were confirmed through surgical findings and pathology results. Group 1 was appendicitis (suppurative, phlegmonous, acute appendicitis), group 2 was perforated appendicitis, group 3 was reactive lymphoid hyperplasia. The exclusion criteria were as follows: (a) appendectomy for reasons other than appendicitis , (b) elective coincidental appendectomy, (c) appendicitis diagnosis while hospitalized for other reasons, and (d) incomplete medical records.

Statistical Analysis

The study data were analyzed using the IBM SPSS version 23.0 software package. Besides descriptive statistical methods expressed a (mean, standard deviation, frequency, minimum and maximum), a Student's t-test was used for the comparison of quantitative data; Fisher's Exact and Chi-square tests were for the comparison of qualitative data; and a Receiver Operating Characteristic (ROC) analysis was conducted for the PAS, Lintula and AIR scores. The results were used to determine the cut-off values, specificity, sensitivity, and positive and negative predictive values of each scoring system. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 226 patients were included in the study, with a mean age of 11.6±3.66 (1-17) years, and 57.1% (n=129) of the patients were female and 42.9% (n=97) were male. Of the total, 17.3% (n=39) of the patients did not undergo a USG examination. Among the remaining 187 patients, the diameter of the lumen was ≥7 mm in 67.3% and ≤6 mm in 15.5%. Pathology results were evaluated under three categories: suppurative (phlegmonous) appendicitis, 74.3%; perforated appendix, 9.7%; and reactive lymphoid hyperplasia, 15.9%. The patients were divided into three groups based on the results of each scoring system, as low, moderate and high risk (**Table 1**).

Table 1. Components of the Pediatric Appendicitis Score (PAS)

Signs/symptoms	Point value
Nausea/emesis	1
Anorexia	1
Migration of pain to RLQ	1
Low-grade fever (≥38.0°C)	1
RLQ tenderness	2
RLQ tenderness to cough, percussion, or hopping	2
Leukocytosis (>10,000/mm^3)	1
Left shift (neutrophilia >75%)	1
Total	10

Abbreviations: RLQ, right lower quadrant.

A ROC analysis was conducted to compare the pathology results with the scoring system results. The mean AIR score was 4.99±1.87. The diagnosis of appendicitis was found statistically significant when the cut-off value of AIR was 3, with a sensitivity of 83.1% and specificity of 61.1% (p <0.05). The positive and negative predictive values of the AIR scoring system were 91.9% and 40.7%, respectively **(Figure 1, Table 2**).

The mean PAS score was 8.18±1.29. It was found that the cut-off value from the ROC analysis and ROC curve yielded accurate results at a rate of 82.1%. Patients with a PAS score >7, which was the cut-off value of PAS, were diagnosed with appendicitis, with a sensitivity of 82.1% and specificity of 69.4% (p <0.05). The positive and negative predictive values of the PAS scoring system were 93.4% and 42.4%, respectively (**Figure 2, Table 2**).

The mean Lintula score was 19.53±4.38. It was found that the cut-off value of Lintula from the ROC analysis and ROC curve yielded accurate results at a rate of 72.3%. The cut-off value for Lintula was calculated as 15 with a sensitivity of 91.5% and a specificity of 38.8%. The positive and negative predictive values of the Lintula scoring system were 88.8% and 46.7%, respectively. The results were statistically significant (p <0.05, **Figure 3, Table 2**).

The comparison of appendix length as measured on USG with the pathology results revealed suppurative (phlegmonous) appendicitis to be more common in the patient group where lumen diameter of the ppendix was ≥7mm. However, this difference was not statistically significant.

The pathology results revealed patients with a perforated appendix to have statistically significantly higher Lintula, PAS and AIR scores ($p < 0.05$, **Table 3**).

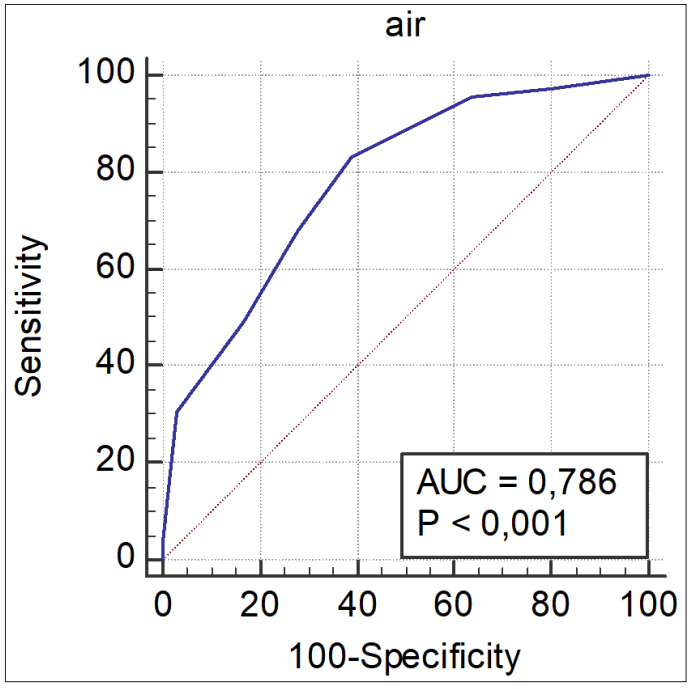

Figure 1. ROC curve of AIR scores

Table 2. Components of the appendicitis inflammatory response (AIR) score

Diagnosis	AIR score
Vomiting	1
Pain in RLQ	1
Rebound tenderness or muscular defense	
Light	1
Medium	2
Strong	3
Body temperature >37.8°C	
Polymorphonuclear leukocytes	**1**
70–84%	1
≥85%	2
WBC count	
10.0–14.9 ×10⁹/L	1
≥15.0 ×10⁹/L	2
CRP concentration	
10–49 g/L	1
≥50 g/L	2
Total score	**12**

Table 3. Lintula appendicitis score.

Parameter	Score
Male gender	2
Intensity of pain severe	2
Relocation of pain	4
Vomiting	2
Pain in RLQ	4
Fever ≥37.5°C	3
Guarding	4
Absent, tinkling, high-pitched bowel sounds	4
Rebound tenderness	7
Total score	32

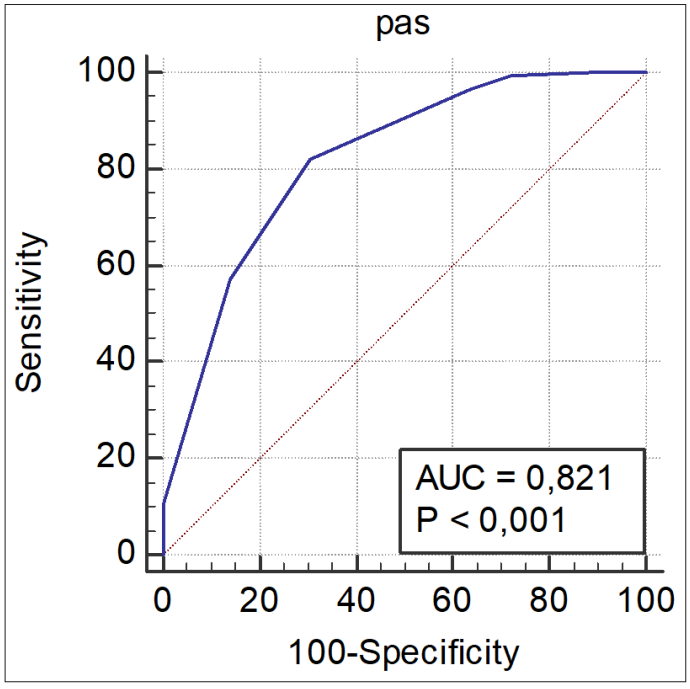

Figure 2. ROC curve of PAS scores

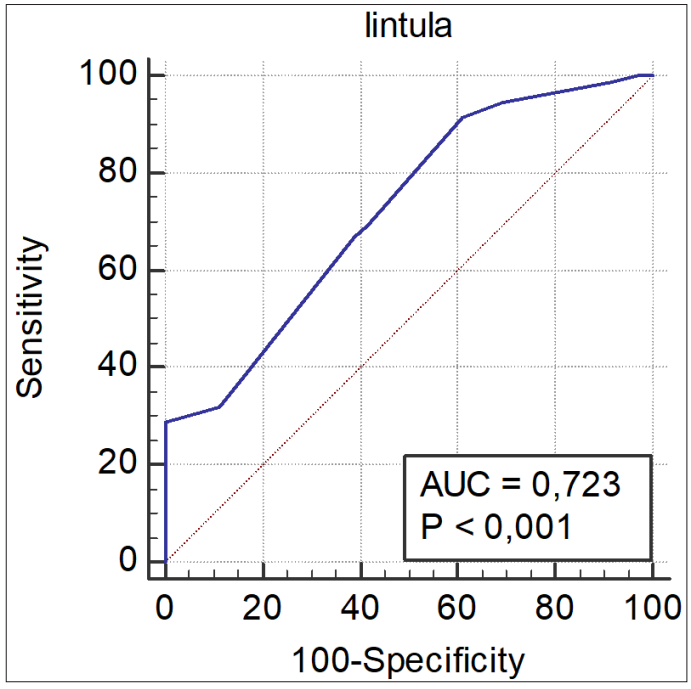

Figure 3. ROC curve of Lintula scores

Table 4.

Parameters		Mean±SD	Min-Max
Age		11.60±3.66	1–17
Lintula		19.53±4.38	6–35
PAS		8.18±1.29	3–11
AIR		4.99±1.87	1–9
		Frequency (n)	**Percentage (%)**
Gender	Male	129	57.1
	Female	97	42.9
USG	<6 mm	35	15.5
	≥7 mm	152	67.3
Pathology	Reactive lymphoid hyperplasia	36	15.9
	Acute appendicitis – suppurative/phlegmonous	168	74.3
	Perforated appendix	22	9.7
AIR	0–4	87	38.5
	5–8	135	39.3
	9–12	5	2.2
Lintula	≤15	30	13.3
	16–20	131	58.0
	≥21	65	28.8
PAS	0–4	4	1.8
	5	7	3.1
	≥6	215	95.1

DISCUSSION

Even though 80% of cases of appendicitis can be diagnosed through anamnesis and physical examination, and despite the availability of supportive laboratory and radiologic examinations, definitive appendicitis diagnoses are still an important issue in pediatric patients.[8,9] The increased complication risk associated with delayed diagnosis in children makes it vital that more efficient diagnostic tools be developed.[10,11]

Appendicitis scoring systems are helpful to establish a diagnosis and make a surgical decision in cases suspected of appendicitis based on patient history and physical examination results. Among these, the Pediatric Appendicitis Score (PAS) is a system developed to facilitate appendicitis diagnosis in pediatric patients, based on simple non-invasive clinical and laboratory assessments. It is easy to teach and apply, without any need for invasive tests. . Patients with PAS scores between 0 and 4 can be monitored in pediatric emergency departments and discharged with possible readmission in case of persistent symptoms. Patients with PAS scores of 5–6 may benefit from radiological examinations. Samuel evaluated the clinical findings of 1,170 patients aged 4–15 and reported a PAS score of ≥6 to be associated with a high probability of appendicitis.[12] A PAS score ≥7 indicated a high risk of appendicitis and such patients were recommended to have surgery without any other imaging techniques. The negative appendectomy (NA) rate was 1.8% in these patients, i.e. significantly lower than in most studies.[13] Several authors have proposed different cut-off values for PAS. For instance, Schneider et al. evaluated 588 suspected appendicitis patients (mean age: 11.9 years) and found the sensitivity and specificity of PAS ≥6 to be 82% and 65%, respectively. In two other studies, the sensitivity and specificity of PAS ≥7 were found to be 97.6–100% and 92–96%, respectively.[5,13] In the present study, the sensitivity and specificity of PAS >7 were found to be 82.1% and 69.4%, respectively.

Most of the appendicitis scoring systems have been initially developed for adult populations. Although these same tools are also used for pediatric cases, more pediatric-focused appendicitis scoring systems are needed toprovide more accurate results, which has led researchers to provide new scoring systems specifically for pediatric population. One of such systems is the Lintula scoring system. However, as this 9-item scoring system includes also non-surgical appendicitis cases, it is not 100% reliable. Therefore, these scoring systems alone are insufficiently precise to steer surgery or discharge decisions, and need to be supported by repeated clinical examinations. Lintula et al. reported negative appendectomy rates to be significantly lower in patients with a score of ≥21.[14] Yoldas et al. evaluated the results of 156 patients and determined the sensitivity and specificity to be 88.1% and 91.6%, respectively.[15] In the present study, the Lintula scoring system had the highest sensitivity value (91.5% for a score of >15), but the lowest specificity (38.8%) among the three appendicitis scoring systems tested. Accordingly, we conclude that the effectiveness of these scoring systems is associated with the determined cut-off values. The appendicitis scores should be combined with repeated clinical examinations. Using effective scoring systems can help support clinical diagnoses and can reduce negative appendectomy rates.

One disadvantage of the Lintula and PAS scoring systems is that they contain somewhat subjective assessment criteria. In contrast, the criteria of the AIR scoring system are more objective and practical for the pediatric patient population, as it excludes such subjective criteria as nausea, loss of appetite and the localization of pain. Macco et al. evaluated 747 patients and reported AIR to have superior positive predictive value and specificity when compared to other scoring systems.16 In the present study, the AIR score yielded more significant results in the perforated appendix patients, which we attribute to the CRP values included in the scoring, and suggest that this can be useful in preventing unnecessary use of imaging techniques.

Appendicitis scoring systems, as combined with following repeated clinical examinations and imaging techniques are used as tools to improve decision-making and appendicitis prediction in selected patients. Such systems also support ED decisions and minimize malpractices. Using scoring systems in clinical practice can even prevent unnecessary hospitalization.

An effective scoring system may serve as a tool to confirm the diagnosis, to determine which pediatric patients require additional diagnostic imaging, and to guide clinical monitoring or discharge decisions. Consistent with the literature, the present study determined that patients with a PAS score of >7 were most likely to be diagnosed with appendicitis, and we concluded that PAS would be a more supportive scoring system when compared to Lintula and AIR scoring systems.

CONCLUSION

There are still challenges in establishing a definitive appendicitis diagnosis, which include the unknown nature of an optimal assessment, the lack of a method with a 100% prediction rate and the presence of deficiencies in all scoring systems. . The use of scoring systems will be beneficial in busy ED conditions, although further studies involving larger populations are needed to improve and develop scoring systems that will aid in the provision of definitive diagnoses.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was granted ethical approval by the Adana City Training and Research Hospital Clinical Trials Ethics Committee (Date: 19/06/2019, Decision Number: 474).

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

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.

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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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.741846
J Contemp Med 2021;11(4):515-518

Orjinal Araştırma / Original Article

Variations in the Number and Drainage Levels of Retroaortic Left Renal Veins

Retroaortik Sol Renal Venlerin Sayı ve Drenaj Düzeylerindeki Varyasyonlar

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Abstract

Aim: Circumaortic left renal vein (CLRV) and retroaortic left renal vein (RLRV) are the most common variations of the left renal vein and have a retroaortic course. We aimed to detect the anatomical variations of retroaortic left renal veins in terms of their number and entrance levels into the inferior vena cava (IVC).

Materials and Method: The computed tomographic (CT) images of 2804 patients who had undergone abdominal CT examinations in our hospital retrospectively were evaluated.

Results: CLRV variations were detected in 139 (4.96%) patients while in another 132 (4.71%) RLRV variations were detected. Double branches were present in 15 (10.8%) patients in the RLRV group, and 3 patients (2.3%) in the CLRV group. The most common drainage levels into the IVC for these variations were the L3 vertebra level and the middle 1/3 infrarenal IVC segment.

Conclusion: CLRV and RLRV may possess single or double retroaortic branches. The entrance levels into the IVC are various in these variations. Knowing these variations is important for surgical and interventional procedures.

Keywords: Renal veins, vena cava inferior, computed tomography

Öz

Amaç: Sirkumaortik sol renal ven (CLRV) ve retroaortik sol renal ven (RLRV), sol renal venin en yaygın varyasyonlarıdır ve retroaortik seyir gösterir. Retroaortik sol renal venlerin anatomik varyasyonlarını sayıları ve inferior vena cava'ya (IVC) giriş seviyeleri açısından tespit etmeyi amaçladık.

Gereç ve Yöntem: Hastanemizde retrospektif olarak abdominal BT incelemesi yapılan 2804 hastanın bilgisayarlı tomografik (BT) görüntüleri değerlendirildi.

Bulgular: CLRV varyasyonları 139 (% 4.96) hastada tespit edilirken, 132 (% 4.71) hastada RLRV varyasyonu tespit edildi. RLRV grubunda 15 (% 10.8) hastada ve CLRV grubunda 3 hastada (% 2.3) çift dal mevcuttu. Bu varyasyonlar için IVC'ye en yaygın drenaj seviyeleri, L3 vertebra seviyesi ve orta 1/3 infrarenal IVC segmentidir.

Sonuç: CLRV ve RLRV, tek veya çift retroaortik dallara sahip olabilir. IVC'ye giriş seviyeleri bu varyasyonlarda çeşitlidir. Bu varyasyonların bilinmesi, cerrahi ve girişimsel prosedürler için önemlidir.

Anahtar Kelimeler: Renal venler, vena cava inferior, bilgisayarlı tomografi.

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Received *(Geliş Tarihi)*: 06.05.2021 **Accepted *(Kabul Tarihi)*:** 23.05.2021

INTRODUCTION

The left renal vein (LRV) normally passes across the aorta from the frontal aspect, before entering the inferior vena cava (IVC). In the retroaortic left renal vein (RLRV) variation, the LRV passes from the posterior aspect of the aorta. In the circumaortic left renal vein (CLRV), there are two LRV branches, one passing in front of the aorta, and the other passing from behind.[1] In CLRV and RLRV, there are further variations in both the number and the entrance levels into the IVC. In this study, we aimed to define variations of retroaortic left renal veins.

MATERIAL AND METHOD

For the study, abdominal computed tomography (CT) examinations of patients referred from various departments with various indications between May 2017 and June 2017 were evaluated retrospectively. Patients with left nephrectomy and renal agenesis, together with those patients whose left renal veins could not be evaluated well enough, were excluded from the study, and the remaining 2804 patients were taken into consideration. These patients were evaluated for the presence of a retroaortic LRV branch.

We classified the retroaortic LRV drainage levels to the IVC according to the IVC segment and the lumbar vertebrae/disc level. The separation of the IVC into its segments was based on the right renal vein. The level that right renal vein reaches to the IVC is renal, above renal is suprarenal, below renal is infrarenal IVC until iliac bifurcation. We divided the infrarenal IVC into three according to its length: proximal, middle, and distal 1/3.

The CT examinations of the patients were performed with two GE Optima 520 scanners. The scanners were products of the year 2014, and they were 16-detector multislice machines. 5-mm-thick slices were obtained for the examinations.

The categorical measurements were defined as numbers and percentages, and the numerical measurements as the mean and standard deviation values. Median and minimum-maximum values were used if necessary, for numerical measurements. The Chi-Square Test was utilized in order to compare and evaluate the variation frequencies in accordance with gender distribution. The IBM SPSS Statistics Version 20.0 pocket program was utilized for all statistical analyses. The statistical significance level was 0.05 in all tests.

RESULTS

Of the 2804 patients, 1581 (56.4%) were males, and 1223 (43.6%) were females. The mean age of the patients was 45.4±20.2 years (± SD). The ages varied between 1 – 112 years and the median was 46.

A retroaortic branch of the LRV was present in 271 (9.7%) patients. The ages of the patients with variations varied between 2 and 90 years and the mean±SD was 44.7±19.6 .

We found the prevalence rates 4.96% and 4.71% for CLRV and RLRV, respectively. In total, variations were detected in 8.6% of males and 11% of females. Our study demonstrated no gender differences in CLRV and RLRV variations. But other than that, we demonstrated that the LRV variations were more frequent in females when the total numbers were considered and the subgroups were not taken into consideration (P=0.030).

The retroaortic branch was singular in 136 (98%) of the 139 CLRV patients, while 3 (2%) patients had double retroaortic branches. In 117 (88.6%) of the 132 RLRV patients, there was a single retroaortic LRV, whereas the remaining 15 (11.4%) patients demonstrated double retroaortic LRVs.

The entrance levels of the retroaortic branches into the IVC in the LRV variations, in accordance with the lumbar vertebra /disc levels, are shown in **Table 1**, and according to the segments of the IVC are shown in **Table 2**.

Table 1. The entrance levels of the retroaortic branches into the IVC in the LRV variations, in accordance with the lumbar vertebra /disc levels.

Lumbar vertebra and intervertebral disc levels	CLRV with single retroaortic branch no. (%)	RLRV with single retroaortic branch no. (%)	CLRV with double branches no. (%)	RLRV with double branches no. (%)	Total no. (%)
L1		4 (3)			4 (1.4)
L1-L2	2 (1)	5 (4)			7 (2.4)
L2	52 (38)	34 (29)	1 (17)	6 (20)	93 (32.2)
L2-L3	24 (18)	15 (13)	2 (33)	7 (23)	48 (16.6)
L3	51 (38)	42 (36)	3 (50)	12 (40)	108 (37.4)
L3-L4	3 (2)	7 (6)		2 (7)	12 (4.2)
L4	1 (1)	9 (8)		3 (10)	13 (4.5)
L4-L5	1 (1)	1 (1)			2 (0.7)
L5					
L5-S1	2 (1)				2 (0.7)
Total	136 (100)	117 (100)	6 (100)	30 (100)	289 (100)

CLRV: Circumaortic left renal vein, RLRV: Retroaortic left renal vein

Table 2. Segmental distribution of IVC entry levels of posterior branches in the left renal vein variations.

IVC segments	CLRV with single retroaortic branch no. (%)	RLRV with single retroaortic branch no. (%)	CLRV with double branches no. (%)	RLRV with double branches no. (%)	Total no. (%)
Suprarenal	1 (1)				1 (0.3)
Renal	4 (3)	10 (8.6)		3 (10)	17 (5.9)
Proximal IR	46 (34)	33 (28.2)	3 (50)	8 (26.7)	90 (31.1)
Middle IR	70 (51)	49 (41.8)	3 (50)	13 (43.3)	135 (46.7)
Distal IR	12 (9)	16 (13.7)		4 (13.3)	32 (11.1)
Bifurcation		7 (6)		1 (3.3)	8 (2.8)
Left iliac vein	3 (2)	1 (1)		1 (3.3)	5 (1.7)
Azygos vein		1 (1)			1 (0.3)
Total	136 (100)	117 (100)	6 (100)	30 (100)	289 (100)

IVC: Inferior vena cava, CLRV: Circumaortic left renal vein, RLRV: Retroaortic left renal vein, IR: Infrarenal

Regardless of the type of variation, the most frequent association that retroaortic branch of the LRV is drained into IVC was between L3 and middle 1/3 infrarenal IVC (22%).

When we classified CLRV preaortic and retroaortic branches according to whether it is separate or connected at the renal hilus , the findings were as follows: in 96 patients with single retroaortic branch they were connected, in 40 patients with single retroaortic branch they were separate and in 3 patients with double retroaortic branches all of them were connected. Of the 139 cases, 99 cases have had connected branches (71.2%) and 40 cases have had separate branches (28.9%).

The diameters of the preaortic and retroaortic branches in the CLRV patients were compared, and thus the dominant branch was evaluated. Dominant anterior branch, equality and dominant retroaortic branch were determined 46%, 32%, and 22%, respectively.

DISCUSSION

Case reports are available on the number of left retroaortic renal veins and entrance levels to the inferior vena cava but, our study is the first study on this subject in the literature. Sabouri et al. have reported a double RLRV case.[2] In our study, we detected this variation to be 0.5 % in the general population and 11.4 % in the RLRV variation population (**Figure 1**). Sutariya[3] reported a double RLRV in which the first one drains into IVC and the second one to the left iliac vein. In our study, one of the 15 double RLRV cases was of this type. We detected the prevalence of this variation as 0.04 % in the general population. Pallangyo et al.[4] have reported a sickle cell trait case, in which both of the preaortic renal veins drained into the IVC, while the posterior divisions drained into the azygos vein in the right and the hemiazygos vein in the left. In one case of our study, the RLRV drained into the azygos vein and had no connection with the IVC. Brancatelli et al.[5] have reported an RLRV which entered into the left iliac vein. Karaman et al.[6] have published an article reporting RLRV variations draining into the left iliac vein in 3 of the 1856 cases they had studied. In our study of 2804 patients, we detected 1 RLRV case with drainage into the left iliac vein. In our 3 CLRV cases, the retroaortic branch drained into the left iliac vein; while there was an IVC drainage at the bifurcation level in 7 RLRV cases and 1 double RLRV case. Nguyen[7] has reported two cases with double left renal veins, both of which demonstrated a first renal vein at the normal location, and second renal veins at abnormal drainage levels. In the first case, this vein drained into the left common iliac vein after crossing the left common iliac artery posteriorly, while in the second case the vessel drained into the distal IVC after crossing the aorta posteriorly. In our study, we categorized these and similar cases as CLRV variations, because of the fact that one of the renal veins crossed the aorta anteriorly, while the other crossed the aorta or left main iliac artery posteriorly.

Matsunaga et al.[8] have reported a CLRV case in which the retroaortic branch followed an oblique course and drained into the IVC at a more caudally located level compared to that of the preaortic branch. The CLRV variation has been defined as a left renal vein complex in which two branches, one preaortic and the other retroaortic, cross the aorta circumferentially and thus form a venous collar.[9] We saw in our study that these two branches are never at the same level, and the preaortic branch is always located more cranially while the retroaortic one is always located more caudally.

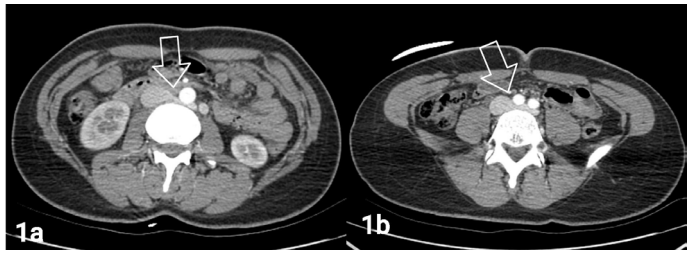

Figure 1. Contrast-enhanced axial upper abdominal CT scans in a 27-year-old female patient with a double RLRV variation. The more cranially located branch drains into the middle 1/3 infrarenal IVC segment, which is approximately the L2 - L3 disc level (**1a**). The more caudally located branch, on the other hand, drains into the left iliac vein, which is approximately at the L4 vertebra level (**1b**).

The drainage levels of the renal veins into the inferior vena cava in the adult population are reported to be at the T12 – L2 levels.[10] We found out that 185 of the 289 retroaortic veins, drained into the IVC below the L2 level (64%). We saw in our study that the retroaortic left renal veins drained into the IVC mostly at the L3 level. The IVC level which the renal veins drain into is called the renal IVC segment. But in our study we found out that the retroaortic left renal veins mostly drained into the IVC at the infrarenal level, the middle 1/3 infrarenal segment being the most frequent one. This means that the retroaortic left renal veins travel on a more angular and oblique course and drain into the IVC more caudally. The reason for this formation might be the compression of the vein between the aorta and the lumbar vertebrae.

When the preaortic and retroaortic branches of the CLRV cases were compared according to their diameters, it was found that mostly the preaortic branch was wider than the retroaortic branch. The main branch is the anterior branch. Again, this may be due to the compression of the retroaortic branch between the aorta and the vertebrae, too.

The limitation of our study is, the patients who have been performed abdominal CT with different indications, will not reflect the general population.

CONCLUSION

Left renal vein variations are not clinically evident, but they are the most commonly encountered renal vein variations. These variations may have further variations in the number of branches and entrance levels into the IVC. Knowing these variations is extremely important for safe surgical and interventional procedures .

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval was obtained from the local Ethical Committee (meeting number: 66 Cukurova University Medical School (07.07.2017)).

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.

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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JOURNAL OF
CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.738510
J Contemp Med 2021;11(4):519-525

Orjinal Araştırma / Original Article

Evaluation of Nursing Students' Nursing Undergraduate Program and Determination of Their Opinions on Education

Hemşirelik Öğrencilerinin Hemşirelik Lisans Programını Değerlendirmeleri ve Eğitime İlişkin Görüşlerinin Belirlenmesi

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Abstract

Objective: This study was conducted to evaluate the nursing undergraduate program of fourth grade nursing students and to determine their opinions on education.

Material and Method: The sample of the descriptive and cross-sectional study consisted of 131 fourth grade nursing students who agreed to participate in the study in the 2018-2019 academic year. The data of the research were collected with The Introductory Information Form and the Bachelor's Degree Nursing Program Assessment Scale. The total score of Bachelor's degree nursing program assessment scale is 100, and the low score indicates that the program's effectiveness is negative and the high score is the program's effectiveness. Frequency, mean, percentage values, correlation analysis and Mann-Whitney U test were used to evaluate the data.

Results: It was found that 53,4% of the students thought to work as a clinician after graduation and 87% thought that there was a difference between theoretical education and clinical practices in the nursing education. The most common reason leading to difference is respectively; It was determined that the number of students was high (74.8%), insufficient application areas (63.4%), and the lack of teaching staff (47.3%). In order to overcome this difference of students; It has been determined that it makes suggestions such as strengthening the cooperation between clinical nurses and teaching staff (61.1%), establishment of simulation laboratories in schools (58,8%) and ensuring that the teaching staff deficit is in clinics (55%). The mean score of the students to evaluate the undergraduate program in nursing was 61.1±19.8.

Conclusion: It was determined that the majority of students stated that there was a difference between theoretical education and clinical practices in nursing and they evaluated the undergraduate program in nursing as close to positive.

Keywords: Nursing education, nursing students, bachelor program, theory

Öz

Amaç: Bu araştırma, hemşirelik dördüncü sınıf öğrencilerinin hemşirelik lisans programını değerlendirmeleri ve eğitime ilişkin görüşlerinin belirlenmesi amacıyla yapıldı.

Gereç ve Yöntem: Tanımlayıcı ve kesitsel tipte olan çalışmanın örneklemini 2018-2019 eğitim-öğretim yılında araştırmaya katılmayı kabul eden 131 dördüncü sınıf hemşirelik öğrencisi oluşturdu. Araştırmanın verileri "Tanıtıcı Bilgi Formu" ve "Hemşirelikte Lisans Programını Değerlendirme Ölçeği" ile toplandı. Hemşirelikte lisans programını değerlendirme ölçeğinin toplam puanı 100 olup, düşük puan programın etkinliğinin olumsuz, yüksek puan ise program etkinliğinin olumlu olduğunu göstermektedir. Verilerin değerlendirilmesinde frekans, ortalama, yüzde değerleri, korelasyon analizi ve Mann-Whitney U testi kullanıldı.

Bulgular: Öğrencilerin %53,4'ünün mezuniyet sonrası klinisyen olarak çalışmayı düşündüğü ve %87'sinin hemşirelik eğitiminde teorik eğitim ve klinik uygulamalar arasında farklılık olduğunu düşündüğü saptandı. Farklılığa yol açan en sık nedenin sırasıyla; öğrenci sayısının fazlalığı (%74,8), uygulama alanlarının yetersizliği (%63,4) ve öğretim elemanlarının öğrencilerin yanında olamaması (%47,3) şeklinde olduğu tespit edildi. Öğrencilerin bu farklılığın giderilmesi için; klinik hemşireleri ile öğretim elemanları arasındaki iş birliğinin güçlendirilmesi (%61,1), okullarda simülasyon laboratuvarlarının kurulması (%58,8) ve öğretim elemanı açığının giderilerek kliniklerde olmalarının sağlanması (%55) şeklinde önerilerde bulunduğu belirlendi. Öğrencilerin Hemşirelikte Lisans Programını Değerlendirme Ölçeği toplam puan ortalamasının ise 61,1±19,8 olduğu saptandı.

Sonuç: Öğrencilerin çoğunluğunun hemşirelikte teorik eğitim ve klinik uygulamalar arasında farklılık olduğunu ifade ettiği ve hemşirelikte lisans programını olumluya yakın olarak değerlendirdikleri tespit edildi.

Anahtar Kelimeler: Hemşirelik eğitimi, hemşirelik öğrencileri, lisans programı, teori

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Received *(Geliş Tarihi)*: 16.05.2020 **Accepted *(Kabul Tarihi)*:** 02.03.2021

INTRODUCTION

Nursing with its independent and collaborative roles is a professional occupational group providing care to every healthy or sick individual, family and society.[1] In recent years nursing profession not only has taken important responsibilities such as protecting and promoting health and healing diseases, but also has played a key role in solving healthcare system problems in the world and in Turkey.[2] Accordingly, it stands out to conduct nursing services effectively. Nursing services ground on nursing education. Education is defined as a process of creating terminal changes in an individual's behaviors. When considering the nursing education process in the world, it is seen that three-or-four-year undergraduate education is provided after 10-12 years of education. The Munich Declaration, which was published in the Second European Conference on Nursing and Midwifery and includes also the approval of Turkey, discussed conducting nursing education in undergraduate and postgraduate programs. In this context, the minimum period of education in nursing undergraduate programs is four years and it is required to complete 4600 hours of theoretical and practical training in order to graduate from this program.[3-5] As is known, nursing education comprises of theoretical and clinical teaching related to nursing profession.[6] For that purpose, theoretical courses are taught in schools, while clinical teaching is conducted in skill or simulation laboratories and clinical practice fields. With clinical teaching, it is aimed to enable students to transfer knowledge into clinical practice and transit from studentship to professionalism.[7] Clinical teaching, which is an important process for training an equipped nurse, comprises the half of nursing education. The most important educational goals of clinical teaching include enabling students to integrate the basic scientific knowledge they have acquired previously into the skills in practice and become competent in diagnosis, treatment and patient care.[8] In order to achieve these goals, students expect support, guidance and assistance especially in applications that require skills in clinical practice fields.[9,10] In order to ensure competence in processes that require skill, it is particularly required that students are supported by both instructors and clinic nurses in the practice field and theoretical training and clinical training substantially coincide.[11-13] However, sometimes theoretical training and clinical practice do not coincide and they even diverge completely at some points. In order to solve these differences, it is crucial that theoretical training and clinical practice are parallel. In this sense, the importance of school and hospital collaboration comes into prominence. This is because the clinical teaching process covers not only students, but also instructors and clinic nurses. In addition to the problems faced by students, determining the problems experienced by instructors and clinic nurses in the clinical teaching process will be effective on generating solutions to the problems.[13] In the literature, studies, examining the problems faced by students in the clinical teaching process, are remarkable.[7,8,14-18] In these studies, the students stated that they tried to give holistic care to patients in clinical practice as taught in theoretical courses; however, the unconformity between theory and practice was confusing, thus resulting in created a dilemma.[19-21] In similar studies examining the first clinical practice experience of nursing students, the students usually stated that there was no connection between theory and practice, the real setting in the clinic was highly different from what was taught in theoretical training, they experienced a gap between theory and practice and because of this gap they were not able to conduct evidence-based applications in the clinics.[20-23] Upon literature review, it has been seen that various problems are faced in nursing education in Turkey; however, the number of studies on the views and recommendations of final year nursing students regarding the differences between theoretical training and clinical practice, is limited.[13,15] Thus, in this study it was aimed to have fourth-year students receiving education in nursing department in a Faculty of Health Sciences assess the nursing undergraduate program and to examine their views on education.

