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EDITORIAL

Our Dear Coleagues,

As you know, our journal is publish 6 times per a year. We are proud to publish the this sixth and last issue of JOMPAC in 2023. The quality of the articles is increasing day by day in our journal. In near future, we want to contribute to international literature at an increasing level and to increase the success bar of our journal by entering valuable international indexes such as SCI-Expanded, Scopus, ESCI, and Pubmed. We would like to thank all the editors and authors who contributed to the publication process our journal. In addition, we would also like to thank everyone who contributed to the journal at any stage.

I hope the new year brings peace and tranquility to all humanity.

Sincerely,

Prof. Aydın ÇİFCİ
Editor in Chief

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The use of intralesional epidermal growth factor in the treatment of diabetic foot ulcers

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ABSTRACT

Aims: The mitogenic and cell protective effects of epidemal growth factor (EGF) in wound healing stimulate the growth, recovering the surface of the wound area. In this research we tried to elucidate the effectiveness of intradermal EGF application on wound healing in diabetic foot ulcers regarding the fact that EGF can accelerate the formation of skin cover layer on the infected surface, even in relatively ischemic cases.

Methods: The data of 68 patients who applied to our institution's orthopedics and wound care outpatient clinic with the diagnosis of diabetic foot ulcer, who underwent wound care, debridement and follow-up were retrospectively analyzed. All of the patients included in this study were classified as Wagner Stage III and Stage IV diabetic foot ulcers and were followed up with standard wound care. EGF application was initiated if there was not enough bleeding on the wound borders and defect floor after debridement.

Results: The rate of patients with 50% or more granulation in the second week of treatment in the groups was 35.7% (n=10) in the standard treatment group, it was 60% (n=24) in the EGF group ($p<0.05$). Complete granulation rates at the fourth week of treatment in patients who did not show complete granulation in the second week of treatment was 30.8% (n=8) in the standard treatment and 61.1% (n=22) in the EGF treatment ($p<0.05$). Similarly, in patients who did not show complete granulation in the fourth week of treatment, complete granulation rates at the sixth week of treatment was found to be 44.4% (n=8) in standard treatment and 85.7% (n=12) in EGF treatment ($p<0.05$).

Conclusion: According to the results of this study, intradermal EGF application in diabetic foot ulcers may positively affect wound healing by accelerating the formation of a skin cover layer.

Keywords: Diabetic foot ulcer, EGF, epidermal growth factor, diabetic ulcer, wound care

INTRODUCTION

World Health Organization (WHO) said that the prevalence of diabetes is expected to rise to 366 million in 2030.[1,2] Diabetic foot ulcer is a significant and