Study Questions

1. Is there any difference between theoretical training and clinical practice in nursing education? If yes, what are the reasons of this difference?
2. What are the recommendations of students to eliminate the differences between theoretical training and clinical practice?
3. How do students assess the effectiveness of the nursing undergraduate program that they are about to graduate from?

MATERIAL AND METHOD

Type of the Study

This is a descriptive study.

Population/Sample

The study was conducted in the nursing department of faculty of health sciences at a university in Turkey. The population of the study consisted of fourth-year students from the nursing department in the aforementioned faculty (N=250). No sample selection was not used for this study and it was aimed to reach the entire population. However, the study was completed with 131 students who agreed to participate in the study and whose verbal consent was obtained. It was determined that participation rate for the study was 52.4%.

Data Collection Tools

The researchers collected the data through face-to-face interview via the "Introductory Information Form" and "Bachelor's Degree Nursing Program Assessment Scale" when the students were available.

Introductory Information Form: Prepared by the researchers in line with the literature, the form has a total of eight questions regarding the socio-demographic characteristics of students such as age and gender as well as nursing education.[24,25]

Bachelor's Degree Nursing Program Assessment Scale (BNPAS): Developed by Demiralp et al.[26] (2014) to evaluate the effectiveness of undergraduate program in nursing, the scale has a total of 40 items. The scale comprises four subscales as; "Assessment of Professional Development and Competence" (11 items), "Assessment of Teaching Process" (8 items), "Assessment of Individual Development" (11 items), "Gaining Universal, National and Professional Values" (10 items). When applying the scale, participants are asked to rate each item from 1 to 10. BNPAS is a tool which can be completed in about 15-20 minutes and has a total score ranging from 40 to 400. When the score obtained is divided into four, the total score given for the program is assessed over 100. The Cronbach's Alpha internal consistency value was found to be 0.97 for the original scale and range from 0.91 to 0.95 for the four subscales. In this study, the Cronbach's Alpha value was found to be 0.64 for the scale and range from 0.61 to 0.80 for the four subscales. Lower scores indicate a negative effectiveness for the program, while higher scores indicate a positive effectiveness.

Data Assessment

The data acquired as a result of the study were analyzed in the Statistical Package for Social Sciences (SPSS) 24.0 package program. Compatibility of the data to normal distribution was performed with Shapiro-Wilk test. Also, the data were evaluated via frequency, percentage, minimum, maximum values, standard deviation, arithmetic mean, Pearson's correlation analysis and Mann-Whitney U test.

Ethical Considerations

Prior to conducting the study, written permissions were obtained from the institution where the study was conducted, Clinical Trials Ethics Committee (Date/Decree no: 2018/303), and the authors who conducted the validity and reliability for the use of the scale. Moreover, the students were informed about the study purpose and their verbal consent was obtained within the scope of voluntariness and willingness principles.

RESULTS

Descriptive Characteristics of the Students

It was determined that mean age of the students was 22.0±1.3 years. Of the students, 65.6% were female and 51.9% were residing in a metropolis. 53.4% of the students considered to work as a clinician after graduation.

Views of the Students on Nursing Education

It was determined that 87% of the students thought that there was a difference between theoretical training and clinical practice in nursing education (**Table 1**).

Views of the Students on the Reasons of the Difference between Theoretical Training and Clinical Practice in Nursing Education

It was determined that the nursing students ordered the reasons of the difference between theoretical training and clinical practices respectively as follows; excessive number of students (74.8%), inadequacy of fields of practice (63.4%), lack of support by instructors for students (47.3%), inadequate number of instructors (44.3%), excessive work load of nurses (40.5%) and insufficiency of instructors and nurses as a role model in the clinic (38.2%) (**Table 1**). Also it was determined that not considering students as a member of the medical team in the clinic (37.4%), inadequate collaboration between clinic nurses and instructors (36.6%), and inability of reflecting works of instructors to clinical practices (36.6%) were among reasons of the difference between theoretical training and clinical practice in nursing education. Moreover, the students indicated that inadequate number of nurses (32.8%), inability of instructors to be assigned actively in the clinic because theoretical courses are taught in school and clinical practices are performed in many different institutions (32.1%) and intense content of theoretical courses (24.4%) were among other reasons of the difference between theoretical training and clinical practice in nursing education (**Table 1**).

Table 1. Views of the students on theoretical training and clinical practice in nursing (N=131)

Is there any difference between theoretical training and clinical practice in nursing education?	Yes	No
	87%	17%
Reasons of the difference	**n***	**%**
Excessive number of students	98	74.8
Inadequacy of fields of application	83	63.4
Lack of support by instructors for students	62	47.3
Inadequate number of instructors	58	44.3
Excessive work load of nurses	53	40.5
Insufficiency of instructors and nurses as a role model in the clinic	50	38.2
Not considering students a member of the medical team in the clinic	49	37.4
Inadequate collaboration between clinic nurses and instructors	48	36.6
Inability of reflecting works of instructors to their studies in clinical practices	48	36.6
Inadequate number of nurses	43	32.8
Inability of instructors to be assigned actively in the clinic because theoretical courses are taught in school and clinical practices are performed in many different institutions	42	32.1
Intense content of theoretical courses	32	24.4

*n multiplied.

Recommendations of the Students to Eliminate the Difference between Theoretical Training and Clinical Practices in Nursing Education

It was determined that recommendations of the students to eliminate the difference between theoretical training and clinical practices were strengthening the collaboration between clinic nurses and instructors (61.1%), establishing simulation laboratories in schools (58.8%) and meeting the instructor deficit and having instructors be available in the clinic at all times (55%).

Other recommendations of the students to eliminate the difference between theoretical training and clinical practice in nursing education included having a guide nurse in every clinic, subjecting her to in-service training by instructors and updating her knowledge (48.9%), sharing the results of academic researches by instructors with clinic nurses and reflecting these results to care (42.7%), updating clinical training program and training objectives regularly (42%), and enabling instructors and clinic nurses to work in collaboration in studies related to nursing profession (38.2%) (**Table 2**).

Table 2. Recommendations of the students to eliminate the difference between theoretical training and clinical practice (N=131)

Recommendations	n*	%
Strengthening the collaboration between clinic nurses and instructors	80	61.1
Establishing simulation laboratories in schools	77	58.8
Meeting the instructor deficit and having instructors be available in the clinics at all times	72	55
Having a guide nurse in every clinic, subjecting her to in-service training by instructors and updating her knowledge	64	48.9
Sharing the results of own researches by instructors with clinic nurses and reflecting these results to care	56	42.7
Updating clinical training program and training objectives regularly	55	42
Enabling instructors and clinic nurses to work in collaboration in studies related to nursing profession	50	38.2

*n multiplied.

The Bachelor's Degree Nursing Program Assessment Scale Mean Score of the Students and Their Score Distribution According to Some Characteristics

It was seen that the Bachelor's Degree Nursing Program Assessment Scale total mean score of the students was 246.18±79.08. As a result of assessing the scale score on the basis of 100 points, it was determined that the BNPAS mean score of the students was 61.1±19.8 (**Table 3**). It was determined that there was no significant correlation between the age of the students and total scale score (r=0.105, p=0.232). Also, there was no significant correlation between the age of the students and the division of the total scale score into four (r=0.105, p=0.234). It was determined that there was no statistically significant difference between the gender of the students (p=0.346), the field they intended to work in after graduation (p=0.894) and the total scale score and the division of the total scale score into four (**Table 3**).

Table 3. The Bachelor's Degree Nursing Program Assessment Scale total mean score of the Students and Their Score Distribution According to Some Characteristics (N=131)

Characteristics	The Bachelor's Degree Nursing Program Assessment Scale Total Score		The Bachelor's Degree Nursing Program Assessment Scale Total Score/4	
	Test statistics	p	Test statistics	p
Age*	0.105	0.232	0.105	0.234
Gender**	-0.943	0.346	-0.943	0.346
Field intended to work in after graduation**	-0.134	0.894	-0.143	0.886

*Correlation analysis **Mann-Whitney U test

DISCUSSION

Nursing education is an educational process in which theoretical training and clinical practice coexist. Main objectives of this education are to add professional nursing skills to students and prepare them to their professional life after graduation.[4,27-30] In this study, most of the final-year nursing students indicated that there was a difference between theoretical training and clinical practice of nursing education. In the national and international studies, nursing students have stated that there is an unconformity and a gap between theoretical training and clinical practices of nursing profession.[20,22,23] The results obtained from this study are compatible with the literature.

Most of the students who were included in the study associated the reasons of the difference between theoretical training and clinical practice in nursing education with excessive number of students and thus inadequacy of fields of practice. Today, most hospitals are unable to accept students for clinical practice within the scope of the Law of Occupational Health and Safety numbered 6331. Limitation of the number of hospitals to conduct clinical practice, which forms the basis of nursing education, brings the problem of students doing practice with more crowded groups into prominence. Despite nursing departments which gradually extend their quota every year, limitation of clinical practice areas affects the quality of nursing education negatively.[4] Also in the studies, practice-related problems included being unable to receive adequate feedback due to overcrowded groups in clinical practice and thus making mistakes more frequently.[17,20] In this study, it was determined that more than half of the students recommended "establishing simulation laboratories in schools" to eliminate the difference between theoretical training and clinical practices. Simulation training, which is a different teaching strategy in nursing education, is among modern techniques in which students take part in education actively and experience nearly the most realistic clinic experience, the trainer is a role model, students have the opportunity of considering and evaluating the knowledge learned, reabsorbing the knowledge and comparing it with the previous knowledge.[31,32]

In the present study, the students indicated that inadequate number of instructors, their lack of support for students, and their inability of being assigned actively in the clinic because theoretical courses are taught in school and clinical practices are performed in many different institutions were among the reasons of the difference between theoretical training and clinical practice. According to the Report of Workshop of Undergraduate Education in Nursing, the number of students per instructor in Turkey is 45 and the number of students per lecturer is 113 by 2017.[33] Moreover in the literature, it is recommended that instructors be integrated into the clinic and the instructor deficit be fulfilled in order to increase the quality in nursing education.[3,34]

The students who were included in the study stated that excessive work load of nurses (40.5%) and inadequate number of nurses (32.8%) were the reasons of the difference between theoretical training and clinical practice. According to the sixth article of the Nursing Regulations (2010), it is stated that nurses conduct training, counseling and research activities related to nursing. They participate in scientific activities related to their profession. They support and contribute to the education of society, student nurses, healthcare professionals and healthcare professional candidates.[35] Accordingly, it can be asserted that clinic nurses play a key role in student education. Morrison and Brennaman[36] (2016) stated that nurses have many responsibilities in the clinic and they need extra time and effort for the professional development of students. In contradistinction to the results of this study, Hanson et al.[37] (2018) stressed in their study that as the time spent by students in the clinic increased, nurses became more ambitious to teach, considered students a burden at a lower rate and spent more time especially with fourth-year students because they would think that these students were closer to the profession. Accordingly, it is believed that factors such as individual characteristics arising from students and nurses, different conditions of the field of application and patient needs may affect the nurse-student collaboration and thus these factors should be taken into consideration.

In the present study, more than one third of the students indicated that instructors and nurses are not adequate in being a role model in the clinic and the collaboration between clinic nurses and instructors was insufficient. In parallel with these results, in the study conducted by Akgün Kostak et al.[38] students stated that nurses were not a good role model, they did not participate in clinical training adequately and they did not take responsibility in clinical training. However, in another study conducted on this issue it was stressed that 77.6% of nurses considered themselves a role model.[39] Clinical instructiveness also contains role modeling and is different from instructiveness. Everyone whom the person interacts with either directly or indirectly and who may affect his/her decisions and behaviors can be a role model.[40,41] As a result of the studies conducted within this scope, it is thought that students will have a difficulty adapting to the clinic, to the profession and putting what they learn in theoretical trainings into practice. For the solution to these problems, it can be recommended to create standards related to clinical teaching, strengthen the school-hospital, instructor and nurse collaboration within the frame of student-centered education and enhance communication. It is because the parameters increasing the quality of nursing education include a good communication between clinician and academician nurses, transfer of knowledge-skills to student nurses, generation of solutions in common problems together and doing collaboration.[42,43] Another approach to increase this communication and collaboration is to reflect the scientific studies conducted by instructors to clinical practices.[42,43]

In this study, more than one third of the students stated that there was a difference between theoretical training and clinical practice due to the inability of instructors to reflect their works to clinical practices. In parallel with this result, nearly half of the students stated that the difference between theoretical training and clinical practice could be fulfilled as long as instructors shared the results of their academic researches with clinic nurses and reflected these results to care. In the study by Özcan[44] it was stressed that school-hospital collaboration could contribute to education. Also, it is indicated that reflecting the results of studies conducted by instructors to the clinic will affect student education and patient care positively.

Nearly one fourth of the students who were included in the study stated that intense content of theoretical courses created a difference between theoretical training and clinical practice. In the literature, it is stressed that curriculum is one of the most important factors affecting the quality of education.[3,4,33] In a different study, the students were asked how a school-hospital correlation should be and a great majority of them (74.9%) explained that theoretical training should be provided adequately not only in school, but also in the hospital or clinic setting. A study conducted by Kayacan Keser et al.[24] support these results.

In this study, it was determined that the students evaluated the effectiveness of undergraduate program in nursing as "close to positive". This result makes us think that theoretical and clinical knowledge, skills, communication, professional tasks and responsibilities in student trainings conducted by instructors and nurses are usually included in nursing education integratedly. However, there are also different results on this issue. In a study, more than half of nursing students stated that the nursing education they received was not sufficient for the scope and processes of the profession, patient services and community services.[45] In a study conducted by Dönmez and Karaöz Weller[46] (2019) to evaluate the education of final year nursing students it was concluded that a limited number of students stated that the education they received in school was adequate for developing their clinical practice. Likewise, Yiğit et al.[47] (2007) reported in their study that only one fifth of students found the education they received to be fully adequate for developing their skills. In the light of these results, it is believed that as long as differences between theoretical training and clinical practice in nursing education are minimized, the quality of nursing profession may increase.

Limitations of the Study: Limitations of the study were that it was conducted in only one institution and the entire population could not be reached. Also, the data acquired were dependent on the form created by the researchers and the scale used.

CONCLUSION

It was determined that most (87%) of the students preparing to graduate from the nursing department thought that there was a difference between theoretical training and clinical practice in nursing education and evaluated the effectiveness of undergraduate program in nursing as "close to positive". In the light of the data acquired, in order to eliminate the difference between theoretical training and clinical practice in nursing education, it can be recommended that;

- field of application and school collaboration be arranged with protocols before clinical practice,
- feedback be received from nurses and students before and after clinical practice,
- guide nurses be used in the application,
- a collaboration be ensured between instructors and clinic nurses and in-service trainings be arranged,
- standards be created for clinical practices.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Clinical Trials Ethics Committee (Date/ Decree no: 2018/303).

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.

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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JOURNAL OF
CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.846646
J Contemp Med 2021;11(4):526-530

Orjinal Araştırma / Original Article

Association of Nurses' Empathic Tendency and Attitudes to Ageism Toward Older Adults

Hemşirelerin Empatik Eğilimi ile Yaşlılara Yönelik Ayrımcılık Tutumları Arasındaki İlişkisi

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Abstract

Objective: This study aims to determine the correlation of nurses empathic tendency and ageism attitudes towards older adults

Material and Method: A descriptive and correlational with a convenience sample of 132 Turkey nurses was conducted in April-June 2017. Structured question form, Scale of Empathic Tendency and Fraboni Scale of Ageism (FSA) were applied to nurses.

Results: The regression model used in the study explains 16% of the factors affecting ageism in nurses. In this model, factors that remained negative attitude toward the elderly were female, obtaining information about the elderly from the media and willingness to care for the elderly ($p<0.05$).

Conclusion: This study found that ageism and empathic tendencies of nurses were at moderate level. It is important to develop the empathic tendencies of nurses in preventing ageism. Accordingly, it can be suggested that nurses' knowledge on this subject should be improved with evidence-based practices.

Keywords: Ageism, empathy tendency, older adult, nursing care

Öz

Amaç: Bu çalışma, hemşirelerin empatik eğilim ve yaşlı ayrımcılığı düzeyleri arasındaki ilişkiyi belirlemek amacıyla yapıldı.

Gereç ve Yöntem: Tanımlayıcı ve ilişkisel tipteki çalışma Nisan-Haziran 2017 tarihleri arasında 132 hemşire ile gerçekleştirildi. Hemşirelere yapılandırılmış soru formu, Empatik Eğilim Ölçeği ve Fraboni Ayrımcılık Ölçeği uygulandı.

Bulgular: Çalışmada kullanılan regresyon modeli hemşirelerde yaşlı ayrımcılığını etkileyen faktörlerin %16'sını açıkladı. Negatif yaşlı ayrımcılığı üzerine kadın olma, yaşlıya dair bilgileri medyadan elde etme ve yaşlı bakımında gönüllü olmamanın etkili olduğu belirlendi.

Sonuç: Bu çalışmada, hemşirelerin yaşlı ayrımcılığı ve empatik eğilim puanları orta düzeydeydi. Yaşlı ayrımlığının önlenmesinde hemşirelerin empatik eğilimlerinin geliştirilmesi önemlidir. Bu doğrultuda hemşirelerin bu konudaki bilgilerinin kanıta dayalı uygulamlarla geliştirilmesi önerilebilir.

Anahtar Sözcükler: Ayrımcılık, empatik eğilim, yaşlı, hemşirelik bakımı

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Received *(Geliş Tarihi)*: 24.12.2020 **Accepted *(Kabul Tarihi)*:** 24.04.2021

INTRODUCTION

Old age is a natural and inevitable process all people will experience. The elderly population in the world and in our country is increasing gradually with decreasing fertility, improved nutritional conditions, improvements in health services and the control over infectious diseases.[1] According to the United Nations data, 12.3% of the world population is comprised of people who are 60 and over.[2] In Turkey, While the proportion of the elderly people in the total population was 7.7% in 2013, it increased to 8.8% in 2018. In 2013, physical dependency rate of the elderly in Turkey was 11.3%, while this figure has recently reached 12.9%.[3] Therefore, to reduce the dependence of the elderly and to maintain their care, a wide service network is needed in all the institutions working in the field of health.[4]

Nurses have an important role in elderly care. Care is the use of nursing knowledge and skills to protect, develop, and promote health based on values such as empathy, compassion, reassurance, and help. Prejudices, negative feelings, beliefs and attitudes that nurses have while giving care to the elderly reduce their empathic approach and the quality of the care they give. One of the attitudes that can negatively affect care is ageism towards the elderly. Ageism is defined as prejudice or discrimination against or to the benefit of older adults because of their age. Ageism to older adults among nurses leads to inadequate allocation of health services and elder mistreatment.[5] Nurses see the health problem the elderly experience as a natural process, yet they prefer to take care of young patients. Moreover, Higgins et al. study revealed that for nurses, giving care to the elderly is "a waste of time".[6] There are many factors such as social, cultural and individual values that affect ageism. Empathic tendency is predicted to be one of these factors. It is important to evaluate the effect of empathic tendency on attitudes towards the elderly in nurses. Empathic tendency in nurses is gaining importance in order to remove the attitudes that increase ageism and to increase the quality of care.[7,8] The empathic tendency is defined asthe willingness to understand and help another person.[9,10]

Empathic tendency, which expresses the possibility of developing empathy, is an innate trait, developed by training and it renders the development of empathic attitude of an individual obligatory by creating the emotional dimension of empathy. This concept includes the ability to understand the emotions of the individuals with problems and to be influenced by their emotional experiences. People with high empathic tendencies show more helping behavior.[11] Empathic sensitivity enables nurses to better understand the patients and to give them better quality care. The elderly feel valuable when they are given individualized care through empathy.[12-14] The best way to understand and care for the elderly is to put yourself in the place of that person, which is best achieved by developing empathy. It is an important skill for nurses, educators, and all the people giving care.[15, 16] This study aims to determine the correlation of nurses empathic tendency and ageism attitudes towards older adults

Research Questions

1. What are the levels of empathic tendencies and ageism in clinic nurses?
2. Is there a relationship between empathic tendency and ageism attitudes towards older adults in clinic nurses?
3. What are the socio-demographic variables affecting the ageism?

MATERIAL AND METHOD

A descriptive and correlational study was conducted at a public hospital and a research and application in Turkey, from April to June 2017. At the began of the study power analysis (G*Power (v3.1.7) was performed using in order to determine the sample size. The sample size was determined as 122 with 0.05 error margin and based on 95% confidence interval. The study was completed with 132 nurses (55 nurses from the research and application hospital and 67 nurses from the public hospital). At the end of the study power analysis that the average score willingness to care for the elderly with the average score Fraboni Scale of Ageism (FSA), the power of the study was found to be 95% at alpha=0.05. Nurses who working in pediatric, neonatal and maternity services were excluded.

Data Collection

The research data were collected using theThe Structured Question Form, Empathic Tendencies Scale and Fraboni Scale of Ageism. The data was collected through face to face interviews with the participants. The data were collected between 2:30 and 3:00 PM outside of treatment hours. Each interview lasted about 20-30 minutes.

The Structured Question Form: The structured question form(Includes a total of 17 questions) was prepared by the researchers by investigating the literature.[9,10,12,14]

Empathic Tendencies Scale: The Likert type Empathic Tendencies Scale (ETS) was designed by Dokmen (1988) and the validity and reliability tests of the scale were conducted.[17] ETS is a 5 point-Likert scale which includes 20 statements. The minimum and maximum scores to be obtained from the scale are 20 and 100. As the score increases, empathic tendency also increases. The reliability coefficient of the ETS is 0.82.[17] In our study, cronbach's alpha was found to be 0.74.

Fraboni Scale of Ageism: The scale was designed by Fraboni in 1990 and Kutlu, Kucuk & Yildiz Findik (2012) conducted the reliability and validity studies of the scale in Turkey.[18,19] The Turkish translation of the scale consists of 25 items. The highest score to be obtained from the scale is 100, while the lowest score is 25. A higher score points to higher levels of ageism. The scale includes three sub-dimensions: Prejudice, Avoidance and Discrimination. The Croanbach's alpha of the original version of the scale was found to be 0.83, while that of the Turkish version is 0.84.[18,19] In our study, cronbach's alpha was found to be 0.77.

Ethical declarations

Approval for the conduct of the study was obtained from the ethics committee of Bozok University Faculty of Medicine Non-Invasive Trial Ethics Committee (Decision Number:2017/12/2). Institution permission was obtained. Written informed consent was obtained from the participants before data collection. The study was conducted in compliance with ethical standards.

Statistical Analysis

SPSS 15.0 (Statistical Package for Social Sciences) was used to analyze the data. The Kolmogorov-Smirnov test and Shapiro-Wilk test were used to assess normally distributed data. Research findings were obtained by percentage, frequency, arithmetic mean, standard deviation and student's t-test. The multiple regression analysis were used. In group comparisons, statistical significance was assessed at 95% confidence interval and at $p<0.05$.

RESULTS

This study 59.8% of the nurses were in the 18-35 years group and mean 32.7±8.3 years; 78.0% of them were female; 18.9% worked in the internal medicine clinic. 15.2% of the participants stated that they acquired the most recent information about the elderly from the media. 44.7% of the nurses said they received training on establishing communication with the elderly. Furthermore, 65.6% of the nurses in our study stated that they did not want to take care of the elderly in the clinic (**Table 1**).

Average FSA score of the nurses is 58.9±8.3 (min:31-max: 80), pointing to a moderate level. The scores for the sub-dimensions of FSA from the highest to the lowest are 29.1±4.8 (min: 11- max: 42) for prejudice, 17.9±3.4 (min: 9- max: 28) for avoidance, and 10.9±2.4 (min: 5- max: 18) for discrimination. ETS total score average of the nurses is 70.9±9.1 (min: 50-max: 91) (**Table 2**).

It was found that total FSA scores and prejudice scores of the female nurses were higher compared to the scores of the male nurses. 36+ age group had higher prejudice scores compared to the 18-35 age group ($p<0.05$). It was found that particularly the nurses who used media to acquire information about the elderly had statistically higher FSA, avoidance and discrimination scores and this way of reaching information had an effect on ageism level. Prejudice, avoidance, and FSA scores of the nurses who did not want to care for the elderly in the clinic were statistically significantly higher compared to those who wanted to work with the elderly ($p<0.01$) (**Table 3**).

Multiple regression was conducted to examine the contribution of significant gender, obtaining information about the elderly from the media, willingness to care for the elderly and empathic tendency. The final model was significant and explained 16% of the variance in ageism. In this model, factors that remained the negative attitude toward the elderly were gender, obtaining information about the elderly from the media, willingness to care for the elderly ($p<0.05$) and empathic tendency ($p>0.05$) (**Tablo 4**).

Table 1. Sociodemographic characteristics of nurses (n=132)

Characteristics	n	%
Years (X +SD)	32.7±8.3	
18–35 years	79	59.8
36+ years	53	40.2
Gender		
Female	103	78.0
Male	29	22.0
Family type		
Nuclear	119	90.2
Extended	13	9.8
Place of residence		
City	85	64.4
Town	47	35.6
Clinic		
Internal medicine	25	18.9
Emergency	23	17.4
Intensive care	21	15.9
Polyclinic	18	13.6
Surgical service	21	15.9
Operating room	15	11.4
Dialysis center	9	6.8
Working time in the profession (X+SD)	11.2±8.5 years	
Receiving care from the elderly during childhood		
Yes	20	15.2
No	112	84.8
Taking care of an elderly		
Yes	65	59.1
No	67	40.9
Obtaining information about the elderly from the media		
Yes	20	15.2
No	112	84.8
Receiving training on communicating with the elderly		
Yes	59	44.7
No	73	55.3
Willingness to care for the elderly		
Yes	45	34.4
No	87	65.6
Reasons behind not wanting to take care of the elderly (n=45)*		
Physically and mentally tiring	31	23.7
Hard to communicate with the elderly	29	22.1
Leading to burnout	27	20.6
Elderly's being grumpy and stubborn	14	10.7

X: Aritmethic mean, SD: Standart deviation * More than one answer was given.

Table 2. Distribution of ETS and FSA score averages of nurses (n=132)

Scales	X ± SD (Min-Max)
ETS score	70.9±9.1 (50-91)
Low (below 63)	17.2%
Average (63-72)	41.4%
High (73 and ↑)	41.4%
FSA score	58.9±8.3 (31-80)
Prejudice	29.1±4.8 (11-42)
Avoidance	17.9±3.4 (9-28)
Discrimination	10.9±2.4 (5-18)

X: Aritmethic mean, SD: Standart deviation FSA: Fraboni Scale of Ageism
ETS: Empathic Tendencies Scale

Table 3. Distribution of FSA and sub-dimension scores based on some characteristics of nurses

Characteristics	Prejudice X±SD	Avoidance X±SD	Discrimination X±SD	FSA X±SD
Age				
18–35	28.4±4.2	18.1±3.2	10.8±2.3	57.3±7.3
36 and above	30.2±5.5	17.7±3.6	11.1±2.5	58.9 ±9.6
p	0.041	0.571	0.582	0.268
Place of Residence				
City	27.1±3.8	17.7±3.4	11.1±2.5	58.4 ±5.5
Town	28.7±4.4	18.4±3.7	10.8±2.7	60.2 ±8.7
p	0.128	0.594	0.811	0.374
Gender				
Female	29.6±4.4	18.2±3.3	10.1±2.4	58.9±7.9
Male	27.1±5.6	17.0±3.5	11.0±2.4	54.6±8.9
p	0.013	0.110	0.170	0.013
Obtaining information about the elderly from the media				
Yes	30.6±4.7	19.4±2.3	12.1±2.9	62.1±86.6
No	28.8±4.8	17.6±3.5	10.7±2.3	57.2±8.4
p	0.119	0.031	0.026	0.015
Receiving training on communicating with the elderly				
Yes	29.1±4.4	17.8±3.5	11.1±2.5	58.0±7.5
No	29.1±5.2	18.0±3.3	10.8±2.3	57.9±8.9
p	0.990	0.752	0.572	0.977
Willingness to care for the elderly				
Yes	27.4±5.2	16.6±3.5	10.5±2.5	54.6±8.6
No	29.9±4.4	18.5±3.2	11.1±2.3	59.6±7.6
p	0.005	0.003	0.175	0.001

Student's t-test FSA: Fraboni Scale of Ageism

Table 4. The effect of various factors on the FSA score of nurses (n=132)

Independent variables	B	SE	β
Constant	67.280	8.119	
Gender	-4.763	1.660	-.241*
Obtaining information about the elderly from the media	-5.441	1.908	-.239*
Willingness to care for the elderly	4.231	1.420	.250*
Empathic tendency	-.007	.076	.007

*p<0.05 R: 0.42 R2: 0.17 Adjusted R2: 0.16 F:8.177 p<0.001

DISCUSSION

Health professionals also have prejudice about aging, which may lead to discriminatory behavior.[15,20-22] The negative prejudice, values, beliefs and attitudes of health professionals, especially the nurses responsible for care, against the elderly influence the quality of the care given to the elderly.[23-27] It was also found that the sub-dimensions of the FSA ageism scale (prejudice, avoidance and discrimination)were at moderate levels. Previous studies in the literature revealed similar results.[7,26,27] The study suggest that the adoption of the belief that the elderly should be respected depending on the cultural significance of aging in the Turkish society and the region where the study was conducted is effective in reducing discrimination.

Regression analyses showed that this model accounted for 16% of the variance in ageism. In this study, more than half of the nurses stated that they did not want to take care of the elderly in the clinic. The main reasons were that taking care of the elderly was perceived as being physically and mentally exhausting, that establishing interaction with the elderly is difficult, and that taking care of the elderly leads to burnout. It was found that the nurses who did not want to take care of the elderly in the clinic exhibited prejudice and avoidancetoward the elderly and were more ageist. A systematic review of 25 studies conducted that all over the world, the positive attitude toward the elderly has been decreasing since 2000, while the negative attitude has been gradually increasing.[28]

Media presents aging as a negative and undesirable process.[29,30] One significant finding of our study is that avoidance and discrimination scores of the nurses who recently acquired some information about the elderly from the mediaare higher and they were found to be more ageist. Thus, it is necessary for countries to increase the sensitivity of the society by taking measures against ageism in media.

Our study further revealed that female nurses over 36 had higher scores of prejudice and ageism. This may be attributed to the fact that due to the cultural norms in Turkey, female nurses take care of the elderly at home as well as at their workplace, and the burden on their shoulders increase with the advance of the age of the elderly; thus their prejudice and ageism against the elderly increase.[24]

Empathic tendency is the determinant of the level of help individuals. Our study revealed that the nurses had moderate level of empathic tendency. In addition, this study revealed that as empathic tendency levels of nurses decrease, they show more avoidance of the elderly. This finding points to the fact that as the empathic tendencies of nurses are reinforced, avoidance from the elderly decreases and consequently, the quality of the care can be increased.[24,31] Because, empathictendency is a vital element in all activities of nursing and is thebasic element of human-oriented holistic and humanistic nursing care.[32,33]

CONCLUSION

This study found that ageism and empathic tendencies of nurses were at moderate level. As health professionals should be aware of their empathic tendencies and improve their empathic skills through professional training and practice.

Limitations

The study has some limitations. The sample of the study consisted of the clinic nurses working in internal and surgery services. Therefore, the fact that the results of the study can not be generalized to clinic nurses is one of the limitations of the study.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for the conduct of the study was obtained from the ethics committee of the faculty (Approval No:2017/12/2).

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

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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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.844873
J Contemp Med 2021;11(4):531-536

Orjinal Araştırma / Original Article

Diagnostic Evaluation of Children Presenting with Chest Pain to a Paediatric Cardiology Policlinic: Effect of the COVID-19 Pandemic on Aetiology

Çocuk Kardiyoloji Polikliniğine Göğüs Ağrısı Şikayetiyle Başvuran Hastaların Tanısal Değerlendirilmesi: Covid 19 Pandemisinin Etiyolojiye Etkisi

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Abstract

Aim: The aim of this study was to evaluate the aetiology of chest pain, the demographic data of patients with chest pain, and the effect of the coronavirus disease 2019 (COVID-19) pandemic on these variables.

Material and Method: The study included patients who presented with complaints of chest pain at a paediatric cardiology policlinic between November 2019 and August 2020. The patients were divided into two groups based on the date 11 March 2020, when restrictions to daily life were implemented because of the COVID-19 pandemic in Turkey. Groups 1 and 2 included patients who presented with chest pain before and after that date, respectively.

Results: Evaluations were made in 251 patients comprising 136 (54.2%) females and 115 (45.8%) males with a mean age of 11.6±2.9 years. The chest pain was felt most often in the precordial area (46.2%) as a needle pricking sensation (64.9%). The most causes of the chest pain were determined to be the musculoskeletal system (55%), psychogenic (16.3%), and idiopathic (13.5%), respectively. A cardiac aetiology was determined in 2.8% of the patients. Psychogenic reasons were more prevalent, and more patients had been referred by a physician and from rural areas,in Group 2 than Group 1 ($p<0.05$).

Conclusion: To prevent repeated policlinic presentations with non-cardiac chest pain, and unnecessary and lengthy tests, the concerns of families must be eliminated. Since the beginning of the COVID-19 pandemic, the number of children with chest pain of psychogenic cause has increased.

Keywords: Chest Pain, COVID-19, pandemic, psychogenic

Öz

Amaç: Çalışmamızda göğüs ağrılarını demografik ve etiyolojik açıdan değerlendirmeyi ve bu değişkenlere corona virüs hastalığı 2019 (COVID-19) pandemisinin etkisini araştırmayı amaçladık.

Gereç ve Yöntem: Kasım 2019- Ağustos 2020 tarihleri arasında çocuk kardiyoloji polikliniğine göğüs ağrısı şikayetiyle başvuran hastalar çalışmaya alındı. Hastaların özgeçmiş ve soygeçmiş bilgileri, göğüs ağrısının özellikleri, fizik muayene bulguları, ekg ve ekokardiyografik bulguları kaydedildi. Hastalar Türkiye'de covid 19 pandemisi nedeniyle toplumsal yaşamda kısıtlamaların uygulanmaya başlandığı 11 Mart 2020 öncesi (grup 1) ve sonrası (grup 2) olmak üzere iki gruba ayrıldı.

Bulgular: Çalışmaya yaş ortalaması 11,6±2,9 yıl olan 136'sı kız (%54,2) toplam 251 hasta alındı. Ebeveynlerin %46'sı, hastaların ise %12'si göğüs ağrısının kardiyak kökenli olduğunu düşünüyordu. Göğüs ağrısı en sık prekordiyal alanda (%46,2) ve iğne batar tarzda (%64,9) hissedilmekteydi. Hastaların 116'sında (%46,2) soygeçmişinde kalp hastalığı mevcuttu. Göğüs ağrısının en sık sırayla kas-iskelet sistemi (%55), psikojenik (%16,3) ve idyopatik (%13,5) sebepli olduğu görüldü. Hastaların %2,8'inde kardiyak sebep saptandı. Gruplararası karşılaştırmada pandemi sonrası (grup II) de psikojenik sebeplerin daha fazla olduğu, hastaların daha fazla hekim sevkiyle ve kırsaldan geldiği saptandı ($p<0,05$).

Sonuç: Nonkardiyak göğüs ağrılarında tekrarlayan poliklinik başvuruları, gereksiz ve uzun süren tetkikleri önlemek için ailelerin endişeleri giderilmelidir. Covid 19 pandemisi sonrasında çocuklarda psikojenik nedenli göğüs ağrılarında artış saptandı.

Anahtar Sözcükler: COVID-19, göğüs ağrısı, pandemi, psikojenik

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Received *(Geliş Tarihi)*: 22.12.2020 **Accepted *(Kabul Tarihi)*:** 26.05.2021

INTRODUCTION

Chest pain is frequently seen in children and adolescents, and in contrast to adults, generally has a benign aetiology. Although it is one of the most common complaints on presentation at paediatric cardiology policlinic, when not managed correctly, chest pain leads to repeated policlinic presentations, unnecessary tests, and family worry.[1-5] The vast majority of instances of chest pain in children are not of cardiac origin.[1,3,5,6] Chest pain is the cause of 5.2% of the consultations requested from the paediatric cardiology policlinic, 13% of emergency department evaluations, and 19% of new patient consultations from the emergency department.[4] However, despite these frequent evaluations, it has been reported that the rate of chest pain of cardiac cause in children is only 0–5%.[2,3,6]

The novel severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) responsible for coronavirus disease 2019 (COVID-19) first emerged in Wuhan, China in December 2019 and spread rapidly around the world. The World Health Organization (WHO) declared COVID-19 a global pandemic on 10 March 2020.[7] The first case in Turkey was reported on 11 March 2020, after which daily life restrictions of varying degrees were implemented, particularly to protect children and the elderly (schools, businesses, and public areas were closed and curfews applied).[7] Somatic symptoms and psychiatric disorders such as anxiety disorder, depressive symptoms, post-traumatic stress disorder (PTSD), feelings of guilt, psychosis, and suicide have been associated with the pandemic.[8-10] Although there are limited data regarding the effects of the pandemic on the mental health of children, situations such as physical and social restrictions during a pandemic, fear, long-term absence from school, or the loss of a close relative can lead to severe psychological problems in children.[10]

The aims of this study were to analyse the patients presenting at our policlinic with complaints of chest pain and, by determining an appropriate approach, to prevent unnecessary tests, eliminate the concerns of patients and their families, and prevent repeated hospital presentations. The study was conducted during the COVID-19 pandemic to examine the effect of restrictions on daily life due to the pandemic on patients presenting with complaints of chest pain.

MATERIAL AND METHOD

The study included a total of 251 patients who presented at the Paediatric Cardiology Policlinic because of complaints of chest pain between November 2019 and August 2020. Data retrieved from patient records included the age and sex of the patients and personal and family histories. The parents' education levels, the ideas of the parents and patient regarding the origin of the pain, the localisation, character, frequency, duration, and spread of the pain, accompanying factors, and physical examination, laboratory test, electrocardiography (ECG), and echocardiography findings were recorded. When necessary, the patients were referred to the paediatric psychiatry department or other departments that treat paediatric diseases. The patients were divided into two groups based on the date 11 March 2020, when restrictions on daily life were implemented because of the COVID-19 pandemic in Turkey. Groups 1 and 2 included patients who presented with chest pain before and after that date, respectively. The groups were compared with respect to demographic data and diagnosis. Approval for the study was granted by the local ethics committee (decision no:2020/593).

Statistical analysis

Data were analysed statistically using SPSS for Windows version 23.0 software. Continuous data witha normal distribution are expressed as the mean±standard deviation and non-parametric data as the median (minimum–maximum). The Chi-square test was applied to compare categorical data and Student's t-test to compare independent groups of measurements with a normal distribution. A value of $p<0.05$ was considered statistically significant.

RESULTS

A total of 251 patients with a mean age of 11.6±2.9 years, comprising 136 (54.2%) females and 115 (45.8%) males, were evaluated. No patient had COVID-19. Of these patients, 176 (70.1%) were referred by another physician, and 75 (29.9%) visited our policlinic directly. The chest pain was felt most often in the precordial area (46.2%) and in the form of needle pricking (64.9%). There was a family history of heart disease in 116 (46.2%) patients. Radiating pain was reported by 53 (21.1%) patients, toward the left arm in 22 (8.8%), toward the back in 9 (3.6%), toward the right side of the chest in 9 (3.6%), toward the neck in 8 (3.2%), towardthe posterior sternum in 3 (1.2%), and towardthe abdomen in 2 (0.8%). The demographic data and characteristics of the chest pain are shown in **Table 1**.

The chest pain was thought to be of cardiac origin according to the parents of 123 (49%) patients and according to 30 (12%) patients themselves, of whom 18 (14.6%) and 10 (33.3%) patients, respectively, were determined to have a psychogenic origin. There was a significantly higher rate of chest pain of psychogenic origin in patients who thought they had heart disease compared to who dont thought ($p=0.015$). The education level of the parents was middle school or higher for 72 (28.7%) patients and primary school for 89 (35%) patients; the parents of 90 (35.9%) patients had not attended school. The chest pain was accompanied by shortness of breath in 25 (9.9%) patients, a burning feeling in the stomach in 16 (6.4%), and palpitations in 3 (1.2%).

On cardiac auscultation, a late systolic click was heard in the apex in six patients, a late systolic murmur in one patient, and a systolic click with a diastolic murmur in the left second intercostal space in two patients. Chest x-ray was performed in 22 patients. One of the radiographs showed pneumonic infiltrations, and three showed skeletal system deformities. Other radiographic findings were normal. Exercise tests were performed in 16 patients with exercise-related chest pain,

but no pathological findings were found. Holter monitoring was performed in 28 patients, but no pathological finding to explain the chest pain was observed. No abnormal values were observed in any of the 34 patients with available troponin level measurements. In patients with a non-cardiac aetiology, specific examinations of the aetiology were performed by the relevant departments.

Regarding the aetiology of the chest pain, the most common cause was the musculoskeletal system in 138 (55%) patients, followed by psychogenic in 41 (16.3%), the gastrointestinal system (GIS) in 16 (6.4%), and the respiratory system in 13 (5.5%). Thelarche pain was determined in two (0.8%) patients, and a cardiac origin was determined in seven (2.8%). In 34 (13.5%) patients, no cause could be found, and these patients were considered to have idiopathic chest pain. The aetiologies of the chest pain are shown in **Figure 1**. The duration of the complaints exceeded 6 months in 28 (82.3%) patients with idiopathic chest pain and 41 (18.9%) patients with a determined cause; the difference was statistically significant (p=0.000). All patients considered to have chest pain associated with the gastrointestinal system were referred to the paediatric gastroenterology department, of whom 12 were diagnosed with gastroesophageal reflux disease (GERD) and 4 with gastritis. Of the patients with chest pain associated with the respiratory system, 1 was diagnosed with pneumonia and 12 with asthma. In those diagnosed with asthma, the lung sounds were normal in all but one. Patients diagnosed with asthma were followed up by the paediatric allergy department. The pathology was determined by echocardiographic examination in 14 (5.6%) patients: mitral valve prolapse (MVP) in 10 patients, bicuspid aorta and mild level aorta failure in 3 patients, and mild mitral failure with a history of rheumatic heart disease in 1 patient. The chest pain in 7 (2.8%) patients with MVP was thought to be associated with a cardiac pathology. On electrocardiographic examination, right branch block was seen in two patients and a short PR interval in one patient; the other evaluations were normal.

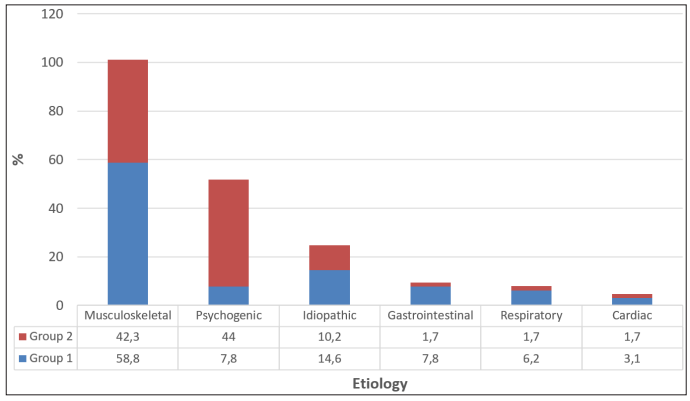

Figure 1. The aetiologies of the chest pain

Table 1. The characteristics of the chest pain

Characteristics of the chest pain		Total n (%)	Group 1 n(%)	Group 2 n(%)	p
Localisation	Precordial, n (%)	116 (46.2)	86 (44.8)	30(50.8)	0.18†
	Epigastric, n (%)	11 (4.4)	9 (4.7)	2 (3.4)	
	Diffuse chest, n (%)	19 (7.6)	15 (7.8)	4 (6.8)	
	Right side of Chest, n (%)	7 (2.8)	6 (3.1)	1 (1.7)	
	Left side of Chest, n (%)	65 (25.9)	55 (28.6)	10 (16.9)	
	Left shoulder, n (%)	9 (3.6)	4 (2.1)	5 (8.5)	
	Posterior Sternum, n (%)	24 (9.6)	17 (8.9)	7 (11.9)	
Character	Needle pricking	163 (64.9)	124 (64.6)	39 (66.1)	0.57†
	Squeezing	67 (26.7)	51 (26.6)	16 (27.1)	
	Burning feeling	8 (3.2)	8 (4.2)	0 (0)	
	Stabbing sensation	7 (2.8)	5 (2.6)	2 (3.4)	
	Pressure	6 (2.4)	4 (2.1)	2 (3.4)	
Duration, minute	0-1	107 (42.6)	85 (44.3)	22 (37.3)	0.28†
	1-10	104 (41.4)	79 (41.1)	25 (42.4)	
	10-30	16 (6.4)	9 (4.7)	7 (11.9)	
	30-60	15 (6)	11 (5.7)	4 (6.8)	
	>60	9 (3.6)	8 (4.2)	1 (1.7)	
Onset of the symptom	0-1 week	69 (27.5)	56 (29.2)	13 (22)	0.16†
	1 week-1 month	64 (25.5)	43 (22.4)	21 (35.6)	
	1 - 6 month	49 (19.5)	41 (21.4)	8 (13.6)	
	6 month- 1 year	50 (19.9)	36 (18.8)	14 (23.7)	
	>1 year	19 (7.6)	16 (8.3)	3 (5.1)	
Spread	Yes	53 (21.1)	44 (22.9)	9 (15.2)	0.12†
	No	198 (78.9)	148 (77.1)	50 (84.8)	
Relationship with effort	Yes	9 (3.6)	9 (4.7)	0 (0)	0.09†
	No	242 (96.4)	183 (95.3)	59 (100)	
Relationship with food	Yes	21 (8.4)	21 (10.9)	0 (0)	0.008†
	No	230 (91.6)	171 (89.1)	59 (100)	
Relationship with position	Yes	15 (6)	15 (7.8)	0 (0)	0.02†
	No	236 (94)	177 (92.2)	59 (100)	
Accompanied symptom	No	195 (77.7)	147 (76.5)	48 (81.4)	0.2†
	Shortness of breath	25 (10)	17 (8.9)	8 (13.6)	
	Palpitation	3 (1.2)	3 (1.6)	0 (0)	
	Burning feeling in the stomach	28 (11.2)	25 (13)	3 (5)	

†: chi-square test

All 41 patients with chest pain of psychogenic origin were evaluated by a paediatric psychiatry specialist. These 41 patients comprised 24 (58.5%) girls and 17 (41.5%) boys; 28 (68.3%) lived in the city, and 21(51.2%) had a family history of heart disease. The mean age was 12.83±3.01 years in patients with pain of psychogenic origin and 11.41±2.8 years in those with pain of non-psychogenic origin. No significant difference in terms of sex, place of residence, or family history of heart disease was determined between patients with and those without chest pain of psychogenic origin (p =0.54, p =0.46, and p =0.48, respectively). The mean age was significantly higher in patients with psychogenic origin chest pain than in those with a non-psychogenic origin (p=0.005). Of the patients with a psychogenic origin, 12 were diagnosed with an anxiety disorder, 11 with PTSD, 4 with a conversion disorder, 6 with mild depression, 3 with moderate depression, 1 with severe depression, and 4 with a panic disorder. The patients were treated with behavioural therapy in 13 patients and behavioural therapy together with medical therapy in 28 patients. Treatment was not continued by 13 patients. In the 28 patients who continued treatment, a significant reduction in complaints was observed. Except for the 13 patients who did not continue treatment, the patients were followed up by the child psychiatry department. The distribution of psychiatric disorders is shown in **Table 2**.

Comparison of Group 1, who presented before the pandemic, and Group 2, who presented during the pandemic, showed that Group 2 patients more often resided in rural areas (p=0.04), were referred by physicians (p=0.005), and had a psychogenic aetiology (p=0.000) compared with Group 1 patients. The comparisons of Groups 1 and 2 are shown in **Table 3**.

Tablo 2. The distribution of psychiatric disorders

Psychiatric Disorder	Group 1, n	Group 2, n	Total, n
Depresion,			
Severe	0	1	1
Moderate	2	1	3
Mild	2	4	6
Anxiety Disorder	3	9	12
PTSD	3	8	11
Panic Disorder	3	1	4
Conversion Disorder	2	2	4
Total	15	26	41

PTSD: Post-traumatic stress disorder

Table 3. The Comparisons Of Group 1 And Group 2.

Parameter	Total (n=251)	Group 1 (n=192)	Group 2 (n=59)	p
Age, year, ort±SS	11.6 ± 2.9	11.59±2.9	11.84±3.1	0.56*
Sex, M/F	115/136	88/104	27/32	0.99†
Living place, City/ Rural	183/68	146/46	37/22	0.04†
Cardiac disease in family, Yes/No	116/135	90/102	26/33	0.7†
Referred, Yes/No	176/75	126/66	50/9	0.005†
Diagnosis	**Total n(%)**	**Group 1 n (%)**	**Group 2 n (%)**	**p**
Musculoskeletal, n (%)	138 (55)	113 (58.8)	25 (42.3)	0.02†
Psychogenic, n (%)	41 (16.3	15 (7.8)	26 (44)	0.000†
Cardiac, n (%)	7 (2.8)	6 (3.1)	1 (1.7)	0.56†
Gatrointestinal, n (%)	16 (6.4)	15 (7.8)	1 (1.7)	0.008†
İdiopathic, n (%)	34 (13.5)	28 (14.6)	6 (10.2)	0.92†
Respiratory, n (%)	13 (5.2)	12 (6.2)	1 (1.7)	0.16†
Telarş, n (%)	2 (0.8)	2 (0.8)	0 (0)	

M: Male, F: Female, *: student t test, †: chi-square test

DISCUSSION

Chest pain due to cardiac causes is extremely rare in children. If the correct approach is not applied in these patients, they often undergo lengthy, unnecessary, and expensive examinations and repeat presentations because of the family's fear of death.[1,3-5,11] The aims of this study were to determine the correct approach to use in patients with chest pain by examining their clinical and laboratory findings, and to evaluate the effect of the COVID-19 pandemic on policlinic presentations due to chest pain.

Previous studies reported that >50% of parents thought that the aetiology of their child's chest pain was heart disease.[2,3,12,13] In a study by Aygun et al. of 782 patients,[14] the parents of 70.8% of patients and 90.2% of patients themselves thought that the chest pain was due to heart disease. In another study, 69% of children with chest pain restricted their activity, 40% did not attend school, 44% thought they had had a heart attack, and 12% thought they had cancer.[15] Anxiety disorder has been reported in up to 60% of patients with non-cardiac chest pain and their families.[3,15] In our study, while the parents of 49% of the patients thought that their child had heart disease, only 12% of the patients themselves believed the origin to be heart disease. Furthermore, of the patients who thought they had heart disease, psychogenic causes were significantly more common than organic causes. Our findings indicate the importance of relieving the heart disease-related concerns of the parents of patients with chest pain admitted to paediatric cardiology outpatient clinics without any evidence of cardiac pathology.

Pathologies of the musculoskeletal system are seen most often.[1,5,6,15-17] These diagnoses must be kept in mind when there is pain in the ribcage with palpation on physical examination, a change in pain with breathing and movement, and a history of sporting activity.[1,3] In the literature, chest pain associated with the musculoskeletal system has been reported at a rate of 7–69%.[3,17] In the current study, chest pain was determined to be of musculoskeletal system origin in 55% of the patients, consistent with the literature.

Chest pain of respiratory system origin has been reported at a rate of 3–12%.[3] Especially in patients diagnosed with asthma, there may be chest pain after effort even if the lung sounds are normal. In the current study, 13 (5.5%) patients had chest pain of respiratory system origin, which was consistent with findings in the literature.

A gastrointestinal system origin should be considered when chest pain is felt in the epigastric region or in the form of burning in the sternum posterior or if it increases when lying down or is associated with food.[1,3] The rate of chest pain associated with the gastrointestinal system is 2–8% in the literature.[2] In the current study, 12 patients were diagnosed with GERD and 4 with gastritis. The chest pain complaints of these patients decreased significantly with treatment. The data obtained in the current study are consistent with previous findings in the literature.

Chest pain for which no aetiology can be found despite the necessary tests and detailed anamnesis and physical examination is defined as idiopathic chest pain, with a reported rate of 12–85%.[2,11,18,19] This kind of pain is generally chronic, the severity of the pain does not change with respiration or position, the physical examination and tests are normal, and the pain goes away spontaneously.[2,17] Despite all of the examinations conducted, no aetiology could be determined in 34 (13.5%) of the patients in our study, and thus the diagnosis was idiopathic chest pain, which was consistent with the literature. The idiopathic chest pain had lasted at least 6 months in 82.3% of patients, of longer duration than that in patients with non-idiopathic chest pain. Informing patients and their families that heart disease is absent is the best approach to eliminate concerns inpatients and their families.

The most important concern of patients presenting at hospitals with chest pain is the possibility of heart disease, which could lead to sudden cardiac death. Despite this concern in more than 50% of patients and their families, the rate of identifying a cardiac pathology in paediatric chest pain is extremely low (0–5%).[1-3,12,13,20] In the presence of a family history of sudden cardiac death at a young age, pain occurring with effort, abnormal findings on physical examination, or abnormal ECG findings, a detailed cardiac evaluation must be made. The main cardiac pathologies causing chest pain are coronary artery pathologies, cardiomyopathies, left ventricle output pathway pathologies, aortic aneurysm and aneurysm rupture, pericarditis/myocarditis, arrhythmia, and MVP.[1,3] In the current study, a cardiac aetiology was determined in 7 (2.8%) patients, which was consistent with the literature. All of these patients had MVP; they were given information and recommendations and then followed up in the paediatric cardiology policlinic.

Psychogenic-origin chest pain is often seen in adolescents aged >12 years.[1-3] In approximately one-third of these patients, a significant stress factor can be determined, such as a death or significant disease in the family or separation from school or family. Anxiety disorder, various degrees of depression, panic disorder, and conversion disorder are among the psychogenic causes of chest pain.[1-3] Chest pain of psychogenic origin in children has a reported rate of 5–30%,[2,3,17] consistent with our rate of 16.3% (41 patients) in the current study. The mean age of these patients was older than that of the other patients. In some recent studies, a greater rate of chest pain of psychogenic origin than organic chest pain has been reported, and depression, anxiety, and suicidal thoughts have been reported at higher rates in those with non-cardiac chest pain compared with control groups.[21] Therefore, it is important that these patients be evaluated by paediatric psychiatry specialists and monitored. All 41 patients in the current study thought to have chest pain of psychogenic origin were evaluated and followed up by a paediatric psychiatry specialist.

COVID-19 disease started in Wuhan, China, and with rapid global spread became a pandemic, which has led to many deaths worldwide.[7,22] The weekly epidemiological update on 5 October 2020 by the WHO reported nearly 35 million COVID-19 cases and more than 1 million deaths.[23] Most children with COVID-19 have mild or no symptoms; however, some children can become severely ill. They might require hospitalization, intensive care, or a ventilator to help them breathe, and in rare cases, they could die. Chest pain is a rare symptom of COVID-19 in children. It was reported that 2.5% of patients diagnosed with COVID-19 under the age of 18 years complain of chest pain.[24] However, this is a concern because of pathologies with high morbidity and mortality, such as COVID-19-associated myocarditis, pulmonary embolism, pneumonia, and multisystem inflammatory syndrome in children (MIS-C), which can be diagnosed in patients presenting with chest pain. COVID-19 was not detected in any of the 59 patients who visited our outpatient clinic during the pandemic period. However, these results may reflect the small number of patients. Studies on this subject with larger patient groups are needed.

Despite that the whole world is affected by the physical effects of COVID-19 and its treatment, there has been in sufficient focus on the psychological effects of the pandemic.[22,25] However, several studies conducted during this period have shown increased rates of psychological disorders, such as anxiety, depression, panic disorder, insomnia, and PTSD, due to the effects of isolation, restricted social activities, fear, hopelessness, and false news and rumours.[9,21,22,25]

The results of the current study showed a significantly higher rate of chest pain of psychogenic origin in patients evaluated after the onset of the pandemic compared with those who presented before the pandemic. Personal and social isolation during the pandemic, written and visual media, and distancing from school and friends may be responsible for the increased rate of psychogenic-origin chest pain. The finding that the rate of psychogenic chest pain in our Group 1 patients was not higher than those in other studies conducted in our country[14] and region[26] suggests that the patients were affected by restrictions on social life rather than by the news. This is the first study to report an increased rate of chest pain of psychogenic origin in children during the pandemic. In addition, after the onset of the pandemic, more patients with chest pain were from rural areas and referred by other physicians. Before the pandemic, the rate of direct,

non-referred presentations was 34.3%; this rate decreased to 15.2% after the onset of the pandemic, which suggests that despite the concerns of families, fear of COVID-19 infection limited the number of direct presentations.

The limitations of this study are the small number of cases, the retrospective design, the lack of screening of patients and parents for cardiovascular risk factors, and the short study duration. More comprehensive and prospective studies are needed.

CONCLUSION

The possibility of cardiac-origin chest pain in children is very low, despite the concerns of families. To reduce repeated presentations and unnecessary and lengthy examinations, the patient and family should be sufficiently informed about non-cardiac chest pain to eliminate concerns regarding cardiac pathologies, and psychiatric evaluations should be performed if necessary. The personal and societal restrictions implemented because of the COVID-19 pandemic have increased the rate of psychogenic chest pain in children. This is the first study to report an increased rate of chest pain of psychogenic cause in children during the COVID-19 pandemic.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was performed in accordance with the local ethics committee (SBÜ Gazi Yaşargil Education and research hospital, 16.10.2020/593).

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.

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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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.851281
J Contemp Med 2021;11(4):537-542

Orjinal Araştırma / Original Article

Changes in Non-culprit Lesion Severity on Follow-up Coronary Angiography after Primary Percutaneous Coronary Intervention

Primer Perkütan Koroner Girişimlerde Sorumlu Olmayan Lezyonların Kontrol Koroner Anjiyografide Değişimleri

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Abstract

Aim: Non-culprit lesion severity has often been exaggerated at the time of acute ST segment elevation myocardial infarction (STEMI). We aimed to determine changes in non-culprit lesions severity on follow-up coronary angiography (CAG) and independent predictors of these changes.

Material and Method: We retrospectively evaluated the changes in non-culprit lesion stenosis on follow-up CAG which was done within 2 months after primary percutaneous coronary intervention (P-PCI) in patients presenting with STEMI.

Results: 154 patients were included in this study and 207 non-culprit lesions (percentage diameter stenosis (PDS) ≥50%) were compared using quantitative coronary analyses (QCA). Minimal lumen diameter (1.30±0.38 mm vs. 1.54±0.46 mm, p<0.001) and reference vessel diameter (2.88±0.66 mm vs. 2.92±0.64 mm, p=0.001) were increased significantly and PDS (54.49±9.38 vs. 47.5±11.17, p<0.001) and percentage area stenosis (78.38±8.65 vs. 71.29±11.84, p= <0.001) were decreased significantly. There was no significant change in lesion length (13.52±5.59 mm vs. 13.25±5.31 mm, p= 0.078). 65 (31.4%) of these significant lesions (PDS ≥50% by QCA) were regressed (less than 50%) on follow-up CAG. In multivariable analyses; current smoking, clopidogrel use after the P-PCI and history of coronary artery disease were the independent predictors of decrease in PDS.

Conclusion: Significant exaggeration of non-culprit lesion stenosis severity occurs at the time of acute STEMI.

Keywords: Primary percutaneous coronary intervention; multi-vessel disease; non-culprit lesion; quantitative coronary analysis

Öz

Amaç: Akut ST segment yükselmeli miyokard enfarktüsü (STEMI) sırasında sorumlu olmayan lezyonlar sıklıkla olduklarından daha ciddi görünürler. Kontrol koroner anjiyografi (KAG)'de sorumlu olmayan lezyonların şiddetindeki değişiklikleri ve bu değişikliklerin bağımsız prediktörlerini belirlemeyi amaçladık.

Gereç ve Yöntem: STEMI ile başvuran ve primer perkütan koroner girişimden (P-PKG) sonraki 2 ay içinde kontrol KAG yapılan hastalarda sorumlu olmayan lezyonlardaki değişiklikleri retrospektif olarak değerlendirdik.

Bulgular: Bu çalışmaya 154 hasta dahil edildi ve 207 (yüzde çap darlığı (YÇD) ≥50%) sorumlu olmayan lezyon kantitatif koroner analizler (QCA) kullanılarak karşılaştırıldı. Minimal lümen çapı (1,30±0,38 mm'ye karşı 1,54±0,46 mm, p <0,001) ve referans damar çapı (2,88±0,66 mm'ye karşı 2,92±0,64 mm, p=0,001) önemli ölçüde arttı ve YÇD (54,49±9,38'e karşı 47.5±11.17, p <0.001) ve yüzde alan darlığı (78.38±8.65 vs. 71.29±11.84, p= <0.001) anlamlı olarak azaldı. Lezyon uzunluğunda anlamlı değişiklik izlenmedi (13,52±5,59 mm'ye karşı 13,25±5,31 mm, p= 0,078). Bu önemli lezyonların 65'i (% 31.4) (QCA'ya göre YÇD ≥% 50) kontrol KAG'de geriledi (% 50'den az). Çok değişkenli analizlerde; mevcut sigara kullanımı, P-PKG'den sonra klopidogrel kullanımı ve koroner arter hastalığı öyküsü, YÇD'deki azalmanın bağımsız prediktörleri idi.

Sonuç: Akut STEMI sırasında sorumlu olmayan lezyonlardaki darlıkların derecesi önemli ölçüde daha artmış olarak izlenmektedir.

Anahtar kelimeler: Primer perkütan koroner girişim; çoklu damar hastalığı; sorumlu olmayan lezyon; kantitatif koroner analiz

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Received *(Geliş Tarihi)*: 09.01.2021 **Accepted *(Kabul Tarihi)*:** 30.05.2021

INTRODUCTION

Acute coronary syndrome (ACS) is a continuum disease process and complete coronary occlusion in the absence of collateral perfusion results in ST-segment elevation myocardial infarction (STEMI). STEMI comprises approximately 25% to 40% of ACS presentations.[1,2] Prompt restoration of myocardial perfusion is vital and primary percutaneous coronary intervention (P-PCI) is the preferred mode of reperfusion.[3,4] Approximately 50% of STEMI patients have significant stenoses in one or more non-culprit arteries[5,6] at the time of P-PCI. Coronary flow also globally slows in acute myocardial infarction (AMI), and relief of the culprit artery stenosis by PCI restores flow in the non-culprit artery as well.[9] Non-culprit stenosis severity may be exaggerated on angiographic assessment at the time of AMI.[7,8] ACS are usually triggered by acute thrombosis, superimposed on a ruptured or eroded atherosclerotic plaque.[10,11] The thrombotic response to plaque rupture is very a dynamic process may result in generation of vasoconstrictors such as thrombin, serotonin and thromboxane A and often associated with vasospasm and distal embolization.[12] Endothelial dysfunction associated with increased risk of thrombosis and abnormal vasomotor response via mediators such as prostacyclin, endothelin-1 and decreased secretion of nitric oxide.[13] Increased sympathetic activity has been documented during acute myocardial infarction and this may cause coronary vasoconstriction in the presence of endothelial dysfunction. Also, activation of the circulating renin-angiotensin system occur during severe ischemia. This neurohormonal activation leads to systemic and possibly to coronary vasoconstriction.[14,15] All of these mechanisms involved in pathogenesis of ACS are possibly contributing to exaggeration of non-culprit vessel stenosis severity during STEMI. Significant stenosis has generally been defined as >50% diameter stenosis of non-culprit artery.[8,9,16] We performed a retrospective analysis of patients who underwent P-PCI for STEMI with significant non-culprit lesions and had another elective coronary angiogram (CAG) within 60 days. We sought to determine changes in non-culprit vessel lesions severity and independent factors associated with these changes.

MATERIAL AND METHOD

Patient population

We reviewed data of all patients who presented with STEMI and underwent P-PCI and had an elective follow-up CAG within 2-60 days between December 2010 and July 2012 at our Hospital. This study was conducted according to the Declaration of Helsinki and approved by the Hospital Clinical Research Ethics Committee (IRB number: 2013/13). Written informed consent was obtained from all patients before the procedures. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study; all study analyses, the drafting and editing of the manuscript, and its final contents.

Patient selection

>18 year-old patients who presented with STEMI and underwent P-PCI within the first 12 hours of the onset of typical ischemic chest pain and found to have significant (visually estimated diameter stenosis of ≥50% on the P-PCI) non-culprit lesions and had an elective follow-up CAG within 2-60 days were included in this study. Patients who had non-culprit lesions with chronic total occlusion (100% stenosis), instent stenosis, CABG to non-culprit arteries and non-matching projections (>5° difference in any plane between P-PCI and follow-up CAG) were excluded from this study. Patients who had follow-up CAG done for ACS were also excluded from this study.

Procedural details

Primary PCI was performed by the percutaneous femoral approach and all patients received a chewable 300 mg aspirin and clopidogrel 600 mg loading dosage before the procedure. The culprit lesion was identified as the site of acute occlusion or impaired Thrombolysis in Myocardial Infarction 3 flow.[17] Non-culprit lesions were defined as lesions in an artery other than the infarct related artery with smooth angiographic borders and no associated thrombus. Heparin (100 IU/kg I.V.) was administered when the coronary anatomy was defined. P-PCI was performed only for culprit lesions. After angioplasty, all patients were admitted to the coronary care unit, where 100 mg aspirin and 75 mg clopidogrel were continued in all patients. The use of glycoprotein IIb/IIIa inhibitors was up to the discretion of the operator.

Quantitative coronary analysis (QCA) measurements

All P-PCI angiograms were reviewed by two experienced operators to find those patients who had a significant non-culprit lesion (visually estimated diameter stenosis of ≥50%). Angiographic images before any intracoronary nitrates were administered were used for comparisons. Coronary angiography (Siemens Artis Zee Ceiling, Erlangen, Germany) was performed in multiple orthogonal projections and non-culprit lesion severity was analyzed with validated QCA 2D coronary quantification software (Scientific QCA Analysis, Siemens, Erlangen, Germany).[18] The contrast filled catheter tip was traced and used for calibration. End-diastolic images in the least foreshortened view were used for the quantitative measurement. Projection that showed the most critical stenosis was chosen and orthogonal projection was identified. Average of the measurements from these 2 projections was obtained. Analysis was performed by two experienced operators and the average of the two was calculated. İnterobserver agreements were 94% and 91% for MLD and PDS, respectively.

Data Collection and Definitions

Patients' demographic and clinical characteristics were obtained from patients' charts and electronic medical record system. Following information was gathered: age, gender, co-morbidities and risk factors for coronary artery disease (CAD) (smoking history, family history, diabetes mellitus,

hypertension, and hyperlipidemia), history of CAD (previous MI, PCI and CABG), time elapsed to follow-up CAG, MI territory, angiographic and procedural details (culprit lesion, non-culprit lesions, PTCA, tirofiban and stent use on P-PCI) and medications on PPCI and follow-up CAG. Angiographic data of the patients were obtained from catheter laboratory records and electronic medical record system. Angiographic images of primary PCI and follow-up CAG were used for QCA. Minimal lumen diameter (MLD), percentage diameter stenosis (PDS), percentage area stenosis (PAS), reference vessel diameter (RVD) and lesion length (LL) were the parameters assessed by QCA.

MLD, RVD and LL defined as the smallest lumen diameter in the segment of interest, the averaged diameter of the coronary artery assumed without atherosclerotic disease and length of the stenosis as measured by 2 points where the coronary margins change direction creating a shoulder between the angiographically normal subsegment and the diseased subsegment respectively. Percentage diameter stenosis and percentage area stenosis are calculated as follows: 100% X (RVD-MLD)/RVD and 100 % X (RVD^2- MLD^2)/ RVD^2 respectively.

STEMI defined as ST segment elevation of at least 1 mm in two or more contiguous leads (2 mm for V1–V3) or new-onset left bundle branch block.[3]

Lesion not responsible for the acute STEMI is defined as non-culprit lesion. Significant lesion is defined as >50% diameter stenosis of artery by QCA.

The primary goal was to assess the changes in non-culprit vessel lesion severity by QCA and secondary goal was to assess the independent predictors of these changes.

Statistical analysis

Continuous variables are expressed as means±SD, and categorical variables are expressed as percentages. Univariable analyses (using the chi-square or the Fisher exact test and McNemar test for paired categorical variables and the t test or Mann-Whitney U test for continuous variables) were performed to identify demographics, baseline clinical characteristics, and peri-procedural variables associated with changes in non-culprit vessel lesion severity (MLD, RVD, PDS, PAS and LL). Angiographic data between the two procedures were compared using paired t tests and changes in medications were compared using McNemar test. Uni-and multivariable predictors of changes in in non-culprit vessel lesion severity were assessed by logistic regression analysis and odds-ratios (OR) are reported. A backward stepwise multivariable logistic regression model was carried out to assess the independent relationship between variables (demographics, baseline clinical characteristics and changes in medications) and changes in non-culprit vessel QCA parameters. Variables exhibiting a P value of <0.1 in the univariable analysis were entered into the multivariable logistic regression model. For all tests, 2-sided P values <0.05 were considered as significant. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 17.0 for Windows (SPSS Inc, Chicago, Illinois, USA).

RESULTS

A total of 1442 consecutive patients who presented with STEMI and underwent P-PCI between December 2010 and July 2012 at a single tertiary care center were retrospectively reviewed. There were 749 (51.9%) patients with operator-reported multi-vessel disease. Initially, 195 patients were identified who had elective follow-up CAG within 2-60 days after primary PCI for non-culprit lesion PCI or before scheduled coronary artery by-pass graft (CABG) surgery. Six patients had instent stenoses, 2 patient had CABG to non-culprit vessels, 4 patients had chronic total occlusion (100% stenosis) and 29 patients had non-matching projections (>5° difference in any plane). After exclusion of those 41 patients, final study population consisted of 154 patients. Of those 154 patient included in this study had total of 207 significant non-culprit lesions.

Demographics and Baseline Clinical characteristics of the study population are shown in **Table 1**. Mean age was 56.1±9.5 (33-88) and 131 (85.1%) of the patients were male. TIMI 3 flow was achieved in all patients after P-PCI. Sixty-four (41.5%) patients had acute anterior MI. Time to follow-up CAG was 25.5±14.2 days (2-60).

Table 1. Patients' Demographics and Baseline Clinical characteristics

Demographics and Baseline Clinical characteristics	Study population (n=154)
Age (yrs)	56.1±9.5 (33-88)
Male	131 (85.1%)
Diabetes mellitus	42 (27.3%)
Hypertension	74 (48.1%)
Current smoker	99 (64.3%)
Hyperlipidemia	83 (53.9%)
Family history of CAD	49 (31.8)
History of CAD	46 (29.8%)
Previous MI	25 (16.2%)
Previous PCI	19 (12.3%)
Previous CABG	2 (1.3%)
Anterior MI	64 (41.5%)
Time to follow up CAG (day)	25.5±14.2 (2-60)
Culprit Vessel	
LAD	64 (41.5%)
Cx	34 (22.1%)
RCA	56 (36.4%)
Non-Culprit Vessel	
LAD	79 (38.2%)
Cx	53 (25.6%)
RCA	75 (36.2%)
Number of Non-Culprit Vessels	
1 Vessel	112 (72.7%)
2 Vessel	33 (21.4%)
3 Vessel	7 (4.5%)
4 Vessel	2 (1.3%)

CABG: coronary artery bypass graft surgery, CAD: coronary artery disease, Cx: circumflex artery, LAD: left anterior descending, MI: myocardial infarction, PCI: percutaneous coronary intervention, PTCA: percutaneous transluminal coronary angioplasty, RCA: right coronary artery.

Angiographic and peri-procedural chracteristics are shown in **Table 2**. Tirofiban was used in 66 (42.9%) patients and 145 (94.1%) patients underwent stent placement on P-PCI. There were significant differences in all medications between at the time of P-PCI and follow-up CAG with very high use of standard optimal medical therapy.

Table 2. Angiographic and Peri-procedural Chracteristics

	P-PCI	Follow-up CAG	p Value
Lesion Characteristics			
MLD (mm)	1.30 ± 0.38	1.54 ± 0.46	< 0.001
RVD (mm)	2.88 ± 0.66	2.92 ± 0.64	= 0.001
PDS (%)	54.49 ± 9.38	47.5 ± 11.17	< 0.001
PAS (%)	78.38 ± 8.65	71.29 ± 11.84	< 0.001
Lesion Length (mm)	13.52 ± 5.59	13.25 ± 5.31	0.078
PDS (≥ 50%)	157 (75.8%)	92 (44.4%)	< 0.001
Procedural details			
Stent	145 (94.1%)		
PTCA	9 (5.9%)		
Tirofiban	66 (42.9%)		
Medications			
ASA	24 (15.6%)	152 (98.7%)	<0.001
Clopidogrel	8 (5.2%)	151 (98.1%)	<0.001
Beta- blocker	12 (7.8%)	150 (97.4%)	<0.001
ACE inhibitor or ARB	34 (22.1%)	143 (92.9%)	<0.001
Calcium-channel blocker	8 (5.2%)	21 (13.6%)	0.002
Statin	13 (8.4%)	148 (96.1%)	<0.001
Nitrate	3 (1.9%)	36 (23.4%)	<0.001

ACE: angiotensin-converting-enzyme, ARB: angiotensin receptor blocker, ASA: acetylsalicylic acid,CAG coronary angiography, MLD: minimal lumen diameter, PAS: percentage area stenosis, PDS: percentage diameter stenosis, P-PCI: primary percutaneous coronary intervention, PTCA: percutaneous transluminal coronary angioplasty, RVD: reference vessel diameter.

Changes in non-culprit lesion severity by QCA

MLD (1.30±0.38 mm vs. 1.54±0.46 mm, p= <0.001) and RVD (2.88±0.66 mm vs. 2.92±0.64 mm, p= 0.001) were increased significantly and PDS (54.49±9.38 vs. 47.5±11.17, p= <0.001) and PAS (78.38±8.65 vs. 71.29±11.84, p= <0.001) were decreased significantly on follow-up CAG compared to P-PCI. There was no significant change in lesion length (13.52±5.59 mm vs. 13.25±5.31 mm, p= 0.078).

Of these 207 non-culprit lesions, MLD and RVD showed absolute increase in 172 (83.1%) and 128 (61.8%) lesions, respectively. Number of significant non-culprit lesions (PDS ≥50% by QCA) was 157 (75.8%) at the time of P-PCI and was declined to 92 (44.4%) on follow-up CAG. This means that severity of the stenosis in 65 (41.4%) of the non-culprit lesions were exaggerated significantly at the time of the P-PCI.

Predictors of changes in non-culprit lesion severity

None of the clinical and demographic variables were significantly associated with increase in RVD in univariable analyses. Variables (hypertension, hyperlipidemia, current smoking, history of CAD and clopidogrel use after the P-PCI) exhibiting a P value of <0.1 in the univariable analyses for the increase in MLD and decrease in PDS were entered into the model for multivariable analyses. In multivariable analyses (**Table 3**); current smoking [Odds Ratio (OR): 10.36, 95% Confidence Interval (CI): 4.06 - 26.41, p <0.001], history of CAD [OR: 0.21, 95% CI: 0.084 - 0.559, p= 0.002] and clopidogrel use after the P-PCI [OR: 20.0, 95% CI: 2.34 - 170.53, p= 0.006] were found to be associated with the increase in MLD. Likewise, current smoking [OR: 10.42, 95% CI: 4.09 - 26.53, p <.001], history of CAD [OR: 0.26, 95% CI: 0.098 - 0.689, p=0.007] and clopidogrel use after the P-PCI [OR: 26.63, 95% CI: 3.06 - 231.30, p=0.003] were found to be associated with decrease in PDS.

Table 3. Independent predictors of increase in MLD and decrease in PDS in multivariable regression analysis

Variable	Odds ratio (95% CI)	P-value
Predictors of changes in MLD		
Current smoking	10.36 (4.06-26.41)	<0.001
History of CAD	0.21 (0.084-0.559)	=0.002
Clopidogrel use after P-PCI	20.0 (2.34-170.53)	=0.006
Predictors of changes in PDS		
Current smoking	10.42 (4.09-26.53)	<0.001
History of CAD	0.26 (0.098-0.689)	=0.007
Clopidogrel use after P-PCI	26.63 (3.06-231.30)	=0.003

CAD: coronary artery disease, CI: confidence interval, MLD: minimal lumen diameter, PDS: percentage diameter stenosis, P-PCI: primary percutaneous coronary intervention.

DISCUSSION

Approximately 50% of STEMI patients have significant stenoses in one or more non-culprit arteries[5,6] at the time of P-PCI. Outcomes and best treatment strategies (complete vs. culprit lesion only) of the patients presenting with STEMI and multi-vessel disease has been investigated in many studies. But only in a few studies changes in the culprit or non-culprit lesions severity assessed by QCA have been reported. Exaggeration of non-culprit lesion stenosis severity might occur at the time of ACS.

The results of this study show that exaggeration of non-culprit lesion stenosis severity occurs at the time of acute STEMI. MLD and RVD were increased significantly and PDS and PAS were decreased significantly on follow-up CAG which was done in non-acute settings. There was no significant change in lesion length. MLD and RVD showed absolute increase in 172 (83.1%) and 128 (61.8%) lesions, respectively. Number of significant non-culprit lesions (percentage diameter stenosis ≥50% by QCA) was 157 (75.8%) at the time of P-PCI and was declined to 92 (44.4%) on follow-up CAG. This means that severity of the stenosis in 65 (41.4%) of the non-culprit lesions were exaggerated at the time of the P-PCI. Independent predictors of both increase in MLD and decrease in percentage diameter stenosis were; smoking, history of CAD and clopidogrel use after the P-PCI.

There was no significant change in lesion length in our study. In a study by Sahin et al. [19] 58 patients with acute ST-segment elevation myocardial infarction (STEMI) were evaluated for changes in diameter of the infarct-related artery (IRA) during primary PCI and after an average of 3 days. CAG was performed

on presentation and TIMI 3 flow was achieved either by simple balloon dilatation and/or thrombus aspiration. Lesion length, RVD, MLD, mean vessel diameter (meanD), and area of stenosis were compared during P-PCI and follow-up CAG. They also found that there was no significant change in lesion length.

RVD was increased significantly on follow-up CAG in our study similar to the reported by Sahin et al.[19] However, Hanratty et al.[8] and Cristea et al.[20] found that there was no change in RVD. Hanratty et al.[8] included 48 patients with 59 non-culprit lesions suitable for analysis in their study. Between infarct and non-infarct angiograms there was a significant change in minimal lumen diameter (1.53±0.51 mm vs. 1.78±0.65 mm, p <0.001) and percentage diameter stenosis (49.3±14.5% vs. 40.4±16.6%, p <0.001) of the nonculprit lesion without significant change in reference segment diameter. Twenty-one percent of patients had lesions >50% at AMI that were <50% at non-AMI angiography. Infarct versus non-infarct setting was the only significant independent predictor of change in non-culprit stenosis. PDS was decreased significantly in our study consistent with the observations of Hanratty et al.[8] and Sahin et al.[19] MLD was increased and PDS was decreased significantly in our study on follow-up CAG. Hanratty et al.[8] and Sahin et al.[19] also reported similar significant changes in MLD and PDS. We also found that current smoking, history of CAD and clopidogrel use after the P-PCI were independent predictors of both increase in MLD and decrease in PDS in multivariable analysis.

Natural progression of coronary artery disease involves two distinct processes. First, fixed and almost irreversible process that causes gradual luminal narrowing slowly over decades (atherosclerosis). Second, a dynamic and potentially reversible process that causes rapid coronary occlusion (thrombosis or vasospasm, or both). Thus, symptomatic coronary lesions contain a variable mix of chronic atherosclerosis and acute thrombosis but, because the exact nature of the mix is unknown in the individual patient, the term atherothrombosis is frequently used. Generally, atherosclerosis predominates in lesions responsible for chronic stable angina, whereas thrombosis constitutes the critical component of culprit lesions responsible for the ACS.[11,12,21,22]

Individuals using clopidogrel after the P-PCI were more likely to have increase in MLD and decrease in percentage diameter stenosis, OR (Odds Ratio): 20.0 (95% CI: 2.34 - 170.53, p= 0.006) and OR: 26.63 (95% CI: 3.06 - 231.30, p= 0.003), respectively. This significant improvement in non-culprit vessel stenosis with the use of clopidogrel can be due to the inhibition of platelet functions which result in inhibition of this second dynamic and reversible process of atherothrombosis at the time of P-PCI as described above.

Individuals with a current smoking history were more likely to have increase in MLD and decrease in percentage diameter stenosis, OR: 10.36 (95% CI: 4.06 - 26.41, p <0.001) and 10.42 times (95% CI: 4.09 - 26.53, p <.001), respectively. Cigarette smoking plays a direct role by constricting coronary arteries through nicotine-mediated action on alpha-adrenergic receptors and by induction of endothelial dysfunction by nicotine and oxidizing chemicals.[23,24] Therefore, smoking is more likely to cause rapid and reversible coronary occlusion in patients with ACS rather than the fixed stenosis.

Individuals with a history of CAD were less likely to have increase in MLD and decrease in percentage diameter stenosis, OR: 0.21 (95% CI: 0.084 - 0.559, p= 0.002) and 0.26 (95% CI: 0.098 – 0.689, p= 0.007), respectively. Individuals with a known history of CAD are more likely to have predominantly atherosclerotic lesions. These are generally fixed fibroproliferative and hardly reversible lesions that cause slow gradual stenosis.

CONCLUSION

Exaggeration of non-culprit lesion stenosis severity occurs at the time of acute STEMI. Deferring the revascularization decision making and further evaluation of these lesions with FFR or intravasküler ultrason may result in more accurate evaluation of the lesions and prevent unnecessary PCI.

Limitations

Retrospective and monocentric characters are the limitations of our study.

ETHICAL DECLARATIONS

Ethics Committee Approval: Study was approved by the Republic of Turkey Ministry of Health, University Of Health Sciences, Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital Clinical Research Ethics Committee (IRB number: 2013/13).

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

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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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.758144
J Contemp Med 2021;11(4):543-549

Orjinal Araştırma / Original Article

Factors Affecting Mothers' Baby Nutrition Attitudes in Postpartum Period

Postpartum Dönemde Annelerin Bebek Beslenmesi Tutumlarını Etkileyen Faktörler

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Abstract

Aim: To investigate the factors affecting mothers' infant feeding attitudes in the postpartum period.

Material and Method: Crosssectional descriptive research was carried out in a public hospital child outpatient clinic. The sample of the study consisted of 173 mothers whose babies were followed up in the pediatric outpatient clinic between April 2018 and April 2019. The data were obtained through the questionnaire form and the Infant Nutrition Attitude Scale.

Results: A statistically significant difference was found in terms of Baby Nutrition Attitude Scale scores according to the mothers' mode of delivery (p=.002) and the breastfeeding status of their babies in the community (p=.002). It was determined that there was a highly positive correlation (p=.000) between the number of maternal controls during pregnancy and the total duration of breastfeeding. It was observed that there was a positive (p=.012) relationship between the number of births of the mothers and the Baby Nutrition Attitude Scale scores. İt is possible to explain approximately 12.3% of the dependent infant feeding attitude variable with the variable of maternal education and breastfeeding status in society.

Conclusion: The breastfeeding attitude of mothers who gave birth by cesarean section is positive compared to mothers who gave birth normally. Mothers who have a positive breastfeeding attitude breastfeed their babies more easily in the society. As the number of mothers during pregnancy increases, the total duration of breastfeeding increases. As the number of births of mothers increases, breastfeeding attitude increases positively.

Keywords: Breast feeding, attitude, infant, nutritional status

Öz

Amaç: Postpartum dönemde annelerin bebek beslenmesi tutumlarını etkileyen faktörleri incelenmek.

Gereç ve Yöntem: Kesitsel tanımlayıcı özellikteki araştırma, bir devlet hastanesinin çocuk polikliniğinde yürütüldü. Çalışmanın örneklemini Nisan 2018-Nisan 2019 tarihleri arasında, çocuk polikliniğinde bebeği izlenen 173 anne oluşturdu. Veriler anket formu ve Bebek Beslenmesi Tutum Ölçeği aracılığıyla elde edildi.

Bulgular: Annelerin doğum şekli (p=,002) ve toplum içinde bebeğini emzirme durumuna (p=,002) göre Bebek Beslenmesi Tutum Ölçeği puanları açısından istatistiksel olarak anlamlı fark olduğu saptandı. Annelerin gebelikteki kontrol sayısı ile toplam emzirme süresi arasında ileri düzeyde olumlu yönde bir ilişki olduğu (p=,000) belirlendi. Annelerin doğum sayısı ile Bebek Beslenmesi Tutum Ölçeği puanları arasında olumlu yönde (p=,012) ilişki olduğu görüldü. Anne eğitimi ve toplum içinde bebeği emzirme durumu değişkeni ile bağımlı bebek beslenmesi tutumu değişkeninin yaklaşık olarak %12,3'ünün açıklanması mümkündür.

Sonuç: Sezaryen ile doğum yapan annelerin emzirme tutumu normal doğum yapan annelere göre olumludur. Emzirme tutumu olumlu olan anneler toplumda bebeğini daha rahat emzirmektedir. Annelerin gebelikteki kontrol sayısı artıkça toplam emzirme süresi artmaktadır. Annelerin doğum sayısı arttıkça emzirme tutumu olumlu yönde artmaktadır.

Anahtar kelimeler: Emzirme, tutum, bebek, beslenme durumu

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Received *(Geliş Tarihi)*: 26.06.2020 **Accepted *(Kabul Tarihi)*:** 30.05.2021

INTRODUCTION

The World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) recommend that breastfeeding should be started within the first hour after birth, exclusive breastfeeding should be given in the first six months, and breastfeeding with complementary foods should be continued until the age of two from six months.[1,2] According to WHO, 40% of infants younger than six months are exclusively breastfed.[3] According to the Turkey Demographic and Health Surveys (TNSA) 2018 report, the rate of infants receiving only breast milk in our country decreases rapidly with age, and 41% of infants aged 4-5 months receive only breast milk.[4] Breastfeeding the newborn within the first hour after birth is very important for breastfeeding success.[3,5] Today, mothers' breastfeeding frequency has decreased and the duration of breastfeeding has been shortened.[6] It has been determined that 71% of babies in Turkey are breastfed within the first hour after birth, and 42% of newborns receive food in the prelacteal period contrary to the recommendation.[4]

The way a mother feeds her baby and the duration of breastfeeding; Factors such as breastfeeding problems that develop in the postpartum period, sociocultural structure, economic situation, family structure, beliefs, breastfeeding attitude affect.[7-10] The mother's lack of breastfeeding experience, not knowing the breastfeeding technique, perception of the mother's milk as inadequate, thinking that the baby is not full, not being supported for breastfeeding and being against breastfeeding affect the success of breastfeeding.[11,10] Studies show that the breastfeeding attitude of the mother significantly affects the feeding of the baby.[13-15] It is noted that the rate of using formula or starting complementary foods early, especially in mothers with a negative breastfeeding attitude, increases.[16,17] In the initiation and maintenance of breastfeeding, mothers' attitudes towards breastfeeding and infant feeding are the main determinants of infant nutrition. For breastfeeding success, mothers should be closely monitored in the first months, breastfeeding attitudes should be evaluated and counseling services should be provided to mothers in the risk group.[16-18]

Although the infant feeding attitude of mothers is very important for the continuation of breastfeeding, the studies on the subject are limited in the literature. This research was conducted to examine the factors affecting the infant feeding attitudes of mothers in the postpartum period.

For this purpose, answers to the following questions were sought;

- Is there a relationship between mothers' socio-demographic characteristics and infant feeding attitudes?
- Is there a relationship between mothers' obstetric characteristics and infant feeding attitudes?

MATERIAL AND METHOD

Type of Study

The research was conducted in cross-sectional and descriptive type.

The population and sample of the study: The population of the study consisted of mothers whose babies were followed in the pediatric outpatient clinic of a state hospital. It was determined that a total of 480 mothers applied to the outpatient clinic with their babies in the first 6 weeks postpartum between April 2018 and April 2019. When the sample size was calculated according to the acceptable error using the sample calculation method with a specific population, it was determined that the recommended sample size should be 174 mothers with a 5% margin of error and a 90% confidence intervalThe data of 1 person who answered the data collection form incompletely during data entry was excluded from the study, and the study was completed with data of 173 mothers.

Inclusion Criteria

- Mothers with a baby whose gestational age is 34 weeks and above,
- Mothers with healthy singleton babies between 0-6 weeks,
- Mothers who could speak Turkish were included in the sample.

Exclusion Criteria

- Mothers who are breastfeeding or have breast-related problems,
- Mothers with acute/chronic diseases that may affect breast milk content.
- Mothers with a disease known to be transmitted through breast milk were not included in the sample.

Data Collection Tools

In the collection of data, the "Survey Form" created by the researchers by scanning the literature. (19,20,21,34-37) and “Iowa Infant Feeding Attitude Scale-IIFAS” was used.

Survey form; It consists of a total of 32 questions, 11 questions about socio-demographic characteristics, 10 questions about obstetric and gynecological features, and 11 questions about breastfeeding features.

Infant Feeding Attitude Scale (Iowa Infant Feeding Attitude Scale-IIFAS); The scale developed by De La Mora and Russell was designed to evaluate women's attitudes towards breastfeeding and to determine the duration of breastfeeding as well as the choice of infant feeding method. In the five-point Likert scale, 9 items evaluate breastfeeding and 8 items evaluate formula feeding. Items evaluating formula nutrition are scored in reverse (1=5, 2=4, 4=2 and 5=1). The total score obtained from the scale ranges from 17 (reflecting a positive attitude in bottle feeding) to 85 points (reflecting a positive attitude in breastfeeding).[22] The

scale has no cut-off value, high scores indicate a positive breastfeeding attitude. Turkish validity and reliability of the scale Ekşioğlu et al. made by In the Turkish validity and reliability study of the scale, Cronbach Alpha values were determined to be 0.71.[21] In this study, the Cronbach Alpha value of the scale was found to be 0.70.

Data collection; The data were obtained by one of the researchers by face-to-face interview method in the polyclinic. It took an average of 10-15 minutes to complete the data collection tools.

Ethical Aspect

Before starting the data collection, ethics committee approval (Date: 30.09.2019 Ethics committee no: 140) and permissions from the scale owner and the institution where the research was conducted were obtained from Haliç University Non-Interventional Clinical Research Ethics Committee. During the research, the rules of the Declaration of Helsinki were complied with. By paying attention to the principle of voluntariness in participating in the study, verbal and written consent was obtained from the mothers by giving information about the purpose of the study before the study.

Statistical Analysis

The data obtained at the end of the research were evaluated using the SPSS 21.0 package program, using parametric and nonparametric descriptive statistical analyzes. From descriptive statistics; number, percentage, mean, standard deviation, and minimum-maximum were used. The conformity of the quantitative data to the normal distribution was evaluated with the Shapiro-Wilk test and graphical examinations. The Mann-Whitney U test was used for the evaluation of the non-normally distributed variables between two groups. Pearson correlation coefficient was used to determine the level of correlation between quantitative data. Statistical significance level was accepted as $p<0.05$. Factors affecting infant feeding attitude were analyzed by multiple linear regression analysis.

RESULTS

It was seen that the mean age of the mothers in the study group was 30.28±5.41, 47.4% had a secondary education (high school) level and 18.5% were working (**Table 1**). It was determined that 72.3% of the participants in the study group had planned pregnancy, 55.5% gave birth by cesarean section and 78.6% had breastfeeding experience. It was observed that there was no statistically significant difference in terms of planning the pregnancy, receiving breastfeeding support, giving formula and pacifier/bottle to their baby and the scores of the Infant Nutrition Attitude Scale ($p>0.05$). A statistically significant difference was found in terms of Infant Nutrition Attitude Scale scores according to the mother's mode of delivery ($p=.002$) and breastfeeding status in the community ($p=.002$) (**Table 2**).

Table 1. Socio-Demographical characteristics of mothers and babies (N=173)

Features	$\bar{x} \pm SS$
Average age of mother (years)	30.28±5.41
Average postnatal age (days) of the baby	23.89±13.54
Average gestational age (weeks) of the baby	38.24±2.01
Educational status	**n (%)**
literate	20 (11)
Basic training	24 (16.2)
Secondary education	84 (47.4)
High School	45 (25.4)
Working status	
Working	32 (18.5)
Not working	141(81.5)
Family structure	
Nuclear family	132 (76.3)
Extended family	36 (20.8)
Broken family	5 (2.9)
Income status	
Income more than expenses	22 (12.7)
Income equal to expenses	90 (52.0)
Income less than expenses	61 (35.3)
Baby's Gender	
Girl	84 (48.6)
Boy	89 (51.4)
Number of children she has	
A child	58 (33.5)
Two children	83 (48.0)
Three children and more	32 (18.5)

Table 2. Comparison of mothers' obstetric-gynecological and breastfeeding characteristics and Infant Nutrition Attitude Scale Scores (N=173)

Features	n (%)	$\bar{x} \pm SS$	MWU(Z);p
Planning pregnancy			
Planed	125 (72.3)	58.96±8.56	-.489;627
Unplaned	48 (27.7)	59.66±8.49	
Type of birth			
Normal birth	77 (44.5)	56.93±7.69	-3.193;.002
Cesarean Birth	96 (55.5)	60.93±8.77	
Breastfeeding experience			
There is	136 (78.6)	59.22±8.56	2.213;.832
No	37 (21.4)	58.89±8.49	
Getting breastfeeding support			
Yes	125 (72.3)	59.27±8.26	2.743;.785
No	48 (27.7)	58.85±9.25	
Breastfeeding in public			
Yes	83 (48.0)	61.22±8.08	3.156;.02
No	90 (52.0)	57.24±8.51	
Feeding the baby with formula			
Yes	93 (53.6)	59.13±7.99	-.027;.979
No	80 (46.4)	59.17±9.15	
Using a pacifier/ bottle			
Yes	113 (65.3)	59.45±8.09	.595;.553
No	60 (34.7)	58.59±9.40	

MWU(Z): Mann Whitney U

When the relationship between demographic-obstetric and breastfeeding-related characteristics and Infant Nutrition Attitude Scale scores were examined; There is a highly positive correlation between the number of controls during pregnancy and the total duration of breastfeeding (r:.965, p:.000), and there is a negative correlation between the number of births of mothers and their Infant Nutrition Attitude Scale scores (r:.916, p:.012) was found to be related (**Table 3**).

Factors affecting infant feeding attitude were examined by multiple linear regression analysis. When the table is examined, it is seen that the established regression model is significant (F: 11.921 and p:0.000). The table also includes the rate at which infant feeding attitude is explained by the variable of maternal education and breastfeeding status in the community. Accordingly, it is possible to explain approximately 12.3% of the dependent infant feeding attitude variable with the relevant regression model. In addition, Durbin-Watson test statistic was calculated as 1.758 and VIF value as 1.026. These values show the suitability of the established model. According to this; It is statistically possible to explain the dependent variable of infant feeding attitude with at least one of the fixed and independent variables. When the table is examined, the coefficients of the variables of constant term, education of the mother and breastfeeding the baby in the community were found statistically significant at the 0.05 significance level. The study also examined the effects of the mother's employment status, baby's gender, pregnancy planning, delivery type, breastfeeding education during pregnancy, breastfeeding experience, breastfeeding support from the spouse/surrounder, the duration of breastfeeding, the use of a pacifier bottle, and the baby's feeding style on the mother's infant feeding attitude. they were excluded from the model because they were not statistically significant (**Table 4**).

DISCUSSION

Despite the recommendations, breastfeeding rates are still not at the desired level. The most important factor in increasing breastfeeding rates and breastfeeding success is the mother's attitude towards infant feeding,[2,13,14] and it is recommended to evaluate mothers' breastfeeding attitudes in the first months.[16-18] The results obtained in this study, which was conducted to examine the factors affecting the attitudes of mothers about infant feeding in the postpartum period, were examined in the light of the literature.

It was determined that 72.3% of the mothers in the study group were supported about breastfeeding, but receiving breastfeeding support did not affect the infant feeding attitude. Gibson et al. (2007) examined the factors affecting mothers' breastfeeding attitudes in a study involving 3567

Table 4. Factors affecting ınfant feeding attitudes

Modal		Non-Standardized Coefficients		Standardized Coefficients	t	p.	Correlations			VIF Value
		B	Std. error	Beta			Zero-order	Partial	Part	
1	Constant term	57.060	2.970		19.213	.000				
	Mother's education	2.456	.675	.265	3.641	.000	.295	.269	.262	1.026
	Breastfeeding in public	-3.259	1.237	-.192	-2.635	.009	-.234	-.198	-.189	1.026

ANOVA test of regression (F)=11.921 p=0.000. R2=0.123

Table 3. Demographic-obstetrics the relationship between breastfeeding characteristics and Infant Nutrition Attitude Scale Scores (N=173)

Variables		Maternal age	Baby's gestational age	Number of births	Number of children	Number of controls during pregnancy	Breastfeeding time only	Total breastfeeding time	‡INAS total score
Maternal age	p	1	-.193*	.438†	.411†	-.178*	.078	.010	.012
	r		.011	.000	.000	.019	.309	.898	.875
Baby's gestational age	p	-.193*	1	-.054	-.072	-.010	-.012	.074	-.063
	r	.011		.482	.346	.894	.880	.335	.412
Number of births	p	.438†	-.054	1	.936†	-.114	.095	.008	-.190*
	r	.000	.482		.000	.136	.215	.916	.012
Number of children	p	.411†	-.072	.936†	1	-.068	.118	.009	-.137
	r	.000	.346	.000		.377	.123	.906	.072
Number of controls during pregnancy	p	-.178*	-.010	-.114	-.068	1	.003	.278†	.144
	r	.019	.894	.136	.377		.965	.000	.059
Breastfeeding time only	p	.078	-.012	.095	.118	.003	1	.156*	.064
	r	.309	.880	.215	.123	.965		.040	.405
Breastfeeding time	p	.010	.074	.008	.009	.278†	.156*	1	.354**
	r	.898	.335	.916	.906	.000	.040		.000
‡INAS total score	p	.012	-.063	-.190*	-.137	.144	.064	.354†	1
	r	.875	.412	.012	.072	.059	.405	.000	

*Correlation is significant at the 0.05 level (2-tailed), †. Correlation is significant at the 0.01 level (2-tailed), ‡Bebek Beslenmesi Tutum Ölçeği

mothers, and found that the support given to mothers did not affect the infant's feeding and breastfeeding attitudes.[23] However, in the literature, it is seen that there are more results indicating that support positively affects mothers' attitudes towards feeding their babies.[24-26] Kervin et al. (2010) found that the support given by health professionals positively affects breastfeeding of the mother.[27] Lassi et al. (2020) examined interventions related to infant and child nutrition and included 66 studies, it was determined that the education and support of health professionals positively affected mothers' breastfeeding attitudes.[28] It is understood that the results regarding the effect of breastfeeding support given to mothers on infant nutrition are different. It suggests that maternal support should be examined with high-evidence studies. In our study group, the personal statements of the mothers were taken as basis, and the scope of the support was not examined.

It has been reported that planned pregnancy facilitates the adaptation of mother and baby in the postpartum period, and positively affects breastfeeding and mother-infant attachment.[29] Aidam et al. (2005), Gölbaşı and Koç (2008) found that planned pregnancy had a positive effect on breastfeeding attitude in their research on the factors related to breastfeeding.[30,31] In our study group, it was determined that the planned pregnancy did not affect the infant feeding attitude. Similarly, Çalık et al. (2017) did not find a significant relationship between mothers' feeding attitudes and planned pregnancy.[32] It is seen that the results of the study are contradictory and the subject should be re-examined in different studies.

It was determined that the breastfeeding attitude of mothers who gave birth by cesarean section was more positive than mothers who gave birth normally. In the study of Çalık et al. (2017) did not find a significant relationship between mothers' feeding attitudes and mode of delivery.[32] Çakır and Alparslan (2018), mothers who gave birth by cesarean section; She stated that she was reluctant to breastfeed because of the pain at the cesarean section incision site and the negative feelings she felt towards her baby and that she breastfed later.[33] In the literature examining the relationship between mode of delivery and breastfeeding, it is noted that mothers who give birth normally have a more positive attitude towards breastfeeding. It is reported that the breastfeeding attitude is more positive due to the fact that mothers with normal delivery have less postpartum pain, perceive their baby positively and start breastfeeding earlier.[12,33-35] The fact that mothers who gave birth by cesarean section in our study group had a positive attitude towards breastfeeding compared to mothers who had normal birth contradicts the current research and literature. It may be suggested to test the subject with different studies. It was determined that the infant feeding attitude was not different according to the mother's giving pacifier and bottle to her baby. Lenja et al. found that mothers with positive breastfeeding attitudes used less pacifiers and bottles.[36] In the literature, it is stated that mothers who use pacifiers and bottles stop breastfeeding early.[8,34,36]

It was determined that as the number of controls during pregnancy of the mothers in our study group increased, the total duration of breastfeeding increased. In addition, it was observed that as the number of births of mothers increased, the breastfeeding attitude increased positively. The sociocultural and economic status of women, employment conditions, access to health services, receiving support, etc. many factors affect.[12,26] Karaçam and Sağlık (2018) stated in their systematic review that mothers' lack of motivation, knowledge and experience negatively affects breastfeeding attitudes.[12] It has been reported that access to health institutions from the prenatal period and communication with health personnel are important factors among the determinants of breastfeeding decisions and attitudes.[26] It can be said that our study findings are in parallel with the literature.

It was determined that the education level of the mothers in the study group was an important explanatory factor on the infant feeding attitude. Lenja et al. It has been reported that there is a significant relationship between maternal education and the attitude of feeding their babies with breast milk.[36] In the literature, there are results[37,38] reporting that maternal education is not associated with breastfeeding attitudes, and there are also results reporting that there is a relationship between education and breastfeeding attitudes in parallel with our research findings. In this study, it was observed that breastfeeding of the mother in public was an important explanatory factor on the infant feeding attitude, and that the mothers with a positive infant feeding attitude could easily breastfeed their infants in public. In our country, associating the breast with sexuality can be seen as a situation that prevents breastfeeding in public places during the breastfeeding process. It is stated that mothers behave differently in this regard, sometimes they behave very comfortably, and sometimes they feel uncomfortable for various reasons.[39,40] In a study conducted in England, it was determined that 42% of mothers prefer to breastfeed in a private area, and only 8% can breastfeed anywhere without the need for a private area. It is stated that when mothers cannot breastfeed in public places, they take a bottle with them and feed the baby with formula when going out to feed the baby.[41] There is a need for new studies examining mothers' breastfeeding behavior in society and the effects of cultural influences on infant feeding attitudes.

CONCLUSION

Breastfeeding experience of mothers, receiving support for breastfeeding, using a pacifier/bottle, and planned pregnancy do not affect infant feeding attitudes. The breastfeeding attitude of mothers who gave birth by cesarean section is more positive than mothers who gave birth normally. As the number of controls during pregnancy increases, the total duration of breastfeeding increasesAs the number of births of mothers increases, breastfeeding attitudes increase positively.

Mothers with a positive breastfeeding attitude breastfeed their babies more comfortably in the society. Midwives and nurses can improve mothers' attitudes towards infant feeding within the scope of their counseling roles. Within the scope of the counseling roles of midwives and nurses, mothers' attitudes towards infant feeding are positively developed.

ETHICAL DECLARATIONS

Ethics Committee Approval: Before starting the data collection, ethics committee approval (Date: 30.09.2019 Ethics committee no: 140) and permissions from the scale owner and the institution where the research was conducted were obtained from Haliç University Non-Interventional Clinical Research Ethics Committee.

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.

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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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.948639
J Contemp Med 2021;11(4):550-554

Orjinal Araştırma / Original Article

Scrotal Involvement in Childhood Immunoglobulin an Associated Vasculitis

Çocukluk Çağı İmmünoglobulin A ile İlişkili Vaskülitte Skrotal Tutulum

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Abstract

Aim: The aim of this study is to evaluate the demographic and clinic findings in immunoglobulin A-associated vasculitis (IgAV) patients with scrotal involvement and also to determine predictive factors for assessing the development of scrotal involvement.

Materiel and Method: The medical records of 181 boys who were diagnosed with IgAV in the Pediatric Rheumatology Clinic of our center between September 2015-January 2021 were evaluated retrospectively.

Results: A total number of 181 boys with IgAV included in the study. Twenty-seven (14.9%) of the 181 boys with IgAV had scrotal involvement. Among the scrotal-involved patients, 23 boys (85.1%) had scrotal swelling, 19 (70.3%) had erythema and 21 (77.7%) had scrotal pain or tenderness. Scrotal involvement was the first symptom of IgAV in one patient. CRP and WBC were significantly higher in the scrotal-involved group compared to the non-involved group (p=0.018, p=0.04, respectively). There were no significant differences in clinical findings and organ involvements between two groups. On ultrasonography, bilateral scrotal soft tissue thickening was observed in all patients. In 20 (74%) patients with scrotal involvement, increased vascularity was detected in the epididymis with swelling.. The size, echogenicity and vascularity of the testicles were within normal limits. Eighty-seven of the patients (48%) were given steroids, 22 of them (11.7%) nonsteroidal anti-inflammatory drug.

Conclusion: Scrotal involvement in boys with IgAV is not rare, it should be considered in the differential diagnosis in patients with scrotal pain, swelling and erythema. In addition, inflammatory markers may be higher in patients with scrotal involvement.

Keywords: Immunoglobulin A-associated vasculitis, scrotal involvement, MEFV, children

Öz

Amaç: Bu çalışmanın amacı, skrotal tutulumu olan immünoglobulin A ile ilişkili vaskülit (IgAV) hastalarında demografik ve klinik bulguları değerlendirmek ve ayrıca skrotal tutulum gelişimini değerlendirmede prediktif faktörleri belirlemektir.

Gereç ve Yöntem: Merkezimiz Çocuk Romatoloji Kliniği'nde Eylül 2015-Ocak 2021 tarihleri arasında IgAV tanısı alan 181 erkek çocuğun tıbbi kayıtları geriye dönük olarak incelendi.

Bulgular: Çalışmaya IgAV'li toplam 181 erkek çocuk dahil edildi. IgAV'li 181 erkek çocuğun 27'sinde (%14.9) skrotal tutulum vardı. Skrotal tutulumlu hastalardan 23'ünde (%85.1) skrotal şişlik, 19'unda (%70.3) eritem ve 21'inde (%77.7) skrotal ağrı veya hassasiyet vardı. Bir hastada skrotal tutulum IgAV'nin ilk semptomuydu. Beyaz küre ve C-reaktif protein, skrotal tutulumu olan grupta, tutulum olmayan gruba göre anlamlı derecede yüksekti (sırasıyla, p=0.018, p=0.04). İki grup arasında klinik bulgular ve organ tutulumları açısından anlamlı fark yoktu. Ultrasonografide tüm hastalarda bilateral skrotal yumuşak doku kalınlaşması izlendi. Hastaların 20'sinde (%74) epididimde artmış vaskülarite ile birlikte şişlik mevcuttu. Testislerin boyutu, ekojenitesi ve vaskülaritesi normal sınırlar içindeydi. Hastaların 87'sine (%48) steroid, 22'sine (%11,7) nonsteroid antiinflamatuar ilaç verildi.

Sonuç: IgAV'li erkek çocuklarda skrotal tutulum nadir değildir. Skrotal ağrı, şişlik ve eritem şikayeti olan hastalarda ayırıcı tanıda düşünülmelidir. Ayrıca skrotal tutulumu olan hastalarda inflamatuar belirteçler daha yüksek olabilir.

Anahtar Kelimeler: Çocuklar, immünoglobulin A ile ilişkili vaskülit, MEFV, skrotal tutulum

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Received *(Geliş Tarihi)*: 07.06.2021 **Accepted *(Kabul Tarihi)*:** 25.06.2021

INTRODUCTION

Immunoglobulin A (IgA)-associated vasculitis (IgAV; formerly known as Henoch Schönlein purpura) is a systemic vasculitis characterised by the deposition of IgA-containing immune complexes in the walls of small vessels such as arterioles, capillaries and venules.[1,2] IgAV is the most common childhood vasculitis, with an incidence of about 22 cases per 100,000 per year.[3,4] The majority of IgAV patients are preceded by an upper respiratory tract infection, immunizations, drugs, insect bites, and foods, suggesting potential triggers.[5,6]

IgAV is characterized by palpable purpura that predominate on the ankles and lower legs. It can have other concurrent clinical involvement such as joints, gastrointestinal (GI) tract, renal and, the central nervous system. Diagnosis of IgAV according to the European League against Rheumatism/Paediatric Rheumatology European Society (EULAR/ PRES) criteria is based on the presence of palpable purpura or petechiae with lower limb predominance (mandatory criterion) plus at least one of the flowing four features: (a) abdominal pain; (b) arthritis/arthralgia; (c) leukocytoclastic vasculitis or proliferative glomerulonephritis with predominant deposition of IgA on histology; (d) renal involvement.[7]

Approximately 50% of patients with IgAV have renal involvement, but extrarenal genitourinary manifestations of IgAV (acute scrotum, ureteritis with associated hydronephrosis, hematoma of the bladder wall, and hemorrhagic spermatic cord) develop much less frequently. Scrotal involvement of disease usually results in pain, tenderness, swelling or bruising of scrotum.[8]

Although pediatricians are well aware of the typical clinical features of IgAV, they may not be sufficiently familiar with its other rare findings such as scrotal involvement and its approach. The aim of this study is to evaluate the demographic and clinic findings in IgAV patients with scrotal involvement and also to determine predictive factors for assessing the development of scrotal involvement.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara City Hospital No:2 Clinical Researches Ethics Committee (Date: 16.06.2021, Decision no: E2-21-605). All procedures were performed adhered to the ethical rules and the Helsinki Declaration of Principles.

We retrospectively evaluated 181 boys of IgAV patients diagnosed at our center from September 2015 to January 2021. The diagnosis of IgAV required the fulfillment of EULAR/ PRES diagnostic criteria.[7]

Three hundred fifteen children and adolescents were diagnosed with IgAV during the study period. In total, 134 of these patients were girls. These patients were excluded from the study. The remaining 181 boys (57.5%) with IgAV were included in the study. In addition, boys who were diagnosed with IgAV during the study period but had missing data were also excluded from the study.

Patients data collected included demographic data, patient's medical history, presenting symptoms, clinical features, laboratory parameters and medications. Extensive investigations included complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum creatinine, urea nitrogen level, proteinuria, hematuria, and immunological parameters including serum C3, C4, antinuclear antibodies.

Gastrointestinal bleeding was defined as occult blood in stool, grossly bloody stools, melena, or hematochezia. Renal involvement was defined as the presence of gross or microscopic hematuria (>5 red blood cells per high-power microscopic field in a centrifuged specimen) and/or proteinuria (urine protein/ creatinine ratio <0.2 in children ≥2 year of age). Neurological involvement included headache, seizure, unconsciousness, or localizing signs. Scrotal involvement was defined as swelling, pain and tenderness in the scrotum. Symptoms or signs of scrotal involvement (scrotal swelling, pain or tenderness) were recorded. Patients with only simple purpuric rash on the scrotum were not considered to have scrotal involvement. Scrotal Doppler ultrasonography findings were evaluated.

Statistical Analysis

IBM SPSS Statistics for Windows, version 26.0 (SPSS Inc, Chicago, IL, USA) was used to perform statistical analysis. Normally distributed continuous variables were expressed as mean±standard deviation while the continuous variables that do not have normal distribution were expressed as median (minimum-maximum). Categorical variables were summarized as counts (percentages). The Chi-square test was used to compare catagorical variables and Mann-Whitney U-test was used to compare non-normally distributed continuous variables. The statistical significance level was accepted as a p-value <0.05.

RESULTS

A total number of 181 boys with IgAV included in the study. The demographic, clinical and laboratory characteristics of patients are summarized in **Table 1**. Presenting features in patients were as follows: palpable purpura in 176 (97.2%), arthritis/arthralgia in 57 (31.4%), GI involvement in 103 (56.9%), renal involvement in 50 (27.7%), and scrotal involvement in 27 (14.9%).

Twenty-seven (14.9%) of the 181 boys with IgAV had scrotal involvement. Among the scrotal-involved patients, 23 boys (85.1%) had scrotal swelling, 19 (70.3%) had erythema and 21 (77.7%) had scrotal pain or tenderness. Scrotal involvement was the first symptom of IgAV in one patient.

Patients were divided into two groups according to the scrotal involvement. The clinical differences of both groups are given in **Table 2**. CRP and WBC were significantly higher in the scrotal-involved group compared to the non-involved group (p=0.018, p=0.04, respectively). There were no significant differences in clinical findings and organ involvements between two groups (**Table 2**).

On ultrasonography, bilateral scrotal soft tissue thickening was observed in all patients. In 20 (74%) patients with scrotal involvement, increased vascularity was detected in the epididymis with swelling. The size, echogenicity and vascularity of the testicles were within normal limits. Testicular torsion was ruled out in all patients by Doppler ultrasonography.

Eighty-seven of the patients (48%) were given steroids, 22 of them (11.7%) nonsteroidal anti-inflammatory drug (NSAID). No patient underwent surgical exploration. The treatments administered, including the treatments given for organ involvements other than scrotal involvement, are summarized in **Table 1**.

Table 1. The demographic, clinical and laboratory characteristics of patients

Characteristics	
Age (mean±SD) (min.-max) (years)	7.93±3.19 (2-18)
Gender; Male /Female n (%)	181/134 (57.5/42.5)
Male Gender	
Age of disease onset (mean±SD) (min.-max) (years)	8.09±3.37 (2-18)
Triggers	
Infections n (%)	
Upper respiratory tract infection	81 (44.8)
Acute gastroenteritis	2 (1.1)
Varicella infection	1 (0.6)
Vaccinations n (%)	5 (2.2)
Clinical findings	
Rash, n (%)	176 (97.2)
Arthralgia, n (%)	42 (23.2)
Arthritis, n (%)	15 (8.2)
Localized edema, n (%)	3 (1.6)
Gastrointestinal involvement	103 (56.9)
Abdominal pain,	52 (28.7)
Occult blood positivity in stool, n (%)	50 (27.6)
Intussusception. n (%)	1 (0.6)
Renal involvement	50 (27.7)
Hematuria n (%)	24 (13.3)
Proteinuria n (%)	26 (14.4)
Testicular involvement, n (%)	27 (14.9)
Laboratory findings (mean±SD) (min-max)	
ESR (mm/hr) (0-20)	25.89±17.9 (2-83)
CRP (mg/dL) (0-8)	3.44±8,52 (0.03-101)
White blood cell (x109/L)	11441±4151 (1200-33500)
Platelets (x109/L)	386413±115500 (47900-895000)
Hemoglobin (gr/dL)	12.9±11.13 (9.6-15.7)
Treatment, n (%)	
NSAID	22 (11.7)
Steroid	87 (48)
Colchicine	5 (2.7)
Cyclophosphamide	6 (3.3)
IVIG	3 (1.6)
Plasmapheresis	1 (0.55)
ACEI	12 (6.6)
MEFV gene analysis, n (%)	27 (14.9)
M694V/M694	1 (0.55)
M694V/M680I	2 (1.1)
M694V/E148Q	1 (0.55)
M694V/-	3 (1.6)
Other heterozygos mutations	6 (3.3)
Negative	14 (7.7)
Recurrence. n (%)	8 (4.4)

SD: standard deviation, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, ANA: Anti-nuclear antibody, NSAID: Nonsteroidal anti-inflammatory drug, IVIG: Intravenous immunoglobulin, ACEI: Angiotensin converting enzyme inhibitors, MEFV: Mediterranean fever,

Table 2. Evaluation of patients according to testicular involvement

Characteristics	Testicular involvement (n:27)	Testicular involvement (-) (n:154)	p value
Age (years)	6.99±2.48	8.28±3.47	0.06
Preceding events			
Infections n (%)	16	68	0.39
Vaccination n (%)	1	4	0.75
Clinical Findings			
Purpura, n	26	152	0.26
Joint involvement, n			0.14
Pain	8	49	
Swelling	5	37	
Intestinal symptoms, n			
Abdominal pain	8	44	0.54
Bloody stool	7	43	0.89
Intusseption	0	1	0.69
Renal involvement, n			
Hematuria	4	20	0.66
Proteinuria	4	26	0.056
Localized edema	1	2	0.71
Laboratory findings			
WBC (x109/L)	13403±3697	11097±4141	0.04
Hb ((gr/dL)	12.69±1.04	12.93±1.15	0.6
Platelets (x109/L)	417,481±140,971	380,966±110,191	0.76
CRP (0-5 mg/L)	7.17±19.95	2.81±4.19	0.018
ESR (0-10 mm/h)	25.88 ±16.24	25.89 ±18.26	0.25
Recurrence	2	6	0.057
MEFV gene positivity (n)	4	23	0.94
	M694V/- (1) E148Q/- (1) Negative (2)	M694V/M694 (1) M694V/M680I (2) M694V/E148Q (1) M694V/- (2) Other heterozygous mutations (5) Negative (12)	

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, MEFV: Mediterranean Fever

DISCUSSION

Immunoglobulin A-associated vasculitis is the most common systemic vasculitis in childhood. The dominant clinical features are palpable purpura, abdominal pain, gastrointestinal bleeding, arthritis, and renal involvement.[1,2] However, there are rare manifestation such as myocarditis, involvement of the nervous system, respiratory system, and scrotal involvement. In this study, we evaluated 27 IgAV patients with scrotal involvement and showed that patients with scrotal involvement had higher inflammatory markers.

Acute scrotum, ureteritis, bladder wall hematoma, hemorrhagic spermatic cord, thrombosis of spermatic veins, and epididymo-orchitis may develop as extrarenal genitourinary manifestations in IgAV patients.[8] The first case of IgAV male genital involvement was published in 1960 and it was shown that 2-38% of IgAV patients may develop scrotal involvement.[9,10] In 2021, Ma et al. reviewed IgAV patients with scrotal involvement in the literature.[8] Between 1986 and 2020, 21 case reports of children with IgAV showed describing scrotal involvement. The mean age of onset of IgAV with scrotal involvement was 5.69±2.12 years. Almost all children

with scrotal involvement had scrotal pain with redness and swelling. Scrotal involvement occurred after the onset of IgAV in 14 cases (67%), before the onset of IgAV in 5 cases (24%), and simultaneously with IgAV in 2 cases (9%). Interestingly, Hardoff et al. reported that in a 4-year-old boy, recurrent scrotal swelling occurred 11 months before the diagnosis of IgAV.[11] We found that in only one of the patients in our study, scrotal findings preceded the typical findings of IgAV. The later appearance of typical palpable purpura may delay the correct diagnosis of IgAV patients presenting with scrotal involvement. These patients can be followed up with the diagnosis of epididymitis, orchitis or testicular torsion.[12] As a result, Doppler ultrasonography and typical clinical findings provide an accurate diagnosis. As is known, the sonographic findings of IgAV patients with scrotal involvement are scrotal skin thickening, epididymal enlargement, hydrocele, and normal-appearing testes with normal intratesticular blood flow. The sonographic findings of scrotal involvement of IgAV can allow distinction from testicular torsion in patients and have high sensitivity (89-100%) and specificity (97-100%).[13] It is important to distinguish between testicular torsion, which requires immediate surgical treatment, and scrotal involvement of IgAV. Because scrotal involvement in IgAV should be managed conservatively, not surgically. In all patients in our study, testicular torsion was excluded and the treatment of IgAV was managed conservatively. Scrotal involvement improved with a short-term administration of steroid therapy and/or NSAID.[12]

Ben-Sira et al. showed that 13 of 87 boys diagnosed with IgAV over a 15-year period had scrotal complaints. Sonographic evaluation was performed in seven patients to determine the extent of scrotal involvement and to consider testicular torsion. Sonographic findings included an enlarged epididymis, thickened scrotal skin, and a hydrocele. The testes themselves were sonographically normal and no signs of torsion were found in any of the patients.[14]

In our study, it was not demonstrated that any organ involvement was associated with scrotal involvement. On the other hand, Tabel et al. showed that scrotal involvement was associated with renal involvement.[15] In contrast, Ha et al. did not report a relationship between scrotal involvement and renal involvement. In addition, serum C4, CH50, IgA, IgG, IgM, IgE, anti-streptolysin O, and ANA were not found to be significantly associated with scrotal involvement.[16]

MEFV gene analysis was performed from patients in our study who had an atypical course, prolonged rash, and a family history of familial Mediterranean fever. It was observed that there was no statistical difference between the results of MEFV gene analysis in patients with and without scrotal involvement. It is known that MEFV mutations are more common in IgAV patients than in the general population. Moreover, mutation carriers may have more severe clinical manifestations and higher inflammatory response. Bayram et al. showed that 47 (43.9%) of 107 IgAV patients had one of the MEFV mutations. Homozygosity for one mutation in eight patients, heterozygosity for one mutation in 33 patients, and compound heterozygosity for two mutations in six patients. Scrotal involvement was statistically more common in patients with MEFV mutations. On the other hand, although the frequency of articular, GI and renal involvement was higher in patients with MEFV mutations in their studies, no statistically significant difference could be found.[17]

The limitation of our study is its retrospective nature and the relatively small number of IgAV patients with scrotal involvement. Multicenter studies are needed to reveal the risk factors associated with scrotal involvement.

In conclusion, scrotal involvement in boys with IgAV is not rare, it should be considered in the differential diagnosis in patients with scrotal pain, swelling and erythema. In addition, as shown in our study, inflammatory markers may be higher in patients with scrotal involvement.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital No:2 Clinical Researches Ethics Committee (Date: 16.06.2021, Decision no: E2-21-605).

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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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.904471
J Contemp Med 2021;11(4):555-559

Orjinal Araştırma / Original Article

Relation Between Syntax Score and Complexity of Carotid Artery Disease

Karotis Arter Hastalığı Şiddeti ile Syntax Skoru Arasındaki İlişki

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Abstract

Introduction: Carotid artery disease may cause severe constriction or complete occlusion in carotid arteries, it may not give any symptoms until it appears. In some people, stroke is the first finding of the disease. One of the most important causes of stroke is carotid artery stenosis and atherosclerosis causes a total of one third of the stroke. Atherosclerosis; It is a specific finding of both coronary and carotid artery disease.The relationship between carotid atherosclerotic diasease and coronary artery disease (CAD) have been in previous reports

Aim: In this study, we aimed to show the relationship between the severity of the carotid artery stenosis(CAS) determined by angiography and the anatomical complexity of CAD assessed by SYNTAX Score (SS).

Material and Method: Our study was carried out in accordance with the Declaration of Helsinki Principles by obtaining the ethics committee approval dated 09.06.17 and numbered E.8640. A total of 45 patients with simultaneously carotid and coronary angiography performed were included in our study. SS, a marker of CAD complexity, was determined by dedicated computer software. The patients were divided into two groups according to the classification of SS: low SS (n=33, SS <22) and intermediate-high SS (n=12, SS ≥22) groups. The severity of CAS was assessed by digital subtraction angiography (DSA) of six distinct segments of the carotid artery included the left and right common, internal, and external carotid arteries. Spearman's correlation coefficients were used to determine the correlations between SS and CAS score.

Results: The CAS severity score was significantly higher in patients with intermediate and high SS group than in the low SS group (3/4/4.75 vs. 1/2/3, p=0.001). There was also significant correlation between SS and CAS severity score (r=0.47, p=0.001).

Conclusions: We revealed that there was a proportional increase in the severity of CAS to CAD complexity using SS. It may suggest that complex multivascular atherosclerotic disease is the systemic nature of atherosclerosis.

Keywords: Carotid artery stenosis, coronary artery disease, constriction, stroke, Syntax score

Öz

Giriş: Karotis arter hastalığı, karotis arterlerde şiddetli daralmaya veya tam tıkanmaya neden olabilir, ortaya çıkana kadar herhangi bir belirti vermeyebilir. Bazı kişilerde, hastalığın ilk bulgusu inmedir. İnmelerin en önemli nedenlerinden biri karotis arter stenozudur (KAS) ve toplam inmelerin üçte birine atheroskleroz neden olur. Atheroskleroz; hem koroner ve hem de karotis arter hastalığının spesifik bulgusudur. Aterosklerotik karotis hastalığı ile koroner arter hastalığı (KAH) arasındaki ilişki önceki çalışmalarda gösterilmiştir.

Amaç: Bu çalışmada anjiyografi ile değerlendirilen karotis arter darlığının şiddeti ile SYNTAX Skoru (SS) ile değerlendirilen KAH' nın anatomik kompleksliği arasındaki ilişkiyi göstermeyi amaçladık.

Gereç ve Yöntem: Çalışmamız 09.06.17 tarih ve E.8640 sayılı etik kurul onayı alınarak, Helsinki İlkeler Deklarasyonu'na uygun olarak gerçekleştirilmiştir. Çalışmamıza eş zamanlı olarak karotis ve koroner anjiyografi yapılan toplam 45 hasta dahil edildi. KAH kompleksliliği özel bir bilgisayar yazılımı olan SS ile belirlendi. Hastalar SS sınıflamasına göre iki gruba ayrıldı: düşük SS (n = 33, SS <22) ve orta-yüksek SS (n = 12, SS ≥22) grupları. KAS şiddeti, karotis arterlerin sol ve sağ carotis communis, internal ve external bölümlerini içeren altı farklı segmentinin dijital subtraksiyon anjiyografisi (DSA) ile değerlendirildi. SS ile KAS şiddeti arasındaki korelasyonları tespit etmek için Spearman korelasyon katsayıları kullanıldı.

Bulgular: KAS, orta ve yüksek SS grubunda, düşük SS grubuna göre anlamlı derecede yüksekti (3/4/4.75 vs. 1/2/3, p=0.001). SS ve KAD ciddiyeti arasında anlamlı korelasyon vardı (r=0.47, p=0.001).

Sonuç: Çalışmamız ile SS kullanarak KAD ile KAS şiddetinde orantılı bir artış olduğunu gösterildi. Karmaşık multivasküler aterosklerotik hastalığın, aterosklerozun sistemik doğası olduğunu düşündürebilir.

Anahtar Kelimeler: Karotis arter darlığı, koroner arter hastalığı, konstriksiyon, inme, Syntaks skoru

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Received *(Geliş Tarihi)*: 29.03.2021 **Accepted *(Kabul Tarihi)*:** 18.07.2021

INTRODUCTION

Atherosclerosis is a systemic process, involving multible arterial territories.[1] Carotid artery stenosis (CAS), that coexists with coronary artery disease (CAD) may indicate an increased burden of atherosclerosis.[2] The presence of significant CAS is directly related to the extent of CAD, though the prevalence of severe carotid stenosis was progressively increased among patients with extensive CAD.[3] The progressive concurrent increase of CAS prevalence with CAD, suggesting that occurence of shared disease is likely to influenced by similar risk factors such as hypertension, diabetes mellitus, hyperlipidemia, and older age. CAS is an important prognostic marker and risk-stratification tool in patients with CAD.[4,5] Clinical manifestations of CAS are strongly suggestive of clinical events in coronary artery territory.[6-9]

The SS is an angiographic score, which represents coronary lesion complexity, has been shown to be useful for predicting clinical outcomes.[11] Previous studies investigated the relationship between carotid artery ultrasound parameters and SS.[12-15] Most of them demonstrated that carotid intima-media thickness (IMT) has predictive value for coronary artery complexity.[13-15] However, the precise relationship between the severity of CAS and CAD complexity as assessed by the SS has not been evaluated.

In this study, we aimed to investigate the relationship between severity of CAS determined by an angiography and complexity of CAD assessed with the SS.

MATERIAL AND METHOD

Study population

The study was carried out retrospectively at a single center from March 2010 to October 2015. A total 614 patients who underwent carotid angiography were analyzed. Amoung them, 45 patients with clinical suspicion of CAD had also coronary angiography performed were enrolled in this study. Patients with a history of coronary or carotid revascularization were excluded. Written informed consent was obtained from all patients and the local ethical committee approved the protocol. Duplex ultrasound and either computed tomography angiography (CTA) or magnetic resonance angiography (MRA) of the carotid arteries were performed in all patients. Carotid angiography was performed in patients with symptomatic internal carotid artery (ICA) stenosis ≥ 50% or asymptomatic ICA stenosis ≥ 60% in CTA /MRA.[16] The indications for coronary angiography were as follows: symptoms to suggest cardiac ischemia, physician recommendation based on the presence of clinical characteristics that suggest high risk for CAD and noninvasive testing indicating a high probability of CAD.

All the angiography procedures were performed by two experienced interventional cardiologists. Selective bilateral conventional and digital subtraction angiography (DSA) of carotid arteries was done using 5 Fr Simmons-2 catheter. The severity of CAS was evaluated by DSA images of six distinct parts of the carotid artery segments which included the left and right common, internal, and external carotid arteries. Each of six carotid artery segments were scored in one of five categories based on their degree of stenosis. The five stenosis categories were included degree of diameter stenosis: 0-49%, 50-74%, 75-90%, 90-99%, and total occlusion. The degree of stenosis was calculated by angiography according to North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria for the common, internal, and external carotid arteries.[17] Low-grade carotid stenosis of less than 50% is considered to be hemodynamically insignificant. Each of the categories was given a score ranging from 0 to 4, with 0 indicating 0-49% and 4 indicating total occlusion.Carotid artery severity was calculated in accordance with the study conducted by Long et al. In 1999. In accordance with this study, the total of segments with stenosis of more than 49% in six segments of the carotid arteries was calculated for each patient.[18]

Coronary Angiography and SS

Coronary angiography was performed by two experienced cardiologists using standard teqniques. CAD was defined as stenosis with a diameter ≥50%. According to the baseline coronary angiogram, each coronary lesion producing stenosis with a diameter ≥50% in vessels ≥1.5 mm diameter was scored separately, and these scores were combined to provide the overall SS, which was calculated using the SS algorithm.[11] available on the SYNTAX website (www.syntaxscore.com).[19] A low SS was defined as ≤ 22, an intermediate score as 23 to 32, and a high score as ≥ 33.[20] The patients were divided into two groups according to the SS: Group 1 with low risk score (score<22), group 2 with moderate and high risk (score≥22). We compared groups by CAS score.

Statistical analysis

Statistical analysis was performed by SPSS 20,0 for Windows program.Categorical variables are shown as counts (n) and percentages (%) and continuous data were presented as the mean ± standard deviation. Chi-Square test was used to compare the categorical variables. Kruskal Wallis H test was used to compare the continuous data among low and moderate-high score groups according to SS (For pairwise comparisons Bonferroni adjusted Mann-Whitney U test

was used). Spearman's correlation coefficients were used to determine the correlations between SS and CAS score. Two-sided p values of <0.05 were considered statistically significant.

DISCUSSION

In this study, we have demonstrated a significant association between carotid artery disease severity and coronary artery disease complexity. We also revealed that CAS score was significantly higher in patients with moderate and high SS as compared to low SS group.

Carotid artery disease is regarded as an established marker of generalized atherosclerosis.[2] The prevalence of concomitant atherosclerotic lesion of the carotid and coronary arteries

increases progressively and is a known predictor of worse outcome in various clinical settings including patients with ischemic stroke, patients undergoing coronary artery bypass grafting and carotid endarterectomy as well as asymptomatic individuals.[21-23] There has been some convincing evidence suggesting that CAD is the leading cause of death in patients who recovering from stroke and patients with asymptomatic CAS are at higher risk for future myocardial infarction than stroke.[4-9] It has been reported that, the co-prevalence of >50% CAS in patients with CAD is 14.5% which is 8.7%, 5.0%, and 4.5% in patients with >60%, >70%, and >80% CAS, respectively.[10] Furthermore, the prevalence of asymptomatic CAS was progressively increased in patients with extensive CAD. Kallikazaros et al.[24] showed that the prevalence of significant CAS (lumen diameter stenosis of ≥50% measured by carotid Doppler ultrasonography (US) was 5%, 13%, 25%, and 40% in patients with single vessel (1VD), double vessel (2VD), triple vessel (3VD) and left main disease (LMD), respectively. In a study conducted on 632 Japanese patients, an ultrasonographic measurement of CAS >50% was found in 14%, 21%, 36% of patients with 1VD, 2VD, and 3VD, respectively.[25] These investigations were evaluated the coronary artery severity based on the number of the diseased coronary artery. However, none of these studies used. SS which has been approved as a standard method in quantification of coronary complexity. SS does not only provide objectively quantifying of the severity and extent of CAD, but also differs from the other methods by allowing us to assess the coronary lesion complexity.[11] Because of its high accuracy and reproducibility, the SS has emerged as a feasible method in clinical use and is useful for decision-making and predicting prognosis among patients who have undergone coronary revascularization.[20,26] In a few studies, a relationship between the carotid Duplex ultrasound parameters and SS of the coronary arteries has been investigated.[12-15] Ikeda et al.[13] demonstrated a significant correlation between the mean carotid intima-media thickness (IMT) and SS. They showed that patients with mean IMT ≥0.9 mm had significantly higher SSs than patients without thickening ($p<0.0001$). Korkmaz et al.[15] were also found a significant correlation between carotid IMT and overall SS in patients with stable coronary artery disease ($p<0.001$). Conversely, a study conducted by Costanzo et al.[12] showed that SS was not correlate with prevalence of significant carotid artery stenosis which was defined as ≥50% diameter stenosis calculated by carotid US.

Our study is quite different from the studies listed above. All these studies reporting coexistence rate of both two diseases were based on carotid duplex ultrasound (US) examination. Indeed, carotid IMT has been reported as a surrogate marker of atherosclerotic burden,[27] it does not provide reliable data regarding the significance of the carotid stenosis. The evidence suggests that the risk of stroke directly increases with the severity of carotid stenosis; the patients with 60-69% CAS has 11% risk of stroke within 3 years, compared with 32% for the patients with ≥90% stenosis.[28-29] The studies mentioned above were used carotid Duplex US to determine the severity of the carotid stenosis. Compared with DSA, the "gold standard" test, carotid duplex ultrasound examination is relatively less accurate in the estimation of ≥70% CAS with the sensitivity varied between 87.5% and 98.6%, and the specificity varied between 59.2% and 75.7%.[30] Depending on the technical skills and experience of operator, stenosis of carotid lesions can under- or overestimated by carotid US in patients with calcified or inaccessible lesions, tortuous vessels and severe contralateral carotid stenosis.

In this study, we used an angiographic scoring system, indicating the severity of CAS which was obtained from DSA images of six distinct parts of the carotid artery system. This scoring method was defined based on a study conducted by Long et al.[18] We demonstrated that patients with SS score ≥ 22 had significantly higher carotid artery severity score. It was suggested that in patients with SS ≥ 22, CABG offered a survival advantage over percutaneous coronary intervention.[20] Thus, most of them have treated with CABG. Presence of CAS has been shown to be a significant risk factor for peri-post-operative stroke in patients undergoing CABG, with a prevalence of 3% in unilateral stenosis, 5% in bilateral stenosis, and 7% in total carotid occlusion.[10,31,32] Therefore, screening for CAS before CABG in patients with intermediate and high SS may be reasonable.

In conclusion, we demonstrated that there was a proportional increase in the severity of CAS to CAD complexity using SS. In addition we have shown that patients with SS ≥ 22 had higher CAS severity score as compared to patients with SS <22. Therefore, we suggest screening for CAS in patients with complex CAD assessed by SS.

Limitations

Some limitations should be noted when interpreting our findings. The main limitation is related to our patient selection. The patients included in this study were selected from a group of consecutive patients who were referred for carotid angiography for suspected carotid artery disease. Thus, this sampling bias means that our results concerning the correlation between SS and the severity of carotid artery disease are relevant only to this specific group and the general population. Small sample size is the other limitation of the study. Further large prospective studies with better adjustment for selection bias are needed to confirm our results.

RESULT

This study revealed a significant relationship between carotid artery disease severity and coronary artery disease complexity. In addition, patients with moderate to high SS had a significantly higher CAD score compared to the low SSd group. Although there have been many studies between carotid and coronary artery disease, this study first evaluated the anatomical lesion distribution and prevalence between the two regions by using SYNTAX Score and Carotid Score. Old studies in the literature have used Carotid Doppler USG to determine the severity of carotid stenosis

Compared to the "gold standard" test DSA, the carotid duplex USG examination is relatively less in predicting 70% CAS, with sensitivity ranging from 87.5% to 98.6% and specificity ranging from 59.2% to 75.7%. It is true.

45 patients with simultaneously carotid and coronary angiography performed were included in our study. The study population included 29 men and 16 women with the mean age of 66.7±8.9 years. The patients were divided into two groups according to the classification of SS: group 1 (n=33, SS <22) and group 2 (n=12, SS≥22). The median SS in group 1 and group 2 were 5 (range 0-20) and 28 (range 22-45), respectively. The baseline clinical characteristics such as age, sex, hypertension, diabetes mellitus, hyperlipidemia, and previous history of stroke were similar in the groups. Demographic and clinical variables of the study population are summarized in **Table 1**.

The CAS severity score was significantly higher in the intermediate and high SS group than in the low SS group (3/4/4.75 vs. 1/2/3, p =0.001) (**Figure 1**). Also, there was significant correlation between SS and CAS score (r=0.47, p=0.001) (**Figure 2**).

Table 1. Demographic and clinical characteristics of the study population

Parameter (Demografic features)	SxScore <22 n=33	SxScore ≥22 n=22	p value
Age (mean, SD)	66.15±8.9	68.2±8.8	NS
Sex (female, n ,%)	12 (36%)	4(33%)	NS
Hypertension (n, %)	29 (88%)	10 (84%)	NS
Diabetes mellitus (n, %)	10 (30%)	6 (50%)	NS
Smoking (n, %)	9 (27%)	3 (25%)	0.756
Total cholesterol, mg/dl	191±39	177.6±46.4	0.441
LDL, mg/dl	125,7±35	115.3±45.3	0.141
HDL, mg/dl	44.9±14.8	45.2±8.8	0.364
CASS (median, IQR,IU/ml)	1/2/3	3/4/4.75	0.001

(LDL, low-density lipoprotein; HDL, high-density lipoprotein; SD, standard deviation, CASS. Carotid artery severity score Data are means±SD for normally distributed variables and median for skewed variables or n (%))

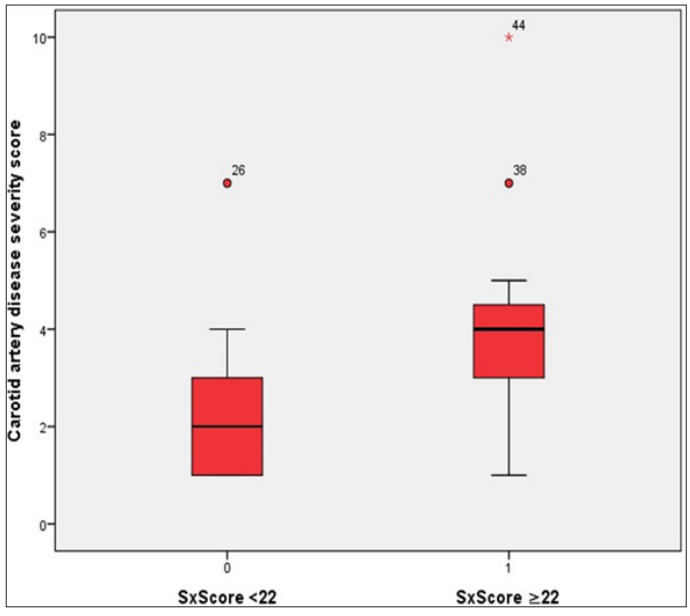

Figure 1. Carotid artery severity score in low and intermediate-high SxScore groups

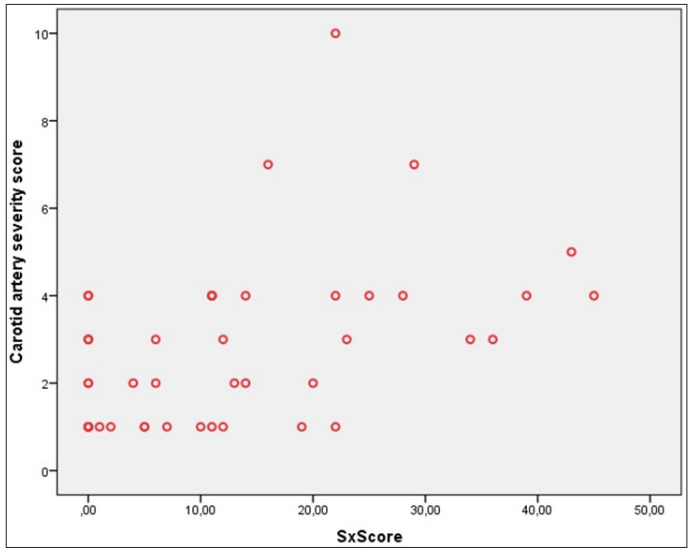

Figure 2. Correlation analysis between carotid artery severity score and SxScore

CONCLUSION

According to the results of our study, we have shown that using SS there is a proportional increase in the severity of CAD's CAD complexity. In addition, we showed that patients with SS ≥ 22 had a higher SAD severity score than patients with SS <22. Therefore, we recommend screening for CAD in patients with complex CAD assessed by SS.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol was approved by the Non-invasive Research Ethics Committee of Sakarya University (Permission granted: 09.06.2017, Decision no:E.86-40).

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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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.910028
J Contemp Med 2021;11(4):560-564

Orjinal Araştırma / Original Article

Indirect Neonatal Hyperbilirubinemia and Associated Risk Factors for Long Phototheraphy Duration in A Baby-Friendly Hospital in Konya, Turkey

Türkiye, Konya'da Bebek Dostu Bir Hastanede İndirekt Neonatal Hiperbilirubinemi ve Uzun Fototerapi Süresi ile İlişkili Risk Faktörleri

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Abstract

Aim: Indirect neonatal hyperbilirubinemia is a common neonatal disorder worldwide which can remain benign if prompt management is available. However there is a higher morbidity and mortality risk in settings with limited access to diagnosis and care. The aim of this study was to evaluate the etiologies of indirect neonatal hyperbilirubinemia, to determine the effectiveness of phototherapy treatment and to specify the associated risk factors for prolonged phototherapy duration.

Material and Method: Infants with ≥37 weeks of gestation, postnatal age of ≤14 days, and diagnosis of hyperbilirubinemia at admission, defined as serum bilirubin level at or above the phototherapy treatment threshold were included in the study. All the study participants were treated with intermittent phototherapy. The data were retrospectively analized and duration of phototherapy was classified as ≤24 hours (early discharge) and >24 hours (late discharge).

Results: A total of 205 newborns were included in the study. The mean birth weight was 3171.12±436.19 g and mean gestational age was 38.87±1.18 (37–39) weeks. Also, ABO incompatibility and cephalic hematoma were found to be the most common etiologies in our series. On the other hand, male gender (p=0.03) and formula as the first prelacteal feeds (p=0.03) were significantly higher in late discharge group. Additionally; male gender, formula as the first prelacteal feed, ABO incompatibility, Rh isoimmunization, cephalic hematoma and sepsis were risk factors for long phototherapy duration of >24 hours.

Conclusion: Determination of possible risk factors for neonatal jaundice can provide early hospital admissions by informing mothers before discharge after birth.

Keywords: Neonatal jaundice, indirect hyperbilirubinemia, etiology, phototheraphy treatment, risk factors

Öz

Giriş: İndirekt neonatal hiperbilirubinemi, dünya çapında yaygın bir yenidoğan hastalığıdır ve hızlı tedavi edilirse benign kalabilir. Bununla birlikte, tanı ve sağlık hizmetine sınırlı erişimin olduğu ortamlarda daha yüksek bir morbidite ve mortalite riski vardır. Bu çalışmanın amacı, indirekt neonatal hiperbilirubineminin etiyolojilerini değerlendirmek, fototerapi tedavisinin etkinliğini belirlemek ve uzun süreli fototerapi süresi için ilişkili risk faktörlerini belirlemektir.

Gereç ve Yöntem: Çalışmaya, serum bilirubin düzeyi fototerapi tedavi eşiğinde veya üzerinde olarak tanımlanan; 37 gebelik haftasından büyük, postnatal yaşı 14 günden küçük ve başvuru anında hiperbilirübinemi tanısı olan bebekler dahil edildi. Tüm vakalar aralıklı fototerapi ile tedavi edildi. Veriler geriye dönük olarak analiz edildi ve fototerapi süresi 24 saatten kısa (erken taburculuk) ve 24 saatten uzun (geç taburculuk) olarak sınıflandırıldı.

Bulgular: Çalışmaya toplam 205 yenidoğan dahil edildi. Ortalama doğum ağırlığı 3171,12±436,19 g ve ortalama gebelik yaşı 38,87±1,18 (37-39) hafta idi. Ayrıca serimizde ABO uyumsuzluğu ve sefal hematom hiperbilirubinemide en sık görülen etiyolojiler olarak bulundu. Diğer taraftan, erkek cinsiyet (p=0.03) ve ilk besin olarak mama kullanılması (p=0.03) geç taburculuk grubunda anlamlı olarak daha yüksekti. Bunlara ek olarak; ABO uyumsuzluğu, Rh izoimmünizasyonu, sefal hematom ve sepsis, >24 saatlik uzun fototerapi süresi için risk faktörleriydi.

Sonuç: Yenidoğan sarılığı için olası risk faktörlerinin belirlenmesi doğum sonrası taburculuk öncesi anneleri bilgilendirerek erken hastaneye yatışları sağlayabilir.

Anahtar Kelimeler: Yenidoğan sarılığı, indirekt hiperbilirubinemi, etyoloji, fototerapi tedavisi, risk faktörleri

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Received *(Geliş Tarihi)*: 05.04.2021 **Accepted *(Kabul Tarihi)*:** 25.06.2021

INTRODUCTION

Neonatal jaundice is usually a physiologic condition and is one of the most common causes of hospital admissions in otherwise healthy newborns.[1] Jaundice can affect>60% of late preterm and term infants. High levels of total serum bilirubin can be toxic to the central nervous system leading to acute bilirubin encephalopathy and kernicterus spectrum disorders, with devastating, permanent neurodevelopmental handicaps or exitus.[2] Recommendations have been developed to prevent acute bilirubin encephalopathy and kernicterus spectrum disorders by establishing total serum bilirubin levels signaling risk for neurological damage at which to start phototherapy treatment, the first-line treatment for neonatal hyperbilirubinemia and, eventually, with exchange transfusions.[3-5] Also, national guideline has been published with the aim of standardizing the starting and stopping of phototherapy, and the monitoring of total serum bilirubin levels during phototherapy.[6]

With implementation of standardized and harmonized guidelines for management of hyperbilirubinemia, the incidence of severe hyperbilirubinemia has decreased markedly in high income countries.[1,7-10] However, it is still an important problem resulting in significant disability and mortality in low and middle income countries.[11-14] Also, the incidence of severe neonatal hyperbilirubinemia and acute bilirubin encephalopathy in southeast region of Turkey is reported to be higher than in high income countries and lower than in low and middle income countries.[15]

Risk factors for the development of severe hyperbilirubinemia include cephalhematoma or significant bruising, early gestational age, exclusive breastfeeding (especially unsuccessful breastfeeding and/ or weight loss of 8% to 10%), isoimmune or other hemolytic anemia, and a sibling with a history of neonatal jaundice.[16] In addition to hyperbilirubinemia, earlier gestational age, hemolysis, sepsis, and low birth weight are associated with the development of bilirubin encephalopathy.[16]

The aim of this study was to evaluate the etiological reasons for the development of neonatal hyperbilirubinemia, to determine the effectiveness of phototherapy treatment and to specify the associated risk factors for prolonged phototherapy duration.

MATERIAL AND METHOD

Study population

This is a single-center retrospective cohort study which was conducted at a baby friendly hospital between July 2016 and June 2020 in the middle region of Turkey. All medical records of patients were reviewed. Infants with ≥37 weeks of gestation, povwstnatal age of ≤14 days, and diagnosis of hyperbilirubinemia at admission, defined as serum bilirubin level at or above the phototherapy treatment threshold according to the guidelines of the American Academy of Pediatrics[4] and national guideline,[6] were included in the study. Infants born at <37 weeks of gestation, with congenital/ chromosomal anomalies and infants that were performed exchange transfusion were excluded from the study.

Hemolytic jaundice was defined as presence of anemia, hyperbilirubinemia, and hemolysis findings in peripheral smear. Direct Coombs test positivity was accepted as a supportive finding for hemolytic jaundice and intravenous immunoglobulin (IVIG) was used in infants having hemolytic findings with direct Coombs positivity.

Sepsis was defined as presence of clinical signs of sepsis associated with a positive blood culture and/or an elevated c-reactive protein level, total leukocyte count of >25,000/mm^3 or <5000/mm^3, an immature to total neutrophil ratio of >0.2, or a band count of >10%.[17]

Phototherapy treatment

All the study participants were treated with intermittent phototherapy and blue lights with wavelengths of 460 nm were used for this treatment. Intermittent phototherapy was performed as intermittent blue light: 3–5 hours of blue light of irradiation and a stop of 2–4 hours in between.[18] The course of treatment for babies was 24 hours or more. The perineum of newborns was protected by black cotton diapers, and the eyes were protected by a black eye mask, and children were appropriately constrained. In order to ensure that the skin of children receives light evenly, the light distance was adjusted to 25 cm, and the blue light wavelength was set as 425–475 nm and the power to 160 W. Also, phototherapy treatment was stopped when total serum bilirubin level was <13–14 mg/dL, after two consecutive decreasing values measured 6–12 h after the beginning of treatment, or once serum bilirubin has fallen to a level of at least 2.9 mg/dL, or just below the phototherapy threshold.[4,5,19] The duration of phototherapy was classified as ≤24 hours (early discharge) and >24 hours (late discharge).

Statistical analysis

Descriptive statistics were calculated using counts, frequencies, medians, and interquartile ranges for patient demographics and sedation procedure characteristics. Categorical data were presented as frequencies (%) and analyzed using Chi-square test. Multivariate binary logistic regression analysis was used to determine the risk factors associated with phototherapy duration. Adjusted odds ratios (OR) and 95% confidence interval (CI) for independent risk factors were determined. Statistical significance was inferred at $p<0.05$. Statistical analyses were done using SPSS for Windows Version 17.0 software (Chicago, IL, USA).

RESULTS

A total of 205 newborns were included in the study. The demographic and laboratory characteristics of study population were summarized in **Table 1**. The infants' mean birth weight was 3171.12±436.19 g and mean gestational age was 38.87±1.18 (37–39) weeks. In total 90 (43.9%) infants were females and 115 (56.1%) infants were males (female/ male=1.27). Also, the mean maternal age was 29.32±8.21

years and the mean parity of mothers was 3.[1-4] Additionally, 122 (59.5%) infants and 83 (40.5%) infants were delivered by vaginal and caesarean section, respectively. The mean Apgar score at 5 minutes of babies was 8.2[7-10] and 129 (62.9%) infants were breastfeed as the first prelacteal feeds. The mean postnatal age at admission was 4.19±2.69 days. The mean indirect serum bilirubin concentration at admission and at discharge was 16.35±3.94 mg/dL and 9.38±2.07 mg/dl, respectively. On the other hand, positive direct coombs was detected in 17 (8.3%) patients and the mean phototheraphy duration was 33.6±26.88 hours.

The etiologies of indirect hyperbilirubinemia in study population was given in **Table 2**. The etiologies; ABO incompatibility, Rh isoimmunization, lack of proper feeding and dehydration (>%10), cephalic hematoma, sepsis, urinary system infections, hypothyroidism, baby of diabetic mother, and unknown were diagnosed in 89 (43.4%), 17 (8.3%), 19 (9.3%), 34 (16.6%), 2 (0.9%), 1 (0.5%), 3 (1.5%), 5 (2.4%) and 21 (10.2%) infants, respectively.

All patients were divided into two groups according to phototheraphy duration; patients who were received phototheraphy <24 hours (84 patients) and that were >24 hours (121 patients). The comparison of demographic and laboratory characteristics of two groups were given in **Table 3.** No statistical difference was achived for gestational age (p=0.745), birth weight (p=0.851), maternal age (p=0.684), mode of delivery (p=0.791 and p=0.103), postnatal age of admission (p=0.561), indirect bilirubin level on admission (p=0.914), indirect bilirubin level at discharge (p=0.136) and positive direct coombs (p=0.583) between the two gorups. However, male gender (p=0.03) and formula as the first prelacteal feeds (p=0.03) were significantly higher in the group that was received phototheraphy of >24 hours.

In multivariate logistic regression analysis; male gender (OR=0.91, 95%CI=0.09-1.1, p=0.02), formula as the first prelacteal feed (OR=7.1, 95%CI=7.3-14.1, p=0.01), ABO incompatibility (OR=2.6, 95%CI=1.3-9.8, p=0.01), Rh isoimmunization (OR=11.5, 95%CI=5.3-22.3, p=0.001), cephalic hematoma (OR=6.2, 95%CI=4.8-10.9, p=0.03) and sepsis (OR=2.1, 95%CI=6.9-10.2, p=0.04) were strongly associated with and risk factors for long phototherapy duration of >24 hours (**Table 4**).

Table 1. Demographic and laboratory characteristics of study population

Variables	N=205 (Mean±SD)	Percentage (%)
Gestational age (weeks)	38.87±1.18	
Birth weight (gr)	3171.12±436.19	
Gender		
Female	90	43.9
Male	115	56.1
Maternal age (years)	29.32±8.21	
Mode of delivery		
Vaginal	122	59.5
Caesarean section	83	40.5
Parity	3 (1-4)	
Apgar score at 5 minutes	8.2 (7-10)	
First prelacteal feeds		
Breastmilk	129	62.9
Formula	76	37.1
Postnatal age of admission (days)	4.19±2.69	
Indirect bilirubin level on admission (mg/dl)	16.35±3.94	
Indirect bilirubin level at discharge (mg/dl)	9.38±2.07	
Positive direct coombs	17	8.3
Duration of phototheraphy (hours)	33.6±26.88	

Table 2. The etiologies of indirect hyperbilirubinemia in study population.

Variables	N (=205)	Percentage (%)
ABO incompatibility	89	43.4
Cephalic hematoma	34	16.6
Lack of proper feeding and dehydration (>%10)	19	9.3
Rh isoimmunization	17	8.3
Baby of diabetic mother	5	2.4
Hypothyroidism	3	1.5
Sepsis	2	0.9
Urinary system infections	1	0.5
Unknown	21	10.2

Table 3. Demographic and laboratory characteristics of patients who were threated with phototheraphy ≤24 hours and >24 hours.

Variables	Phototherapy duration		P value
	≤24 hours	>24 hours	
Gestational age (weeks)	37.17±2.11	38.01±2.08	0.745
Birth weight (gr)	3052.10±136.79	3101.25±114.21	0.851
Gender			
Female	50	40	0.125
Male	34	81	0.03
Maternal age (years)	28.17±6.12	29.10±3.51	0.684
Mode of delivery			
Vaginal	46	76	0.791
Caesarean section	38	45	0.103
First prelacteal feeds			
Breastmilk	67	62	0.06
Formula	17	59	0.03
Postnatal age of admission (days)	4.09±2.11	4.29±0.17	0.561
Indirect bilirubin level on admission (mg/dl)	15.31±1.14	16.13±3.10	0.914
Indirect bilirubin level at discharge (mg/dl)	9.01±2.14	9.03±1.11	0.136
Positive direct coombs	8	9	0.583

Table 4. Multivariate logistic regression analysis of risk factors associated with phototherapy duration of >24 hours.

Variables	OR	95% CI	P value
Male gender	0.91	0.92–1.1	0.02
Formula as the first prelacteal feed	7.1	7.3–14.1	0.01
ABO incompatibility	2.6	1.3-9.8	0.01
Rh isoimmunization	11.5	5.3–22.3	0.001
Cephalic hematoma	6.2	4.8–10.9	0.03
Sepsis	2.1	6.9–10.2	0.04

DISCUSSION

This retrospective study confirmed that, most of the term livebirths were treated for indirect neonatal hyperbilirubinemia due to the certain etiologies such as ABO incompatibility, Rh isoimmunization, lack of proper feeding and dehydration (>%10), cephalic hematoma, sepsis, urinary system infections, hypothyroidism and baby of diabetic mother. In addition, male gender, formula as the first prelacteal feed, ABO incompatibility, Rh isoimmunization, cephalic hematoma and sepsis were found to be strongly associated with long phototherapy duration of >24 hours in our study.

Jaundice caused by indirect neonatal hyperbilirubinemia is a common condition and a frequent cause for admission in health care facilities all around the world.[3] Without timely admission and appropriate management, indirect neonatal hyperbilirubinemia can lead to devastating neurologic disorders.[2,10] Cerebral palsy, auditory disturbances and gaze abnormalities are classical sequelae of indirect neonatal hyperbilirubinemia.[20,21] Worldwide, 80% of severe indirect neonatal hyperbilirubinemia occurs in resource-limited settings with an estimated mortality rate of 25% and with a 13% risk of developing neurological sequelae.[1,2,20,21] Also, risk factors for indirect neonatal hyperbilirubinemia and acute bilirubin encephalopathy has been widely researched.[1-3,8-11]

The Turkish Neonatal Jaundice Registry revealed that the most common risk factors for development of severe neonatal jaundice and indirect neonatal hyperbilirubinemia were hemolytic reasons, improper feeding, and dehydration.[15] Also, the most common hemolytic etiology was ABO blood group incompatibility in this registry and related literature.[11,13,15,16] Similar to these results, our study showed ABO blood group incompatibility was the most common etiology and also a risk factor for long phototheraphy duration. Additionally, Rh isoimmunization also caused indirect neonatal hyperbilirubinemia, as seen in our results. In a previous research, hemolytic disease or direct Coombs test positivity was found to be associated with higher risk of acute bilirubine encephalopaty and permanent neurological abnormalities.[22] Although, we found the direct coombs test rate as 8.3% in our study, we did not find any association with long duration of phototherapy.

Male gender is also another risk factors for neonatal indirect hyperbilirubinemia. The studies showed that male/female ratio ranges between 1.2-1.6 in newborns with indirect hyperbilirubinemia.[1,3,5,15] In our study, we determined the female/male ratio as 1.27 in accordance with the literature. Also, our study showed that male gender is a risk factor for long duration of phototherapy.

Although the gold standard for infant nutrition, exclusive breastfeeding has traditionally been considered a risk factor for the development of neonatal indirect hyperbilirubinemia.[23] Current guidelines for the management of neonatal hyperbilirubinemia include the recommendation that hospitals promote and support successful breastfeeding, acknowledging that inadequate milk intake during breastfeeding may contribute to the development of hyperbilirubinemia.[4-6] Also, in a study of Hudson et al. they found that implementation of baby-friendly hospital initiative for breastfeeding in a single hospital center was significantly associated with reduced rates of neonatal hyperbilirubinemia and phototherapy treatment among newborns, without increased rates of 30-day hospital readmissions for the treatment of hyperbilirubinemia.[24] In our study, we found that the formula was the first prelacteal feed in babies who received phototheraphy treatment >24 hours period. Also, statistical significance was achived between the two groups for first prelacteal feed. Additionally, our study revealed that formula as the first prelacteal feed was a risk factor for long phototheraphy treatment >24 hours period.

Currently, phototherapy treatment is a widely used method for treating neonatal jaundice. Phototherapy decreases the progression to severe hyperbilirubinemia in infants with moderate hyperbilirubinemia. The effect of phototherapy depends on the intensity of radiation (which in turn depends on the characteristics of radiation, number of radiation sources, and exposed body area) and the distance between the body and the source of radiation.[25] Phototherapy causes minor increases in transepidermal skin water loss in full-term infants. Side effects include temperature instability, intestinal hypermotility, interference with maternal-infant interaction and, rarely, bronze discolouration of the skin. Also, eye patches should be used to protect the developing retina.[26] Current guidelines suggest continuous or intermittent phototheraphy treatment for neonatal jaundice.[4-6] Intensity can be increased by using multiple phototherapy units or moving the unit closer to the infant.[25,27] Recent studies suggested that in term and late preterm infants with non-hemolytic moderate hyperbilirubinemia, intermittent phototherapy with 12 hours on and 12 hours off cycles is as efficacious as continuous phototherapy.[28,29] In the recent study, we used intermittent phototheraphy treatment for indirect neonatal hyperbilirubinemia.

Limitations of the study were; firstly, the babies that were required exchange transfusion were not included in the study. However, during the study period no exchange transfusion was required in our hospital. Secondly, the side effects of phototheraphy treatment were not evaluated. Another limitation was that the incidence of kernicterus and permanent neurologic sequelae due to bilirubin induced neurotoxicity were not known.

CONCLUSION

Our study showed that ABO incompatibility and cephalic hematoma were the most common etiologies in indirect neonatal hyperbilirubinemia. Additionally, male gender, formula as the first prelacteal feed, ABO incompatibility, Rh isoimmunization, cephalic hematoma and sepsis were the risk factors for phototherapy treatment >24 hours period. Also, determination of possible risk factors for neonatal jaundice can provide early hospital admissions by informing mothers before discharge after birth.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical clearance was sought and obtained from T.C. Sağlık Bakanlığı, Konya İl Sağlık Müdürlüğü Ethical Committee (IRB Number: 86737044-806.01.03).

Informed Consent: Parents of study participants were asked to provide informed voluntary written consent. Assent was also signed by parents for participants to be included in the study.

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: Concept: E.K.A. Design: E.K.A. Data Collection or Processing: E.K.A. Analysis or Interpretation: E.A.K. Literature Search: E.K.A. Writing: E.K.A.

Acknowledgement: We thanks to Ahmet Midhat Elmacı, Assoc. Prof. for the statistical analysis.

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.936729
J Contemp Med 2021;11(4):565-569

Orjinal Araştırma / Original Article

Have We Got Used to It Despite the Challenges? Mask Usage Habits and Usage Difficulties During Covid-19 Pandemic

Zorluklarına Rağmen Alışabildik Mi? Covid-19 Pandemisinde Maske Kullanım Alışkanlıkları ve Kullanım Zorlukları

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Abstract

Aim: In this study; It is aimed to identify the use of masks, which has become mandatory due to the Covid-19 epidemic since March 2020, the habits of individuals living in Turkey and the difficulties they face during the use of masks.

Material and Method: The study was performed as an questionnaire research with multiple -choice determinative questions, 1524 volunteers were randomized on the questionnaire platform. The data obtained were expressed in percentiles and inferences proportional to the purpose were obtained.

Results: Ninety percentage of participants use the surgical mask, 31.4% of them have double masks and 46.3% need to change masks within the day. The ratio of participants warn those who do not wear a mask was found as 67.2%. We asked about the reason of mask usage and got "always" feedback from 75.9% of the respondents for the statement that; "I use the mask to protect my health". Similarly, 76.2% said "always" to the statement "I use the mask to protect the health of the people around me". Finally, 48% of the participants stated that the radical extension of the Covid-19 epidemic process increased their sensitivity to mask use, and 34.3% stated that they could continue to use masks after the pandemic process is over.

Conclusion: With this study, it was concluded that there is a high probability of encountering various problems in the use of masks and despite these problems that may negatively affect daily life, individuals show sensitivity in using masks in order to protect their health and those around them.

Keywords: Covid-19, pandemics, masks

Öz

Amaç: Bu çalışmada; Mart 2020'den itibaren Covid-19 salgını nedeniyle zorunlu hale gelen maske kullanımının, Türkiye'de yaşayan bireylerin maske alışkanlıkları ve maske kullanımı sırasında karşılaştıkları güçlüklerinin tespit edilmesi amaçlanmaktadır.

Gereç ve Yöntem: Çalışma, çoktan seçmeli belirleyici sorular içeren bir anket araştırması olarak gerçekleştirildi, anket platformunda 1524 gönüllü rastgele seçildi. Elde edilen veriler yüzdelik dilimler halinde ifade edilerek amaca orantılı çıkarımlar elde edilmiştir.

Bulgular: Katılımcıların %90'ı cerrahi maske kullanmakta, %31,4'ü çift maskeli ve %46,3'ü gün içinde maske değiştirme ihtiyacı duymaktadır. Maske takmayanları uyaranların oranı %67,2 olarak bulundu. Maske kullanım nedenini sorduğumuzda ankete katılanların %75,9'undan "Sağlığımı korumak için maske kullanıyorum"a "her zaman" geri bildirimini aldık. Benzer şekilde, "Maskeyi çevremdeki insanların sağlığını korumak için kullanırım" ifadesine de katılımcıların %76,2'si "her zaman" cevabını vermiştir. Son olarak, katılımcıların %48'i Covid-19 salgın sürecinin radikal uzantısının maske kullanımına karşı duyarlılıklarını artırdığını, %34,3'ü pandemi süreci bittikten sonra da maske kullanmaya devam edebileceklerini belirtti.

Sonuç: Bu çalışma ile maske kullanımında çeşitli sorunlarla karşılaşma olasılığının yüksek olduğu ve günlük yaşamı olumsuz etkileyebilecek bu sorunlara rağmen bireylerin sağlıklarını ve çevrelerini korumak için maske kullanımında hassasiyet gösterdikleri sonucuna varılmıştır.

Anahtar Kelimeler: Maske, Covid-19, pandemi

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Received *(Geliş Tarihi)*: 14.05.2021 **Accepted *(Kabul Tarihi)*:** 18.07.2021

INTRODUCTION

The SARS-CoV-2 virus, which is also defined as COVID-19 in the literature, is a virus that emerged in Wuhan, China in the last quarter of 2019 and spread by affecting many countries virally in a short time. In the ongoing process, Covid-19 was declared as a global emergency by World Health Organization on January 30, 2020 (1). After the first Covid-19 case statements from China, especially Wuhan, the first cases began to appear in Europe. With this rapid spread, a state of emergency was declared in Spain on 14 March and the authorities announced that the necessary measures will be taken (2). On March 11, 2020, the first COVID-19 case in Turkey was announced by the Ministry of Health (3).

Viruses spread from infected patients to healthy individuals, and this spread can be caused by droplets that taken by individuals during inhalation or by contamination of the eye and nasal mucosa (4). Although meaningful results for foodborne contamination are not available in the literature, some studies have emphasized that contaminated foods may pose a risk (5).

In researches that aimed to prevent the spread of the virus; Hand and respiratory hygiene, practice of social distance and the usage of mask have suggested on the grounds that spread can be prevented (5). It has also been reported that the usage of a multi-layer mask is a more effective method of protection from viruses than a single-layer mask (6).

There are studies applied on healthcare professionals in Turkey in order to determine habits about the usage of masks, which have important effects in preventing the viral transmission (7). In the United States, modeling studies have been carried out with some predictive data in order to predict the mask use habits of the people (8). As can be understood from the examples of the two studies, it is important to determine the mask usage habits of individuals and to get reactions about this issue to increase the usage of mask concretely. The aim of this study is in similar directions, to determine the mask useage habits and the problems encountered during mask usage in individuals living in the Republic of Turkey.

MATERIAL AND METHOD

Study sample; consists of individuals aged 18 and over, without a history of major psychosocial illness. (In the study, the lower limit is under 18 years of age and the upper limit was not set, but the upper limit due to the inability to obtain data for individuals aged 70 and over is considered to be 70 years in this study.) The online survey forms were shared with 1524 participants determined in this context between January 16 and February 16. The questionnaire forms prepared to collect data consist of two parts. The first part contains nine questions about the sociodemographic information of the participants. The second part consists of twenty questions that will be evaluated within the scope of mask usage habits and difficulties (Ethics committee approval number: E-46418926-050.01.04--5426).

Percentage, mean and standard deviation were used in descriptive statistics. Chi-square test was used in comparative analysis. A p value less than 0.05 was considered statistically significant.

RESULTS

Totally 1524 participants were included into thge study, with the ratio of 60.2% of women. The average age of the participants was found to be 23.8 (± 7.893) years. Other sociodemographic information of the participants is shown in **Table 1**.

Table 1. Demographic and general information data of the study

		N	%
Gender	Female	918	60.2
	Male	606	39.8
Age	18-24 years old	1171	76.8
	25-39 years old	243	15.9
	40-70 years old	110	7.3
Education Status	High school and below	152	15
	University	1372	85
Mask Type	Surgical	1371	90
	N95	37	2.4
	Washable/homemade	74	4.9
	Another	42	2.7
Mask supply location	Pharmacy	521	34.2
	Market	596	39.1
	Internet	219	14.4
	Homemade	22	1.4
	Another	166	10.9
Priority order when buying masks	Approval status from the ministry of health	494	32.4
	3 Floors	604	39.6
	Be cheap	196	12.9
	Another	230	15.1
Use of double masks	Yes	1046	31.4
	No	478	68.6
Changing masks during the day	Yes	819	46.3
	No	705	53.7
Using the mask so that the mouth and nose are completely covered	Yes	60	96.1
	No	1464	3.9
The feeling of warning people who do not wear a mask	Yes	263	67.2
	No	1024	17.3
	It does not matter	237	15.6

When the findings are evaluated in terms of gender and age;

In the study, a significant correlation was found between gender and double mask use status, changing the mask during the day and warning when seeing people who do not wear masks ($p < 0.05$). In addition, no significant correlation was found between gender and wearing the mask with the mouth and nose closed ($p > 0.05$). When age and double mask use were examined, a significant relationship could be established between changing the mask during the day and alerting people who did not wear a mask ($p < 0.05$), while

no significant relationship was found between gender and wearing the mask with the mouth and nose closed completely (p <0.05). > 0.05) (**Table 2**).

Table 2. Mask usage habits in terms of gender

		Female		Male		P value
		N	%	N	%	
Use of double masks	Yes	354	38.6	124	20.5	p<0.05
	No	564	61.4	482	79.5	
Changing masks during the day	Yes	257	48.8	257	42.4	p<0.05
	No	470	51.2	349	57.6	
Using the mask so that the mouth and nose are completely covered	Yes	883	96.2	581	95.1	p>0.05
	No	35	3.8	25	4.1	
The feeling of warning people who do not wear a mask	Yes	669	72.9	355	58.6	p<0.05
	No	137	14.9	126	20.8	
	It does not matter	112	12.2	112	12.2	

Within the scope of the study, a significant relationship was found between gender-age and the reason for using masks (p <0.05) (**Table 3**).

Table 3. Reasons to use masks in terms of gender

		Female		Male		P value
		N	%	N	%	
I use the mask to protect my own health	Never	30	3.3	28	4.6	p<0.05
	Sometimes	33	3.6	50	8.3	
	Usually	95	10.3	132	21.8	
	Always	760	82.8	396	65.3	
I use the mask to protect the health of the people around me	Never	32	3.5	21	3.5	p<0.05
	Sometimes	36	3.9	44	7.3	
	Usually	107	11.7	122	20.1	
	Always	743	80.9	419	69.1	
I use the mask because it is mandatory	Never	227	24.7	148	24.4	p<0.05
	Sometimes	176	19.2	126	20.8	
	Usually	122	13.3	114	18.8	
	Always	393	42.8	218	36	

While a significant correlation was found between gender and difficulty in breathing, nasal flushing while wearing a mask, and being disturbed by the smell of the mask (p <0.05), no significant correlation was found between gender and ear pain when wearing a mask (p> 0.05).

No significant correlation was found between age and difficulty in breathing, nasal flushing while wearing a mask, being uncomfortable with the smell of the mask, and ear pain while wearing a mask (p> 0.05) (**Table 4**).

Finally, evaluation of the relationship between mask wearing difficulties and mask type;

While there was no significant relationship between the mask type used while wearing a mask, difficulty in breathing, discomfort in the mask odor and pain in the ear (p> 0.05), a significant relationship was found between the type of mask used and nasal flushing. (p <0.05) (**Table 5**).

Table 4. Difficulties in using masks in terms of gender

		Female		Male		P value
		N	%	N	%	
Difficulty breathing while wearing a mask	Yes	678	73.9	393	64.9	p<0.05
	No	240	26.1	213	35.1	
Nasal flushing when wearing a mask	Yes	346	37.7	176	29	p<0.05
	No	572	62.3	430	71	
Being uncomfortable with the smell of the mask	Yes	559	60.9	322	53.1	p<0.05
	No	359	39.1	284	46.9	
Ear pain when wearing a mask	Yes	552	60.1	368	60.7	p>0.05
	No	366	39.9	238	39.3	

Table 5. Difficulties of using the mask according to the mask type

		Yes		No		P value
		N	%	N	%	
Difficulty breathing while wearing a mask	Surgical mask	950	69.3	421	30.7	p>0.05
	N95	29	78.4	8	21.6	
	Homemade/washable	57	77	17	23	
	Another	35	83.3	7	16.7	
Nasal flushing when wearing a mask	Surgical mask	449	32.7	922	67.3	p<0.05
	N95	18	48.6	19	51.4	
	Homemade/washable	35	47.3	39	52.7	
	Another	20	47.6	22	52.4	
Being uncomfortable with the smell of the mask	Surgical mask	790	57.6	581	42.4	p>0.05
	N95	18	48.6	19	51.4	
	Homemade/washable	49	66.2	25	33.8	
	Another	24	57.1	18	42.9	
Ear pain when wearing a mask	Surgical mask	820	59.8	551	40.2	p>0.05
	N95	22	59.5	15	40.5	
	Homemade/washable	45	60.8	29	39.2	
	Another	33	78.6	9	21.4	

DISCUSSION

Masks provide protection for their users only when used correctly (9). Kim MC et al. conducted a study to investigate the filtering properties of masks and found that surgical masks inhibited less viral particles than N95 masks and their equivalents (10). On the other hand, no determination has been made about why individuals turn to surgical masks.

It has been confirmed by research that masks provide the prescribed protection together with physical distance and hygiene (11). Olgun et al., by scanning 27 articles on the use of masks, suggesting to consider the differences according to the usage environments and the people intended to use the masks, suggesting that the protection levels of the masks; N95 and similar (like FFP2, FFP 3) masks > surgical/medical masks > non-medical (such as polypropylene, cotton, polyester, silk) masks. Most of the participants in our study stated that they used surgical masks. As the reason for this result obtained in the research; Surgical masks are thought to be cheaper and more readily available. In addition, it may be that the ministry and WHO encourage the use of surgical masks outside of risk groups.

In the study conducted by Jacek and, in a population including 2135 students, it was found that the mask type that caused the most irritation in the nose (especially considering itching) was N95 + fpp. (12). Supporting the study, it was determined that the mask type that causes the most irritation in the nose is N95 in our study. In summary, in both studies, it was determined that N95 type masks cause more irritation in the nose compared to other masks.

Morishima and Kichida, in their study in Japan in 2009, 2012 and 2015; Similar questionnaires were applied to determine the rate of mask use, purpose of use, and problems reported while wearing masks. According to the results obtained, while the reason for using masks was to protect men from the flu in 2009, it turned into the prevention of colds in 2012 and 2015. Considering the common problems in male individuals; Moisture in the mask, condensation in the glasses and difficulty in breathing are in the first three places. The reason for using masks in women was to prevent colds. Considering the common problems, the first three reasons for female individuals are the same as for male individuals, and makeup deterioration due to masks during the day has also been identified as a problem (13). In this study, the most common problems on the basis of male individuals are; Difficulty in breathing, pain in the ear, discomfort from the smell of the mask and redness of the nose. Considering the most common problems in the use of masks in women, respectively; Difficulty in breathing, discomfort from the smell of the mask, pain in the ears and redness in the nose were determined.

Çağdaş and Emre; In their research on healthcare professionals, they examined the rate of earache as a result of the use of masks in two groups. During the use of masks, ear pain in the first group (healthcare professionals group using surgical masks) was measured twice as 60 and 180 minutes. 29.6% in the measurement made after 60 minutes; In the measurement made after 180 minutes, 39.5% complaints of ear pain were detected. In the second group (healthcare workers using ffp N95 type mask) when the same measurement was made, it was 41.9% after 60 minutes; After 180 minutes, 51.9% of ear pain complaints were found (7). Same problem in this article; dealing with earache and complaints; 59.8% in surgical mask, 59.5% in N95 type mask and 60.9% in homemade mask. If we look at the studies from a common point, it is thought that the reason why healthcare workers experience lower levels of ear pain is due to the use of masks at normal times outside the pandemic process due to professional requirements. But; In this study, while the rates of ear pain caused by the use of N95 and surgical masks (surgical mask 59.8% N95 59.5% homemade 60%) were close to each other, it was higher in healthcare workers (60min 41.9% 180min 51.9%). Despite the complaints of healthcare professionals, it can be concluded that the habit of using masks is more correct. In the study included in this article, a significant relationship was found between the mask type and the occurrence of nasal redness while using a mask. The relationship between the mask type and nasal flushing when using a mask is that 32.7% of the use of surgical mask and 48.6% of the use of a N95 mask are complaints. In the study conducted on healthcare workers, it was found that in the first group, 22 (27.2%) people had 60th minute, 32 (39.5%) had 180th minute; In the second group, 14 (45.1%) people felt discomfort at the 60th minute and 20 (64.5%) at the 180th minute, and there was no significant correlation between the masks until the 60th minute, while a correlation was found at the 180th minute. In both studies, the higher rate of N95 mask users may indicate that those who use N95 masks used masks for a longer time and more accurately (by fully covering the mouth and nose). On the other hand, in our research, "Do you cover your nose while using a mask?" 92% of the answer given to the question weakens the thesis that individuals do not use masks correctly and for a long time as much as healthcare workers.

CONCLUSION

In order to reach concrete results in the studies on masks in the literature, there are limited data with laboratory studies without including user opinions. In this study, it is aimed to create a data by evaluating the difficulties experienced by individuals during mask use, based on gender and mask types. In this study, in which mask usage habits were examined, a significant difference was observed between male and female populations in the difficulties encountered in using masks, but no significant difference was observed in terms of age. No concrete link was found between the type of mask and the problems encountered while using the mask.

Since it is known that breathing is the most important transmission route of the disease in the Covid-19 process, the use of masks significantly reduces the risk of transmission. With the use of masks being so important, it was concluded in this study that despite all the difficulties, individuals use masks to protect both their own health and the health of those around them. It is foreseen that it is not known exactly when the pandemic process will end and the use of masks will become even more important in the next new normal world order. For this reason, it is thought that it is very important for individuals to use masks more comfortably by solving the problems experienced during mask use. From this point of view, with this study, inferential conclusions about mask usage habits and difficulties were reached and data was created for the literature.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Health Sciences University Hamidiye Scientific Research Ethics Committee (Date: 15.01.2021, Decision No: E-46418926-050.01.04--5426).

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.

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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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.941055
J Contemp Med 2021;11(4):570-576

Orjinal Araştırma / Original Article

Evaluation of Patients with Severe Asthma Exacerbation treated in a Pediatric Intensive Care Unit: 8 Years of Single-Center Experience

Çocuk Yoğun Bakım Ünitesinde Tedavi Edilen Şiddetli Astım Ataklı Hastaların Değerlendirilmesi: 8 Yıllık Tek Merkez Deneyimi

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Abstract

Aim: In this study, we aimed to evaluate the demographic and clinical characteristics of pediatric patients followed in a tertiary pediatric intensive care unit (PICU) due to severe asthma exacerbation (SAE) and to discuss the optimal intensive care management for these patients.

Material and Method: We retrospectively analyzed a total of 103 patients between the ages of 12 months and 18 years who were followed up in the PICU with a diagnosis of SAE between 2013 and 2020.

Results: On the evaluation of data in terms of respiratory support, it was observed that 34 (33%) of the patients were treated during follow-up with, nasal oxygen cannula or standard non-rebreather oxygen face mask (NC/NRB), 13 (12.6%) with high-flow nasal cannula oxygenation (HFNC), 46 (44.7%) with non-invasive mechanical ventilation (NIMV), and 10 (9.7%) with invasive mechanical ventilation (IMV). When the respiratory supports applied by years were evaluated, the rate of invasive mechanical ventilation usage decreased significantly in recent years compared to the first years (5.6% and 20%; respectively; $p < 0.001$). Pneumothorax developed in one (1%) patient. No patient died among 103 patients who were followed up.

Conclusion: We think that early initiation of HFNC or NIMV in combination with bronchodilators, systemic corticosteroids, and if necessary, intravenous magnesium sulfate is a safe and viable treatment option for SAE treatment. In SAE cases in the PICU, the pediatric intensive care specialist should systematically evaluate the patient and quickly decide whether there is a need for respiratory support and additional treatment.

Keywords: Severe asthma exacerbation, pediatric intensive care, non-invasive mechanical ventilation

Öz

Amaç: Bu çalışmada, Şiddetli astım atağı (ŞAA) nedeniyle üçüncü basamak çocuk yoğun bakım ünitesinde (ÇYBB) izlenen çocuk hastaların demografik ve klinik özelliklerini değerlendirmeyi ve bu hastalar için optimal yoğun bakım yönetimini tartışmayı amaçladık.

Gereç ve Yöntem: 2013-2020 yılları arasında ÇYBB'de ŞAA tanısıyla izlenen 12 ay ile 18 yaşları arasında toplam 103 hastayı geriye dönük olarak inceledik.

Bulgular: Solunum desteği açısından değerlendirildiğinde; hastaların 34'ünün (%33) nazal kanül yada geri soluması oksijen maskesi, 13'ünün (%12,6) yüksek akışlı nazal kanül oksijenizasyonu (YANKO), 46'ünün (%44,7) non-invaziv mekanik ventilasyon (NIMV), 10'unun (%9,7) da invaziv mekanik ventilasyonda (IMV) takip edildiği görüldü. Yıllara göre kullanılan solunum destek tedavileri değerlendirildiğinde, son yıllarda IMV kullanım oranımız, ilk yıllara göre istatistiksel olarak azalmıştı (%5.6 vs %20; sırasıyla; $p<0.001$). Bir (% 1) hastada pnömotoraks gelişti. İzlenen 103 hastadan ölen hasta olmadı.

Sonuç: Bronkodilatörler, sistemik kortikosteroidler ve gerekirse intravenöz magnezyum sülfat ile birlikte YANKO veya NIMV'in erken başlatılmasının ŞAA tedavisi için güvenli ve uygulanabilir bir tedavi seçeneği olduğunu düşünmekteyiz. ÇYBÜ'de ŞAA'da, çocuk yoğun bakım uzmanı, hastayı sistematik olarak değerlendirmeli, solunum desteği ve ek tedavi ihtiyacına hızlı bir şekilde karar vermelidir.

Anahtar Kelimeler: Şiddetli astım atağı, çocuk yoğun bakım, non-invaziv mekanik ventilasyon

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INTRODUCTION

Severe asthma exacerbation (SAE) is a life-threatening asthma attack that does not respond to acute asthma treatment. Children with acute asthma attacks generally respond to bronchodilators, corticosteroids, and oxygen therapy.[1] Some patients need treatment in the pediatric intensive care unit (PICU) for advanced treatment and respiratory support. In patients with SAE, apnea, cardiac arrhythmia, and respiratory depression may develop and cause morbidity and mortality if acidosis, hypoxia, and hypercarbia are not treated.[2,3] Risk factors associated with SAE include inadequate asthma treatment, poor compliance with current treatment, delayed admission to hospital, and a history of the previous hospitalization for asthma.[1-3] Patients transfer to intensive care if there are signs of severe exacerbation, or if the patient drowsy, confused, or has a silent chest.[2-3]

Respiratory support in SAE consists of oxygen therapy, high-flow nasal cannula oxygenation (HFNC), non-invasive mechanical ventilation (NIMV), and invasive mechanical ventilation (IMV). The majority of cases can be managed without the use of endotracheal intubation and mechanical ventilation. NIMV offers an alternative to IMV for the treatment of acute respiratory failure.[4] Many studies are supporting the safety and efficacy of NIMV for asthmatic patients.[4-6] However, the most recent Cochrane review concluded that there is no sufficient evidence to evaluate the positive effects of NIMV on critical asthmatic patients.[7]

In general, there are different approaches among the centers in follow-up and treatment practice in SAE, which require PICU. There are no detailed guidelines regarding invasive and non-invasive respiratory support options and treatment timing in SAE. This study aims to evaluate the demographic and clinical characteristics of pediatric patients followed in tertiary PICU due to SAE and to discuss the optimal intensive care management for these patients.

MATERIAL AND METHOD

The study was performed between February 1, 2021, and May 1, 2021, in the PICU of Ankara City Hospital. The study was designed as a retrospective, single-center, descriptive study. The approval for our study was obtained from the Clinical Research Ethics Committee of Ankara City Hospital (with approval number E200/15). The study was carried out by the principles of the Declaration of Helsinki.

Participant Selection

Four of the 110 pediatric patients with asthma were excluded from the study because we could not be reached patients' data. Patients (n=103) aged between 12 months and 18 years who were followed up in the PICU with a diagnosis of SAE between 2013 and 2020 were included in the study. The following three basic criteria were determined as the inclusion criteria: 1) presence of diagnosed asthma with objective diagnostic criteria, such as pulmonary function test, early reversibility test, bronchial provocation tests, before intensive care admission, 2) patients who were treated in PICU due to their first attack, but then followed up in the pediatric allergy and immunology clinic due to recurrent attacks, 3) patients who have a maintenance treatment report for asthma registered in the electronic prescription system. Patients who do not respond to first-line asthma treatment (inhaled/oral steroid and oxygen therapy) and who have signs of severe airway obstruction (wheezing or silent chest, tachypnea, tachycardia, usage of accessory respiratory muscles, altered consciousness, acidosis, hypoxia, hypercarbia) were defined as SAE. Respiratory supports in the PICU (oxygen, HFNC, NIMV, or IMV) and the decision of additional treatments (intravenous magnesium sulfate, inhaled adrenaline) were left to the pediatric intensive care specialist. The age group under 12 months was excluded because the clinical condition could be confused with bronchiolitis in this group. In addition, patients with other chronic diseases besides asthma-related to the respiratory or cardiovascular system, such as cystic fibrosis, pulmonary hypertension, bronchiectasis, bronchopulmonary dysplasia, congenital heart disease, were not included in the study.

Data Collection Tools

All patients included in the study were evaluated with a form consisting of three parts. This form included sociodemographic data form, clinical evaluation form, the mortality and morbidity assessment form consisting of standard scales prepared by the authors.

1. **Sociodemographic Data Form:** This form includes sociodemographic characteristics, such as age, sex, personal history, and family history, as well as asthma history (previous exacerbation, severity of exacerbation, hospitalization history, prescribed maintenance treatment data) which was obtained from the medical records of the patients.
2. **Clinical Evaluation Form:** Data including indication for intensive care admission, examination and laboratory findings, clinical course, treatments applied, durations, and clinical responses to treatments, if any, treatment complications were obtained from the follow-up charts of patient used during the intensive care period. In addition, the duration of PICU stay and hospital stay, and the clinical condition of the patients during hospital discharge were also evaluated.
3. **Mortality Assessment Form:** Pediatric Risk of Mortality III (PRISM III) scoring was applied to all patients to determine the severity of the disease, to predict recovery from the disease, to examine the mortality rate, and to evaluate the performance of our intensive care unit.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics software for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean and

standard deviation for normally distributed data, and as the median and interquartile range (IQR, 25th–75th percentile) for non-normally distributed data. Chi-square test was used to compare nonparametric data, Kruskal–Wallis test was used to compare continuous variables between groups. The value of p <0.05 was considered statistically significant.

RESULTS

Demographic Data and Asthma History

The number of patients with the diagnosis of SAE was determined to be 103 among a total of 6086 patients followed up in the PICU between January 1, 2013, and December 31, 2020, accounting for 1.6% of all hospitalizations. Fifty-six (54.4%) of the patients were male and 47 (45.6%) were female. The mean age was 44.9±38.5 months.

When the clinical indications for admission to the PICU are evaluated, it was observed that 92 (89.3%) patients had respiratory distress/tachypnea, 21 (20.4%) patients had cyanosis, and 10 (9.7%) patients had respiratory failure. Considering the acid-base status of patients during the application for the PICU, median pH was determined as 7,35 in arterial blood gas (IQR: 7.30 - 7.38), median $PaCO_2$ was 40 mmHg (IQR: 35.7 - 50), median PaO_2 was 47,2 (IQR: 38.4–53.3). The highest number of hospitalizations was observed in March and April. The distribution of hospitalizations by months is shown in **Figure 1**.

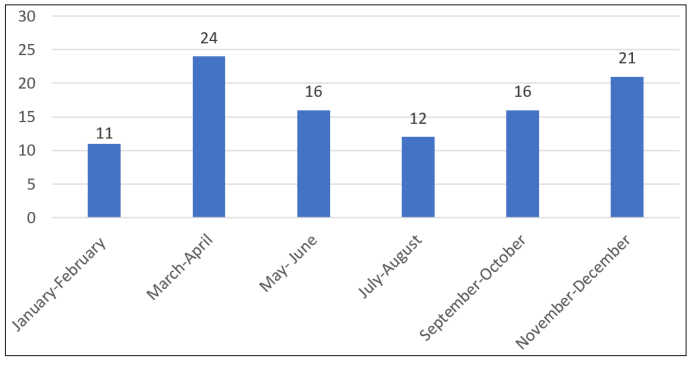

Figure 1. The distribution percentage of hospitalizations by months

The mean age at diagnosis of asthma was 30.76±25.42 months. Seventy-eight of the patients (75.7%) applied to the hospital within 24 hours after the onset of their symptoms. Eleven (10.7%) patients had a family history of asthma. 13.6% of the patients were exposed to passive smoking. It was found that 58 patients (56.3%) had a previous hospitalization, and 8 patients (7.7%) had an asthma attack that required PICU admission. The demographic data of the patients are shown in **Table 1**.

Clinical Evaluation and Treatment Data

On the evaluation of data in terms of respiratory supports, it was observed that 34 (33%) of the patients were treated during follow-up with free oxygen, nasal oxygen cannula, or standard non-rebreather oxygen face mask (NC/NRB), 13 (12.6%) with HFNC, 46 (44.7%) with NIMV, and 10 (9.7%) with intubation. **Figure 2** shows the change in respiratory supports treatment methods applied in SAE patients in our unit monitored over the years. The mean duration of NIMV was 73.2±31.4 hours, and the mean follow-up time with IMV was 5.7±4.6 days. One (1%) patient who was followed up with IMV, developed pneumothorax due to positive pressure ventilation, and a chest tube was required for drainage. Although other respiratory support techniques and medical treatment were successful in most of the patients, 10 (9.7%) patients required intubation and IMV support. When patients were divided into groups according to respiratory support needs, in the group requiring IMV, the median pH value in blood gas was lower, the median $PaCO_2$ value was higher, the median length of stay in the intensive care unit and the hospital was longer, and the PRISM III scores were higher than the other groups, and these were statistically significant (**Table 2**).

Table 1. The demographic and clinical data of the patients (n = 103)

Parameter	n=103
Male, n (%)	56 (54.4)
Mean age (SD), month	44.9±38.5
Tachypnea, n (%)	92 (89.3)
Cyanosis, n (%)	21 (20.4)
Respiratory Failure (%)	10 (9.7)
Admission pH median, (IQR)	7.35 (7.30-7.38)
Admission $PaCO_2$, median (IQR)	40 (35.7-50)
Admission PaO_2, median (IQR)	47.2 (38.4-53.3)
Asthma diagnosis age, mean (sd),	30.76±25.42
Previous hospital stay, n (%)	58 (56.3)
Smoking in the family, n (%)	15 (14.6)
Family history, n (%)	11 (10.7)
Respiratory support	
NR/NRB, n (%)	34 (33)
HFNC, n (%)	13 (12.6)
NIMV, n (%)	46 (44.7)
IMV, n (%)	10 (9.7)
Treatment	
Systemic corticosteroid, n (%)	103 (100)
Inhale ipratropium, n (%)	31 (30.1)
Inhale adrenaline, n (%)	17 (16.5)
Intravenous magnesium sulphate, n (%)	67 (65)
Systemic antibiotics, n (%)	59 (57.3)
Sedation, n (%)	36 (35)
Inotrop support, n (%)	2 (1.9)
Outcome	
PICU LOS, day, median (IQR)	3 (2-5)
Hospital LOS, day, median (IQR)	7 (6-9)
PRISM III, median, (IQR)	2 (2-2)
Complication, n (%)	1 (1)
Mortalite, n (%)	0

SD: standard deviation, IQR: Interquartile range, NC/NRB: Nasal oxygen cannula or standard non-rebreather oxygen face mask, HFNC: high-flow nasal cannula oxygenation, NIMV: non-invasive mechanical ventilation, IMV: invasive mechanical ventilation, PICU: pediatric intensive care unit, LOS: length of stay, PRISM III: Pediatric Risk of Mortality score

Table 2. Demographic findings, medical treatments, and clinical findings of the patients according to their respiratory support requirement

Parameter	NC/NRB (n = 34)	HFNC (n = 13)	NIMV (n = 46)	IMV (n=10)	P
Male (%)	19 (55.9)	6 (46.2)	25 (54.3)	6 (60)	0.909
Mean age (SD), month	54.08±44.88	41.84±35.47	33.80±22.54	69±60.08	0.056
pH median, (IQR)	7.35 (7.32-7.37)	7.37 (7.35-7.39)	7.36 (7.31-7.38)	7.22 (7.09-7.28)	<0.001*
$PaCO_2$, median (IQR)	38.5 (35.3-44.2)	38 (36.1-41)	42.3 (35-50.2)	63.3 (54.75-83,5)	<0.001*
PaO_2, median (IQR)	41.9 (35.9-52-87)	46.9 (40-53.15)	50 (40.37-56.3)	47.25 (36.9-51,3)	0.293
Asthma diagnosis age, mean (sd),	36.94±28.21	26.84±22.55	24.23±18.63	44.90±37.21	0.051
Previous hospital stay, n (%)	17 (50)	9 (69.2)	25 (54.3)	7 (70)	0.447
Smoking in the family, n (%)	6 (17.6)	2 (15.4)	6 (13)	1 (10)	0.474
Family history, n (%)	4 (11.8)	1 (7.7)	5 (10.9)	1 (10)	0.772
Treatment					
Systemic corticosteroid, n (%)	34 (100)	13 (100)	46 (100)	10 (100)	
Inhale ipratropium, n (%)	10 (29.4)	5 (38.5)	13 (28.3)	3 (30)	0.812
Inhale adrenaline, n (%)	5 (14.7)	2 (15.4)	7 (15.2)	3 (30)	0.661
Intravenous magnesium sulphate, n (%)	19 (55.9)	8 (61.5)	35 (76.1)	5 (50)	0.302
Systemic antibiotics, n (%)	8 (23.5)	6 (46.2)	35 (76.1)	10 (100)	<0.001*
Sedation, n (%)	0	3 (23.1)	23 (50)	10 (100)	<0.001*
Inotrop support, n (%)	0	0	0	2 (20)	0.02*
Outcome					
PICU LOS, day, median (IQR)	2 (2-3)	2 (2-4.5)	4 (3-5)	7.5 (4.5-18)	<0.001*
Hospital LOS, day, median (IQR)	6 (4-7)	7(4-7.5)	8 (7-9.25)	15.5 (9.75-22.25)	<0.001*
PRISM III, median, (IQR)	2 (2-2)	2 (2-2)	2 (2-2)	4 (3-4.5)	<0.001*
Complication, n (%)	0	0	0	1 (10)	0.102
Mortalite, n (%)	0	0	0	0	

SD: standard deviation, IQR: Interquartile range, NC/NRB: Nasal oxygen cannula or standard non-rebreather oxygen face mask, HFNC: high-flow nasal cannula oxygenation, NIMV: non-invasive mechanical ventilation, IMV: invasive mechanical ventilation, PICU: pediatric intensive care unit, LOS: length of stay, PRISM III: Pediatric Risk of Mortality score, *P< 0.05

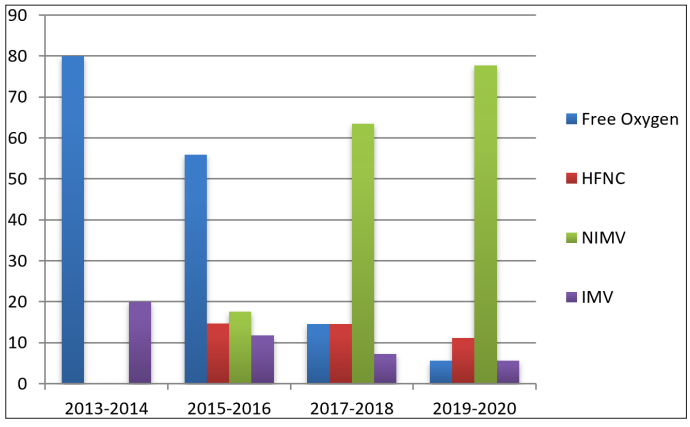

Figure 2. The changes in respiratory support treatment over the years in our PICU HFNC: high-flow nasal cannula oxygenation, NIMV: non-invasive mechanical ventilation, IMV: invasive mechanical ventilation

Sedation was applied to 3 (23.1%) patients followed up with HFNC and 23 (50%) patients with NIMV treatment to ensure patient coordination and effective treatment. Dexmedetomidine was used for sedation during HFNC and NIMV. During mechanical ventilation application, all patients received sedation (dormicum and fentanyl) to enable safe and effective mechanical ventilation. Neuromuscular blockade (vecuronium) was used to maintain stable respiratory parameters in 4 patients (40%) with IMV, whose respiratory synchronization could not be achieved despite severe sedation. Inotropic support (adrenaline infusion) was given to 2 (20%) patients who were followed up intubated.

Antibiotic treatment was given to 59 (57.3%) patients, a systemic corticosteroid to all (100%), inhaler steroid to 31 (30.1%) patients and intravenous magnesium sulphate to 67 (65%) patients. **Table 2** summarizes the demographic findings, medical treatments, and clinical findings of the patients according to their respiratory support requirements.

Outcome

The median length of stay in the intensive care unit of our patient group was 3 (IQR=2–5) days. The median length of stay in the hospital was 7 (IQR=6–9) days. The median PRISM III score of the study group was 2 (IQR; 2–2). Among the 103 patients who were followed up due to SAE in PICU, no patient died.

DISCUSSION

SAE in children is one of the most difficult causes of respiratory failure to manage. Previous studies have shown that SAE is more common in men.[1-4] The reason for this situation has not been clearly explained; however, it is estimated that it is associated with a narrower airway size in boys compared to girls and a rapid decline in lung function.[8] In our study, we observed that boys were admitted to the intensive care unit more frequently than girls, which can be explained by the higher prevalence of asthma in boys. It was observed that the highest number of hospitalizations occurred in March and April. This situation is thought to be related to the fact that March and April are the peak period for viral infections in our country, such as rhinovirus and influenza virus.

Respiratory Support

HFNC is a device that is currently used as the primary respiratory support for respiratory distress, especially in emergency rooms.[9,10] HFNC reduces anatomical dead space in the nasopharyngeal cavity and CO_2 clearance. In addition, depending on the flow rate applied and the effectiveness of the cannula, it provides a certain level of positive end-expiratory pressure (PEEP) (2–7 cmH_2O) and reduces inspiratory resistance.[11,12] Follow-up of patients with HFNC can also be performed inwards other than intensive care in our hospital. The number of patients we apply HFNC is less than NIMV because we accept more severe patients who need NIMV or IMV in our intensive care unit.

With the widespread use of NIMV and HFNC treatment and its effective use in intensive care units, patients with SAE can be successfully treated without IMV. However, in SAE, 6%–20% of children may not respond to treatment and may progress to life-threatening respiratory failure that requires positive pressure ventilation.[13] NIMV has been suggested as a safer, intermediate alternative technique that potentially reduces the need for endotracheal intubation in patients with SAE, considering the risks and morbidity associated with IMV.[15] In addition, there are randomized controlled studies proving the effectiveness of NIMV in reducing the respiratory load in SAE together with nebulized bronchodilator and anti-inflammatory therapy.[15-17] This study showed that NIMV is the most common ventilation method used in patients with SAE hospitalized in the PICU. NIMV is used in our unit as primary respiratory support for children with SAE.

The frequency of IMV requirement in SAE has been reported as 3.7%–33.3% in the literature.[2,3,13,18] IMV requirement was found to be at a rate of 9.7% when all patients in the study were evaluated. When the respiratory supports applied by years were evaluated, the rate of IMV usage decreased significantly in recent years compared to the first years (5.6% and 20%; $p < 0.001$). We think that this situation is related to the absence of a PICU specialist in our unit in the first years of the study and therefore ineffective use of HFNC and NIMV. In addition, we think that HFNC and NIMV therapy and early initiation of additional therapies by making a quick decision in SAE treatment may play a role in reducing the need for intubation.

Bronchospasm and mucosal obstruction are important factors affecting the duration of mechanical ventilation.[3,8] Bronchospasm regresses and the patient can be extubated in a short time with treatment. In the literature, data are showing that IMV prolongs the duration of the PICU stay.[18,19] In our study, the duration of stay in PICU and hospital was found to be longer in patients receiving IMV ($p < 0.001$).

Hon et al. stated that the most important difference between the NIMV and IMV groups was the presence of CO_2 retention.[2] When the patient groups were evaluated according to the respiratory support need, it was observed that the group in need of IMV support had a significantly lower median pH value and significantly higher median PCO_2 value ($p < 0.001$, $p < 0.001$, respectively). Early treatment of these variables, which is an indicator of respiratory failure symptoms, with appropriate respiratory support is important for morbidity and mortality. In the laboratory follow-ups of the patients during treatment, blood gas values remained within normal ranges.

Co-infection

Difficulty in distinguishing viral and bacterial infections is one of the clinical problems faced by pediatric intensive care professionals in SAE follow-up. Empirical antibiotics are often used in the initial phase of any curable bacterial co-infections. Rapid diagnosis of respiratory viral infections in children is important because it can cause a reduction in antibiotic use and prevent unnecessary isolation for respiratory viruses. Chiang et al. stated that 57% of the patients who required PICU stay for SAE had bronchopneumonia.[3] In our study, chest radiography was performed in all patients. It was observed that 59 (57.3%) of them had findings indicating pneumonia in addition to asthma, and antibiotics were added to the treatment.

Treatment and Outcome

Data in the literature indicate that a single dose of intravenous $MgSO_4$ contributes positively to the clinical course in SAE that does not improve with standard initial treatments.[20] In previous studies, the rate of intravenous $MgSO_4$ usage in SAE in need of intensive care was reported to be 17%–36%.[18,21] In recent years, nebulized $MgSO_4$ treatment has also been used in the treatment of SAE.[22] In our study, it was observed that 67 patients (65%) received $MgSO_4$ treatment. $MgSO_4$ was given 40 mg/kg/dose four times a day (up to a maximum of 2 g daily). We did not encounter any significant side effects in any of the patients who received $MgSO_4$. The rate of use of $MgSO_4$ in our intensive care unit has been found to be higher than in the literature since we mostly follow severe attacks that are unresponsive to initial treatments and have found that it benefits the treatment.

In a study, the rate of intensive care rehospitalization of patients in intensive care due to asthma was reported as 17%.[23] In our study, the number of patients re-admission to PICU due to asthma was found to be 8 (7.7%). According to the information obtained from the patient data, the common feature of these patients was that they were not regularly followed up for asthma in the clinics. We think that not regularly attending asthma polyclinic controls makes disease control difficult and increases the risk of readmission to intensive care.

In the literature, it has been shown that 0%–8% of children admitted to the PICU with SAE developed one or more complications during their treatment. The most common complications are aspiration pneumonia, ventilator-associated pneumonia, pneumomediastinum, pneumothorax, and rhabdomyolysis.[15,24,25] In our study, it was found that pneumothorax developed in 1 patient (1%).

In intubated children, the risk of morbidity and mortality is higher due to the longer stay in the intensive care unit and the invasive nature of the procedure. Previously reported mortality rates for SAE ranged from 0% to 18%.[2,3,17] Respiratory failure, barotrauma, or hypotension are among the most frequently reported causes of death. In our study, all patients survived and were discharged from the hospital without clinically significant respiratory sequelae after service follow-up. Early transfer of children with SAE to intensive care, initiation of appropriate treatment as soon as possible, and optimal management of therapy are important in terms of providing positive results.

Limitation

Our study has limitations because it is a retrospective and descriptive study and there is no comparison group. Clinical scoring of asthma severity is difficult, and physiological markers and PRISM III data may not be accurate indicators of respiratory distress. The Global Initiative for Asthma consists of a table of physical findings, blood gas values, and peak expiratory flow rates to assist clinicians in assessing asthma severity, but does not include a scoring system recommendation.[26] For this reason, a scoring system was not used in our study.

In response to these limitations; the strength of our study is to summarize the systematic treatment approach followed in the PICU together with the clinical characteristics of our cases with SAE over a sufficient number of pediatric patients in a limited number of literature data.

CONCLUSION

Although our data indicate the survival of all patients, asthma management requiring PICU may be associated with high morbidity and even mortality. We think that early initiation of HFNC or NIMV in combination with bronchodilators, systemic corticosteroids, and if necessary, intravenous magnesium sulfate is a safe and viable treatment option for SAE treatment. In our study, we showed that the need for IMV in the SAE has decreased with the arrival of our pediatric intensive care specialist in our unit in recent years. In SAE cases in the PICU, the pediatric intensive care specialist should systematically evaluate the patient and quickly decide whether there is a need for respiratory support and additional treatment. Multi-center randomized controlled studies should be conducted to assess NIMV effectiveness in SAE. Patient follow-up by a pediatric allergist after the PICU hospitalization and the regulation of maintenance treatment will be effective in terms of asthma control and reduction of re-admission.

ETHICAL DECLARATIONS

Ethics Committee Approval: The approval for our study was obtained from the Clinical Research Ethics Committee of Ankara City Hospital (with approval number E200/15).

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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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.839575
J Contemp Med 2021;11(4):577-581

Orjinal Araştırma / Original Article

Association Between Hyperuricemia and Non-Traditional Adiposity Indices in Pre-Menopausal Women

Menapoza Girmeyen Kadınlarda Hiperürisemi ve Geleneksel Olmayan Adipozite Belirteçleri Arasındakı İlişki

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Abstract

Aim: Hyperuricemia is a risk factor for hypertension, type 2 diabetes mellitus, dyslipidemia, metabolic syndrome, cardiovascular diseases. Body adiposity index (BAI), lipid accumalation pruduct (LAP), cardiometabolic index (CMI) and visceral adiposity index (VAI) are non-traditional parameters used to evaluate visceral obesity. There are not enough studies on the relationship between non-traditional adiposity markers and hyperuricemia. In this study, we aimed to investigate the relationship between hyperuricemia and non-traditional adiposity markers in pre-menopausal women.

Material and Method: 86 premenopausal women were included in the study. Height, weight, waist circumference (WC) and hip circumference measurements were made, Body mass index (kg/m^2) was calculated. Blood pressure was measured from both arms after 10 minutes of rest. Blood samples were taken after 12 hours of fasting.

Rusults: 43 women (%50) had hyperuricemia. In the group with hyperuricemia, traditional and non-traditional (BAI, LAP, VAI, CMI) adiposity markers were increased. A positive correlation was found between serum uric acid (UA) levels and adiposity markers. WC, LAP and CMI were found to be independent adiposity markers of serum UA.

Conclusion: In our study, we determined that WC, LAP and CMI were independent adiposity markers for serum uric acid value.

Keywords: Cardiometabolic index, lipid accumalation pruduct, visceral adiposity, uric acid

Öz

Amaç: Hiperürisemi hipertansiyon, tip 2 diyabet, dislipidemi, metabolik sendrom ve kardiyovasküler hastalıklar için bir risk faktörüdür. Vücut yağ indeksi (VYI), lipit biriktirme ürünü (LBÜ), kardiyo metabolik indeks (KMI) ve viseral adipozite indeksi (VAI) viseral adipoziteyi değerlendirmek için kullanılan geleneksel olmayan parametrelerdir. Hiperürisemi ve geleneksel olmayan adipozite belirteçleri arasındaki ilişkiyi inceleyen yeterli sayıda çalışma yoktur. Biz bu çalışmada menapoza girmemiş kadınlarda hiperürisemi ve geleneksel olmayan adipozite belirteçleri arasındaki ilişkiyi incelemeyi amaçladık.

Gereç ve Yöntem: Çalışmaya 86 menapoza girmemiş kadın dahil edildi. Boy, kilo, bel çevresi (BÇ), ve kalça çevresi ölçümleri yapıldı. VKI (kg/m^2) hesaplandı. Kan basıncı 10 dakikalık dinlenmeden sonra her iki koldan ölçüldü. Kan örnekleri 12 saatlik açlıktan alındı.

Bulgular: 43 kadında (% 50) hiperürisemi tespit edildi. Hiperürisemi grubunda, geleneksel ve geleneksel olmayan (VYI, LBÜ, VAI, KMI) adipozite belirteçleri artmış olarak bulundu. Serum ürik asid ve adipozite belirteçleri arasında pozitif korelasyon tespit edildi. BÇ, LBÜ ve KMI serum ürik asidin bağımsız adipozite belirteçleri olarak bulundu.

Sonuç: Çalışmamızda, BÇ, LBÜ ve KMI in serum ürik asid için bağımsız adipozite belirteçleri olduğunu belirledik.

Anahtar Kelimeler: Kardiyo metabolik indeks, lipid biriktirme ürünü, viseral adipozite, ürik asit

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Received *(Geliş Tarihi)*: 12.12.2020 **Accepted *(Kabul Tarihi)*:** 16.06.2021

INTRODUCTION

Hyperuricemia is a risk factor for hypertension (HT), type 2 diabetes mellitus (DM), dyslipidemia, metabolic syndrome, cardiovascular diseases (CVD).[1-4] In addition, hyperuricemia increases cardiovascular mortality.[5]

Since uric acid is an antioxidant, increased plasma uric acid (UA) concentration is thought to have a compensatory role in response to oxidative stress.[6] While UA has antioxidant activity in extracellular environment; It has harmful effects after entering the cells, including vascular smooth muscle cells and adipocytes.[7]

The most commonly used clinical parameter today to determine visceral obesity is the waist circumference (WC).[8] Visceral obesity is associated with increased adipocytokin production, proinflammatory activity, impaired insulin sensitivity, increased risk of DM, high triglyceride (TG)/low HDL cholesterol, HT, and atherosclerosis.[9]

Waist circumference, body mass index (BMI), waist hip ratio (WHR) and waist height ratio (WHtR) are traditional parameters used to classify and define obesity. Body adiposity index (BAI), lipid accumulation pruduct (LAP), cardiometabolic index (CMI) and visceral adiposity index (VAI) are non-traditional parameters used to evaluate visceral obesity. Since visceral fat measurement rather than obesity is more important for cardiovascular risk, these new parameters is developed.[10]

Although methods such as magnetic resonance (MR) imaging, computed tomography (CT), dual X-ray absorptiometry (DEXA) are used to evaluate visceral adiposity, these methods are not useful because they are costly and time consuming.[11,12] In recent studies, it has been shown that new parameters (BAI, LAP, CMI, VAI) created with mathematical models including both anthropometric (BMI, WC) and atherosclerotic (TG and HDL) parameters can be used to evaluate visceral obesity.[10,13]

There are not enough studies on the relationship between traditional and non-traditional adiposity markers and hyperuricemia. In this study, we aimed to investigate the relationship between hyperuricemia and traditional and non-traditional adiposity markers in premenopausal women.

MATERIAL AND METHOD

86 premenopausal women aged 18-50 years, who applied to our hospital's Internal Diseases, Endocrinology and Metabolic Diseases polyclinics, were included in the study. Consecutive subjects who agreed to participate in the study were included in the study. All procedures performed in this study were 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. Ethics committee approval was obtained from the local ethics committee with the number 2016/692 prior to the study. Volunteers were given detailed information about this study and those who wanted to participate were included in the study after the informed consent form was signed.

An anamnesis was received in detail from all volunteers who wanted to participate in the study. The patients were evaluated in terms of known and previous diseases, smoking, alcohol, drug and drug history. After the anamnesis, physical examination of all women was done. They were primarily evaluated for any focus of infection. Height, weight, WC and hip circumference (HC) measurements were made, BMI (kg/m^2) was calculated. Blood pressure was measured from both arms after 10 minutes of rest and recorded as systolic (SBP) and diastolic (DBP) blood pressure. Blood samples were taken to measure triglyceride (TG), HDL-cholesterol, UA, glucose and insulin after 12 hours of fasting. Hyperuricemia was defined as the serum UA level higher than 6.0 mg/dL. The cases were divided into 2 groups according to their UA levels. Cases with UA level ≥ 6 mg/dL were determined as high UA group, and cases with UA level < 6 mg/dL were determined as normal UA group.

Exclusion criteria;

- Under 18 and postmenopausal women,
- Pregnant or breastfeeding women,
- Those who use drugs that affect the level of UA. (allopurinol, thiazide etc)
- Those with known DM or those taking antidiabetic medication,
- Those who use drugs that affect insulin sensitivity,
- Those who use steroid or immunosuppressive therapy, lipid-lowering drugs, antihypertensive drugs, hormone replacement therapy,
- An active infection focus was detected in the physical examination,
- Those with known malignancies, kidney failure, liver failure, rheumatological disease or gout disease, hypothyroidism
- Women using cigarettes and alcohol.

Biochemical Analysis

Glucose (used glucose hexokinase method), HDL-cholesterol (used antigen-antibody complex method), TG (used enzymatic reaction method) and UA (used enzymatic uricase method) were studied an Olympus AU 5800 (Becman Coulter Inc. USA) device. Insulin Chemiluminescence method and Immulite 2000 Immunoassay System (Siemens Health Care Diagnostic, Germany) was studied.

Data Analysis

- Homeostasis Model Assessment of Insulin Resistance (HOMA-IR):
- (Fasting glucose (mg/dL) x fasting insulin (µU/mL))/22.5
- Body Mass Index (BMI): Body Weight (kg)/length^2 (m^2)
- Visceral Adiposity Index (VAI) (female): (WC/(36.58+(1.89xBMI))]) x [(TG mmol/l/0.81) x (1.52/HDL mmol/l)]
- Body Adiposity Index (BAI): ((HC cm)/Height1.5 m) -18
- Lipid Accumulation Product (LAP) (female): ((WC cm) -58) * TG mmol/l
- Cardiometabolic Index (CMI): (TG mmol/l/HDL mmol/l) * (WHtR cm)

Statistical Analysis

The SPSS 22.0 package program was used for statistical data analyses Descriptive statistics were shown for normal distribution of continuous variables as mean±standard deviation, while numerical parameters without normal distribution were shown with median (minimum-maximum). Categorical variables were represented by numbers and percentages. Continuous numerical variables were checked by the Kolmogorov-Smirnov Test to determine normality of distribution. In the comparison of the two groups, those with normal distribution were performed with the T-test, and those with abnormal distribution were performed with the Mann Whitney U test. Spearman correlation analysis and lineer regresyon analysis was used to determined the parameters related with serum UA levels. Logistic multivariate regression analysis was performed to determine traditional and non-traditional adiposity parameters associated with hyperuricemia. Independent parameters included in Backward linear regression analysis were WC, WHR, BMI, LAP, CMI, BAI and VAI. P<0.05 was considered significant in all analyses.

RESULTS

Of the 86 women included in the study, 43 women (%50) had hyperuricemia. In the group with hyperuricemia, traditional (BMI, WC, WHR) and non-traditional (BAI, LAP, VAI, CMI) adiposity markers, SBP, DBP, HOMA-IR, insulin, fasting blood glucose and TG values were increased (in all of them p <0.001) (**Table 1**). In the correlation analysis of serum UA level with the above parameters; A positive correlation was found between serum UA levels and all parameters. In addition, a negative correlation was found between serum UA level and HDL-cholesterol (**Table 2**). In addition,;WC, LAP and CMI were found to be independent adiposity markers of serum UA in the multivariate linear regression analysis (**Table 3**). WHR, BMI, BAI and VAI were not found to be significant in multivariate linear regression analysis. No correlation was detected between the parameters included in the regression analysis. The WC was only found to be independent adiposity marker of hyperuricemia in binary logistic regression analysis (OR=0.902, p=0.003) (**Table 4**).

DISCUSSION

The relationship between hyperuricemia and obesity and especially visceral obesity has been shown in previous studies.[14-17] In recent years, new markers (LAP, CMI, BAI, VAI) have been identified that determine visceral obesity. A limited studies have been conducted on the relationship between these new non-traditional visceral adiposity markers and UA, especially in Asian communities.[10,18,19] To our knowledge, our study is one of the first to exclude factors that may affect serum UA in the western population.

Hyperuricemia is a risk factor for HT, type 2 DM, dyslipidemia, metabolic syndrome, and CVD.[1-4] In addition, hyperuricemia increases cardiovascular mortality.[5]

Table 1. Demographic and laboratory characteristics of women with and without hyperuricemia.

Parameters	High UA UA ≥ 6 mg/dL (n=43)	Normal UA UA < 6 mg/dL (n=43)	p
Age (years)	35.4±10.2	35.2±7.1	0.923
BMI (kg/m²)	36.3±6.0	25.8±6.4	<0.001
WC (cm)	102.2±12.8	77.2±12.8	<0.001
WHR	0.87±0.06	0.77±0.05	<0.001
SBP (mmHg)	126.3±12.4	113.0±11.9	<0.001
DBP (mmHg)	80 (56-97)	70 (58-91)	<0.001
Glucose (mg/dL)	100.5±12.8	87.8±12.9	<0.001
İnsülin (µU/mL)	14.6 (2.0-49.1)	7.4 (2.0-32.6)	<0.001
HOMA-IR	68.4 (8.0-257.5)	28.5 (5.9-180.3)	<0.001
Uric acid (mg/dL)	6.7 (6.0-9.9)	4.0 (2.0-5.8)	<0.001
HDL (mg/dL)	44 (29-70)	49 (30-83)	0.039
TG (mg/dL)	148 (69-512)	85 (33-456)	<0.001
VAİ	2.71 (1.13-9.86)	1.28 (0.32-7.96)	<0.001
LAP	71.2 (21.8-280.8)	13.9 (0-123.6)	<0.001
CMI	0.88 (0.35-3.01)	0.31 (0.08-2.20)	<0.001
BAI	37.7 (28.9-54.0)	28.5 (22.4-51.0)	<0.001

BMI: Body mass index, WC: Waist circumference, WHR: waist to hip ratio, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, TG: Triglycerides, VAI: Visceral adiposity index, BAI: Body adiposity index, LAP: Lipid accumulation pruduct, CMI: Cardiometabolic index, UA: Uric acid.

Tablo 2. Spearman's correlation of determinants of serum UA

Parameters	r
BMI (kg/m²)	0.753**
WC (cm)	0.766**
WHR	0.662**
VAİ	0.598**
BAI	0.694**
LAP	0.687**
CMI	0.640**
HOMA-IR	0.526**
Glucose (mg/dL)	0.523**
İnsülin (µU/mL)	0.486**
SBP (mmHg)	0.583**
DBP (mmHg)	0.484**
TG (mg/dL)	0.544**
HDL-Cholesterol (mg/dL)	-0.407**

BMI: Body massindex, WC: Waistcircumference, WHR: waist to hip ratio, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, TG: Triglycerides, VAI: Visceral adiposity index, BAI: Body adiposity index, LAP: Lipid accumulation pruduct, CMI: Cardio metabolic index. ** p<0,001 for spearman's correlation

Tablo 3. Backward linear regression analysis of determinants of serum UA (Adjusted R2= 0.602)

Parameters	r	Standardized β	p
WC (cm)	0,766**	0.620	0.001
LAP	0.687**	- 0.574	0.023
CMI	0.640**	0.565	0.007

WC: Waistcircumference, LAP: Lipid accumulation pruduct, CMI: Cardio metabolic index. Independent parameters included in linear regression analysis were WC, WHR, BMI, LAP, CMI, BAI and VAI.

Table 4. Binary logistic Regression Analysis for hyperuricemia

	Model 1 (Backward) R^2=0.503			Model 6 (Backward) R^2= 0.495		
Parameters	**p**	**Exp (B)**	**CI (%95)**	**p**	**Exp (B)**	**CI (%95)**
Constant	0.011	1.436E+10	-	<0.001	2803538271	-
WC cm	0.455	0.925	(0.753-1.135)	0.003	0.902	(0.843-0.965)
WHR	0.206	0.000	(0.000-10089.159)	0.058	0.000	(0.000-1.718)
BMI	0.318	0.878	(0.669-1.139)			
BAI	0.804	1.039	(0.766-1.411)			
LAP	0.861	1.004	(0.958-1.052)			
CMI	0.708	5.670	(0.001-49632.351)			
VAI	0.649	0.579	(0.055-6.101)			

BMI: Body massindex, WC: Waist circumference, WHR: Waist to hip ratio, VAI: Visceral adiposity index, BAI: Body adiposity index, LAP: Lipid accumulation pruduct, CMI: Cardio metabolic index.

The first study to report that non-traditional visceral adiposity markers (LAP, CMI and BAI) are independent risk factors for hyperuricemia have been conducted very recently with Wang H et al.[19] In this study, it was reported that Chinese female individuals with 5937 hyperuricemia were older and BMI, WC, WHR, WHtR, BAI, LAP, CMI, SBP, DBP, fasting blood sugar and TG levels were higher than those without hyperuricemia. However, hyperuricemia has been reported to be higher in patients with DM (619 patients), HT (2841 patients), and patients with a history of heart disease (701 patients). While these comorbid conditions known as risk factors for hyperuricemia were not included in our study; the traditional (BMI, WC, WHR, HC) and non-traditional (BAI, LAP, VAI, CMI) adiposity markers, SBP, DBP, TG, fasting blood glucose, insulin and HOMA-IR values showed strong positive correlation with serum UA levels (r> 0.500, p <0.001 in all individuals). In addition, we determined that WC, LAP and CMI were adiposity markers for serum UA level.

In another recent study in China; Liu XZ et al.[10] investigated 174698 individual. Similarly, in this study, all traditional and non-traditional adiposity markers (except BMI and VAI) were found to be significantly higher in hyperuricemic individuals. In the correlation analysis in women; While only positive correlation was detected between LAP and CMI and serum UA level (r=0.235, r=0.264 p, respectively, p <0.001), no correlation was found with other non-traditional adiposity markers (BMI, VAI). In another Chinese study last year; Huang X et al.[18] examined the relationship between hyperuricemia and visceral adiposity in 1284 individuals over 40 years old without malignancy and chronic kidney disease. They reported that independent determinants of serum UA level increased age, VAI and LAP.

The first study investigating the relationship between non-traditional adiposity markers (VAI and BAI) and hyperuricemia was performed with Dong H et al.[20] and they were reported that VAI has a strong relationship with hyperuricemia. Then, in the second study in men who did not have metabolic syndrome; It has been reported that VAI is strongly associated with hyperuricemia.[21]

Yamada et al.[22] investigated the relationship between visceral adiposity and hyperuricemia. The study included 801 Japanese men who did not use any medication that affected uric acid levels (antidiabetic and antihypertensive etc), and did not have any kidney, cardiovascular or malignant diseases. Visceral adipose tissue and hepatic adipose tissue were evaluated using computed tomography. Visceral adipose tissue and hepatic adipose tissue have been shown to be independently associated with hyperuricemia.

In a retrospective study involving 1498 patients by Amato et al.[13] it has been reported that VAI is an independent risk factor for cardiovascular and cerebrovascular events. However, the same relationship could not be shown for WC and BMI. This effect is thought to be due to the indirect reflection of non-traditional risk factors such as the production of cytokines, lipolytic activity and increased plasma free fatty acids. This study shown that VAI is an important indicator of visceral adipose tissue function and insulin sensitivity and that VAI is strongly associated with cardiometabolic risk.

There are important differences between the subcutaneous adipose tissue and the visceral adipose tissue in the abdominal cavity. Visceral adipose tissue contains more inflammatory cells and a larger percentage of adipocytes than subcutaneous adipose tissue, Visceral adipose tissue carries more glucocorticoid and androgen receptors than subcutaneous adipose tissue. Visceral adipocytes are metabolically more active, more sensitive to lipolysis and have more insulin resistance. For this reason, visceral adipose tissue is more associated with cardiometabolic mortality.[23] In a study by Takir et al.[24] the relationship between lowering uric acid level and insulin resistance was investigated in individuals with asymptomatic hyperuricemia without DM. 73 people were included in the study and 40 people were administered allopurinol for 3 months. As a result of the study, it was found that administration of allopurinol in hyperuricemic individuals reduces uric acid levels and improves insulin resistance. In our study, we found that HOMA-IR, which is an indicator of insulin resistance, was higher in the group with hyperuricemia.

The most important of our study's limitations may be the low number of cases. However, since we exclude all possibilities that may affect the serum uric acid level in our study, the number of cases can be considered sufficient. Our second limitation; Since it is a cross-sectional study, we cannot show the cause-effect relationship exactly.

CONCLUSION

As a result; in our study, we determined that WC, LAP and CMI were independent adiposity markers for serum uric acid value. We also found that the independent adiposity marker for hyperuricemia is WC.

ETHICAL DECLARATIONS:

Ethical approval: Ethics committee approval was obtained from the local ethics committee with the number 2016/692 prior to the study.

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

Referee Evaluation Process: Externally peer reviewed.

Conflicts of interest: There are no conflicts of interest.

Financial Disclosure: The authors declared that this study has received financial support.

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.944765
J Contemp Med 2021;11(4):582-585

Case Report / Olgu sunumu

Hemophagocytic Syndrome; A Mortal Progressing Case Despite Early Diagnosis and Treatment

Hemofagositik Sendrom; Erken Teşhis ve Tedaviye Rağmen Ölümcül İlerleyen Bir Vaka

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Abstract

In this case, we discussed with a hemaphagocytic syndrome in a patient who was investigated for jaundice. Hemophagocytic syndrome; fever, hypertriglyceridemia, hepatosplenomegaly, bone marrow involvement is a multisystemic disease. This is due to excess cytokines released from the cells. Hemophagocytic syndrome, can occur as a familial or sporadic disorder, and it can be triggered by a variety of events that disrupt immune homeostasis.

Keywords: Hemophagocytic syndrome, jaundice, pancytopenia

Öz

Bu vakada, sarılık sebebiyle araştırılan bir hastada hemafagositik sendromu tartıştık. Hemofagositik sendrom; ateş, hipertrigliseridemi, hepatosplenomegali, kemik iliği tutulumu olan multisistemik bir hastalıktır. Bunun nedeni hücrelerden aşırı salınan sitokinlerdir. Hemofagositik sendrom, ailesel veya sporadik bir bozukluk olarak ortaya çıkabilir ve bağışıklık homeostazını bozan çeşitli olaylar tarafından tetiklenebilir.

Anahtar Kelimeler: Hemofagositik sendrom, sarılık, pansitopeni

INTRODUCTION

Hemophagocytic syndrome is in the group associated with macrophages within the histocytosis group of diseases. HLH does not constitute a single disease, but a picture of different conditions that produce the same type of inflammatory response. In this article, we will talk about the methods followed for diagnosis and a case that was mortal despite treatment.

CASE

A 51-year-old male patient with a history of known hypertension and coronary artery disease was admitted to the emergency department of our hospital with the complaint of jaundice that started 5 days ago. The patient had no history of drug use other than acetylsalicytic acid 1×100 mg and ramipril 1×5 mg. In the questioning made with suspicion of intoxication, the patient stated that he did not use mushrooms, herbal tea, drugs, cannabis. Physical examination revealed body temperature 39.2 degrees, blood pressure 100/60 mmhg, pulse 120/min, icteric appearance and hepatosplenomegaly.

Table 1. Laboratory parameters and normal ranges

WBC	4,000-11,000 10e^3/dL	AST/ALT	0-30 U/L
Hb	11- 15 g/dL	GGT	70-120 U/L
PLT	150-450 10e^3/dL	ALP	30-120 U/L
Urea	8-21 mg/dL	ferritin	2-400 ng/mL
Creatinin	0.3-1.1mg/dL	LDH	0-250 U/L
CRP	0.5-6 mg/dL	Total Bilirubin	0.3-1.2 mg/dL
Fibrinojen	180-400 mg/dL	Triglyceride	50-150 mg/dL

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Received *(Geliş Tarihi)*: 31.05.2021 **Accepted *(Kabul Tarihi)*:** 25.06.2021

White blood cells (WBC) in examinations; 8000 10e^3/dL, Hemoglobin (Hb); 9 mg/dL, platelet (PLT); 102.000 10e^3/dL, urea; 52 mg/dL, creatinine, 0.9 mg/dL, aspartate aminotransferases (AST); 213 U/L, alanine aminotransferases (ALT); 178 U/L, gamma-glutamyl transpeptidase (GGT); 74 U/L, alkaline phosphatase (ALP); 96 U/L, lactate dehydrogenase (LDH); 479 U/L , total bilirubin; 20.4 mg/dL , direct bilirubin; 18.7 mg/dL, CRP; It was found to be 9 mg/dL. In all abdominal ultrasonography; hepatosteatosis and hepatosplenomegaly were observed. Toxication analysis sent in urine and serum viral markers (Anti-CMV IgM, EBV-VCA IgM, EBNA IgM, Anti-HIV, Anti-HAV, HBsAg, Anti-HbS, Anti-Hbc IgM, Anti-HBC, rubella, parvovirus B- 19, HSV-1-2, influenza, adenovirus), rose bengal and tuberculin skin test negative, ferritin 13000 ng/mL, triglyceride 380 mg/dl, fibrinogen resulted in 50 mg/dL. Pancytopenia was observed in the examined peripheral blood smear, no atypical cells were seen. It was reported that the liver and spleen were increased in size and the appearance was compatible with hepatitis in dynamic MRI imaging of the whole abdomen. Cholestatic causes were excluded due to the absence of obstructive lesions in intra-extra hepatic bile ducts Contrasted cranial MRI imaging was performed when the patient complained of headache, no feature was observed. Neurology was interviewed for puncture (LP) indication. However, tension-type headache was considered because the patient had a short-term headache, no pathology in the neurological examination, and normal cranial examination. LP was not indicated. Liver biopsy was performed from the patient for the etiology of hyperbilirubinemia. Bone marrow biopsy was performed to elucidate the etiology of cytopenia. Intense inflammatory cells and hemophagocytic cells were observed in the aspiration (**Figure 1**). The patient also had fever, bicytopenia, hepatosplenomegaly, high ferritin level, hypertriglyceridemia, hypertriglyceridemia. After the diagnosis was made (**Table 2**), dexamethasone 10 mg 1×1 treatment was initiated and his etiology investigation continued.

Stool direct examination, culture, clostridium difficile, helicobacter pylori tests were negative. In the complete urinalysis, +3 bilirubin and legionella antigen in urine were negative. The direct examination of the sputum sent was normal, there was no growth in the culture, and infectious causes were excluded when the sputum sent three times was negative for ARB. The sent autoimmune markers (ANA, Anti-ds DNA, Anti LKM antigen, ASMA, AMA) were negative. Since primary hemophagocytic syndrome can be seen rarely in adults, a genetic examination was sent, but no abnormal gene mutation was found. Secondary etiology was continued to be investigated.No pathological finding was determined. Gastroscopy revealed erythematous gastritis, and the colonoscopy was normal. The patient underwent PET-CT, diffuse FDG uptake in the liver and spleen (SUV. max 7.0), bilateral inguinal LAP of 20 mm (SUV.max 2.4), the largest number of 36 mm LAP in the abdomen and pelvic region (SUV. Lymph node biopsy was planned. As a result of liver biopsy and bone marrow biopsy, hemophagocytic cells and dense inflammatory cells were reported in accordance with the diagnosis of hemophagocytic syndrome. Edema and neutropenia developed during follow-up. The etiology could not be clarified, the patient was given intravenous

Table 2. Hemophagocytic syndrome-2004 diagnostic criteria[7]

The diagnosis of HLH may be established:

A. Molecular diagnosis consistent with HLH: pathologic mutations of PRF1, UNC13D, Munc18-2, Rab27a, STX11, SH2D1A, or BIRC4

B. Five of the 8 criteria listed below are fulfilled:

1. Fever >38.5°C
2. Splenomegaly
3. Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood) Hemoglobin <9 g/dL (in infants 4 weeks: hemoglobin 10 g/dL) Platelets 100×10^3/mL Neutrophils $<1\times10^3$/mL
4. Hypertriglyceridemia (fasting, 265 mg/dL) and/or hypofibrinogenemia (<150 mg/dL)
5. Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver
6. Low or absent NK-cell activity
7. Ferritin >500 ng/mL
8. Elevated sCD25 (alfa-chain of sIL-2 receptor)

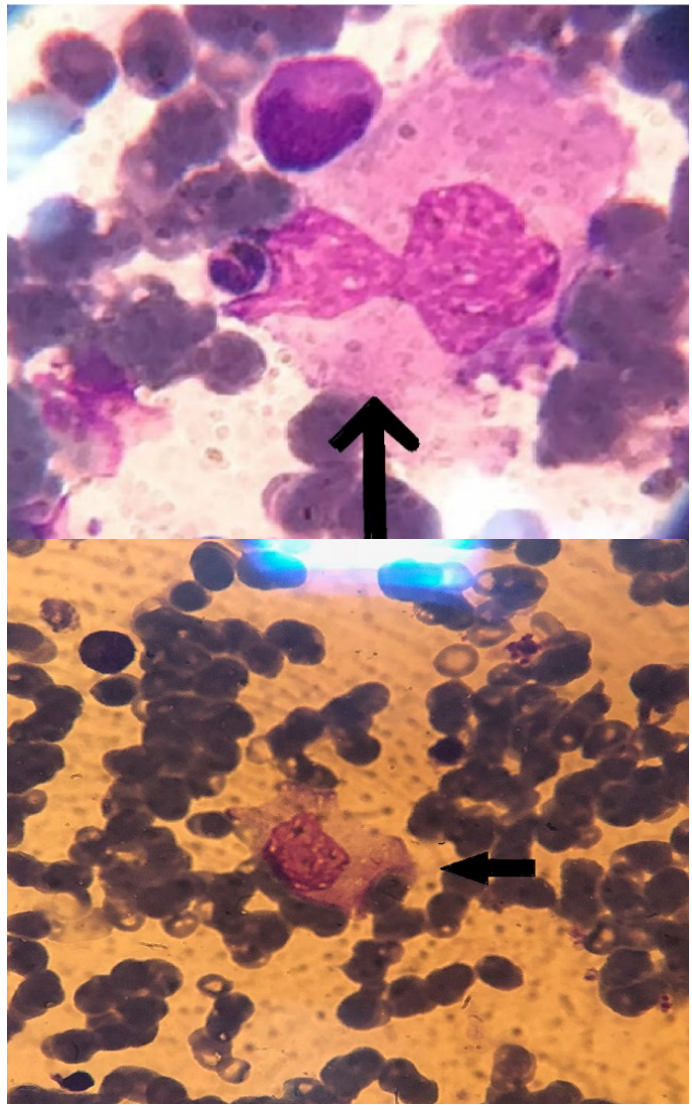

Figure 1. Bone marrow aspiration image, showing phagocytosing hemophagocytic cell (H.E x100, x400)

immunoglobulin for 3 days when there was no response to dexamethasone. During the follow-up, the patient had persistent fever. No growth in blood, urine, and sputum cultures taken when the patient was admitted and when he had a fever, CRP did not increase procalcitonin, it was considered as malign fever. 10 kg loss was detected. The patient's ferritin level reached 21000 ng/mL, total bilirubin 25 mg/dL, and WBC 32×10^3/uL. The patient whose general condition deteriorated within days was lost.

DISCUSSION

Hemophagocytic syndrome, also known as hemophagocytic lymphohistiocytosis (HLH), is in the group of diseases related to macrophages in the group of diseases in the histiocytosis group. and a clinical picture with predominant cytopenia. [1] Hemophagocytic syndrome usually occurs in the course of hematological malignancies, primary or secondary immunodeficiency, autoimmune diseases, viral, bacterial or parasitic infections. Both primary and secondary HFS can be triggered by infections or other autoimmune events. In practice, the distinction between primary or secondary is not important in the management of the disease.[2,3] Primary HFS can be seen in the course of genetic and immunosuppressed diseases. Chediak-Higashi syndrome 1 (CHS 1), Griscelli syndrome 2 (GS 2), X linked lymphoproliferative syndrome, Hermanski-Pudlak syndrome, lysinuric proteinuria. Genetic ones are seen in newborn babies, the ratio of female to male is 1:1 and males are more prone in adults. PRF1, UNC13D, STX11 mutations are seen with a high rate in individuals of Turkish origin.[4] Infection-related hemophagocytic syndrome can be caused by endogenous products (tissue damage, metabolic products, radical stress), rheumatic diseases, macrophage activation syndrome, and malignant diseases.[5] HFS is not a type of cancer, it occurs as a result of destruction in tissues as a result of abnormal immune activation and excessive inflammation. Interferon-gamma, tumor necrosis factor-alpha, interleukin-2, IL-6, IL-10, IL-12 are found to be high. Hematopoietic cells phagocyted by macrophages can often be demonstrated histologically in bone marrow, lymph nodes, liver and spleen. Although they are cytologically benign in all organs, they can be infiltrated by lymphohistiocytic cells showing active phagocytosis.[2] The most common detecting infectious agent for HFS is Ebstein-Barr virus (EBV). In one study, the organism that triggered HFS was detected in 163 of 219 HFS cases, Ebstein-Barr virus infection.[6] EBV can examine HFS due to cellular cytotoxicity as well as other diseases.[7] HFS starts with fever, which may be of concern to many systems. Fever and hepatosplenomegaly are major findings. Lymphadenopathy, icterus, edema, ascites, convulsions, PRES, and cranial nerve paralysis are less common findings. As laboratory findings, anemia and thrombocytopenia develop in the early period, leukocyte count is high in some of the cases in the acute period, and neutropenia develops in some. While triglyceride, ferritin, transaminases, direct bilirubin and lactate dehydrogenase values are high, fibrinogen level is found to be low. Demonstration of hemophagocytosis in bone marrow aspiration helps in diagnosis.[7] HLH-2004 diagnostic criteria are used in HFS (**Table 2**). In our study, HFS was shown to be most frequently associated with hematological malignancies in its etiology in adults.[8] In our case, the absence of a familial hematological disease suggested that the patient was adult, and the detected HFS may be secondary. However, the causes that may lead to secondary HFS were investigated and HFS Its etiology has not been clarified. It is recommended to initiate chemotherapy against overactivated lymphocytes and macrophages in patients who are not immunosuppressed or in whom no underlying infectious agent has been detected. Etoposide and dexamethasone, which are toxic to macrophages, have been reported to be effective in the treatment.[9] Other treatment options are intravenous immunoglobulin, colony stimulating factor, plasmapheresis, and bone marrow transplantation in immunocompromised cases for whom an underlying infectious agent was not detected.

CONCLUSION

While bile duct pathologies are observed most frequently in the etiology of direct hyperbilirubinemia, infiltrative diseases should be kept in mind. The first step in determining the treatment method is to determine the etiology. Bone marrow transplantation has a great place in cases caused by genetic factors. 3-year survival in cases with stem cell transplantation is 64%. In cases where the etiology cannot be clarified despite early diagnosis, cases may be mortal when the treatments given by specialist physicians are insufficient.

ETHICAL CONSIDERATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Status of Peer-review: 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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JOURNAL OF
CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.872812
J Contemp Med 2021;11(4):586-588

Case Report / Olgu sunumu

A Rare Cause of Torticollis in Children: Atlantoaxial Rotatory Subluxation

Çocuklarda Nadir Bir Tortikolis Nedeni: Atlantoaksiyel Rotatuar Subluksasyon

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Abstract

Torticollis is one of the common causes of admission to the emergency department among children which can make parents worried. This could be related to many traumatic and non-traumatic conditions. One of the rare causes of acute onset of torticollis is atlantoaxial rotatory subluxation, which is characterized by limitation of neck rotation, increased pain by movement. It is generally associated with a past trauma history. Although it is known as a temporary and self-resolving condition, if it is not diagnosed earlier it may lead to severe rotational deformity of the cervical spine. Therefore, detecting certain causes and providing proper treatment are highly important. Physical examination and history are usually enough to make the diagnosis, yet cervical X-ray and CT scan can be considered for indefinite cases. Even though treatment options depend on symptoms and the patient's general status, conservative approach with cervical collar and anti-inflammatory drugs are recommended as a first step. We would like to present our case, a 13 year-old girl who has been diagnosed with atlantoaxial rotatory subluxation in our clinic to increase awareness of this condition which is often misdiagnosed in children.

Keywords: Atlantoaxial rotatory subluxation, children, torticollis, pediatric emergency

Öz

Tortikollis, özellikle aileleri endişelendirebilmesi nedeniyle, çocuklarda yaygın acile başvuru nedenlerinden birisidir. Bu durum travmatik veya non travmatik olmak üzere pek çok durumla ilişkili olabilir. Ani başlangıçlı tortikolisin nadir nedenlerinden biri de, boyunda rotasyon kısıtlılığı ve hareketle artan ağrı ile karakterize olan atlantoaksiyel rotasyonel subluksasyondur. Genellikle geçirilmiş bir travma öyküsü ile ilişkilidir. Geçici ve kendini sınırlayan bir durum olarak bilinse de, erken tanı konmadığı takdirde ciddi rotasyon deformitelerine neden olabilmektedir. Bu sebeple, nedeni saptamak ve uygun tedaviyi sunmak oldukça önemlidir. Tanı için fizik muayene ve anamnez büyük ölçüde yeterli olsa da, arada kalınmış vakalarda direkt grafi ve bilgisayarlı tomografi göz önünde bulundurulabilir. Tedavi seçenekleri semptomlara ve hastanın genel durumuna göre değişmekle birlikte, ilk aşama olarak boyunluk kullanımı ve anti inflamatuar ilaçlarla konservatif yaklaşım önerilir. Çocuk yaş grubunda çoğunlukla atlanan bu tanı açısından farkındalığı arttırmak adına, kliniğimizde atlantoaksiyel rotatuar subluksasyon tanısı koyduğumuz 13 yaşındaki kız hastamızı sunmak istedik.

Anahtar Kelimeler: Atlantoaksiyel rotatuar subluksasyon, çocuk, tortikolis, pediatrik acil

INTRODUCTION

First and second cervical vertebrae (C1-C2) and their ligaments are the crucial structures for neck movements.[1] Important structures, such as transverse ligament, synovial capsule and tectorial membrane are located here to stabilize the joint and provide support for movement. Amount of these types of soft tissue components is greater in children than adults, therefore they can be affected by environmental factors easily and that can lead to more frequent clinical findings.[2,3] The main difference between atlantoaxial rotatory subluxation (AARS) and normal cervical movement is the limitation in returning to the natural position of C1-C2 facet joints which can cause torticollis.[4]

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Received *(Geliş Tarihi)*: 02.02.2021 **Accepted *(Kabul Tarihi)*:** 07.04.2021

Many traumatic or nontraumatic factors may play a role in etiology. Hence, a detailed history should be taken initially. In case of a trauma suspicion, appropriate position should be given, then the dislocations and fractures which may cause life threatening situations should be ruled out.[5]

Except from trauma, past infection history, autoimmune inflammatory diseases should also be investigated. There are many cases in the literature that develop following head and neck infections.[6-8] With this case report, our aim is to address the issue of AARS, increase awareness about the situation, and help to provide early diagnosis and treatment for patients.

CASE

A 13-year-old girl was admitted to our pediatric emergency clinic complaining with severe neck pain and limitation of neck movements for 2 days. It was said that there was no known trauma history but the pain started after jumping rope. Patient's general status was good, she was conscious, oriented and cooperated. Her vital findings were normal and her past medical history and family history were unremarkable. There was no neurological deficit and sensitivity was not detected in the spinal process. There was rotation restriction to the lesion side and pain increasing with movement. Other system examinations were normal. The head was fixed in the appropriate position and further investigations were planned. Blood results were within normal range. Cervical computed tomography (CT) was ordered due to suspicious appearance on the cervical X-ray that may correspond to listhesis of cervical vertebrae (**Figure 1**). The patient's age, clinic, vague trauma history, imaging results were assessed as atlantoaxial rotatory subluxation.

Neurosurgery consultation was requested, and treatment was arranged with a nelson-type cervical collar and an appropriate dose of nonsteroidal anti-inflammatory drugs (NSAIDs). She was discharged to continue follow-up in an outpatient clinic. The patient, who has not had any complaints in follow-ups, recovered without any sequelae.

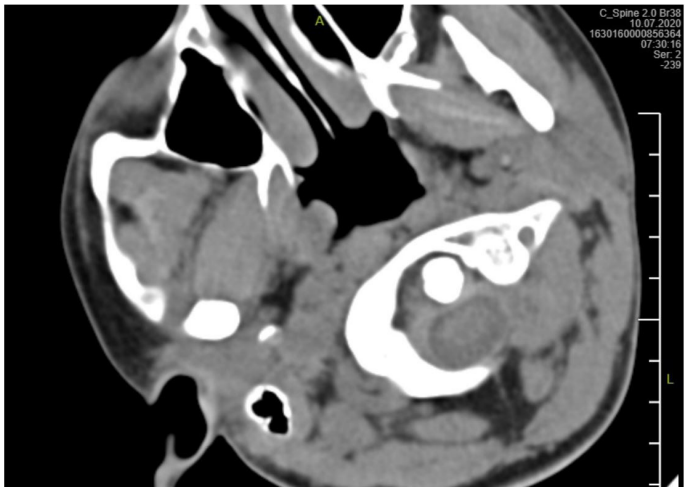

Figure 1. Cervical computed tomography image of Atlantoaxial Rotatory Subluxation

DISCUSSION

Atlantoaxial rotatory subluxation is a rare condition in which patients present with the new onset of torticollis. AARS represents a spectrum of disease from muscle spasm to a fixed mechanical block to reduction of the atlantoaxial complex.[4] The most important point in the diagnosis of atlantoaxial rotatory subluxation is to detect the underlying cause as early as possible and to make a follow-up and treatment plan for it. The most important step for a correct diagnosis is suspicion, as in all diseases. AARS should always be considered in patients who have a severe neck pain and limitation of neck movements and whose clinic features do not resolve despite symptomatic treatment. Although history and physical examination are generally enough to make the diagnosis, cervical X-ray may also be recommended to rule out life threatening conditions.[9] Cervical CT scan is considered in patients with ongoing clinical suspicion.[5] Treatment options depend on the patient's general condition, however most of the cases tend to be self-limiting. NSAIDs and cervical collars alongside rest are recommended as a first stage of treatment.[5] Hospitalization may be required for advanced treatment methods such as cervical traction or surgical interventions in patients whose complaints do not regress.[8] Publications have shown that most of the patients recovered with conservative treatment without any sequelae, as in our case, and further treatment methods were needed in very few of them.[8]

Atlantoaxial rotatory subluxation is a condition that should be considered as a differential diagnosis, especially in children presenting with neck pain and restricted rotation. The fact that it is not a relatively common condition and the milder progress in children may cause this diagnosis to be missed, especially in intensive emergency services. Once detected early and given proper treatment, recovery can be achieved without sequelae, but it may cause serious anatomical and structural deformities in patients whose diagnosis is delayed, who do not receive appropriate treatment or left uncontrolled.[10] Therefore, an appropriate treatment plan and close follow-up are very important for an effective recovery.

CONCLUSION

It is very important for physicians working in pediatric emergency services to be suspicious of AARS in patients present with neck pain and abnormal head-neck position with a difficulty in returning to the neutral position, in terms of providing early diagnosis and treatment.

ETHICAL CONSIDERATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Status of Peer-review: 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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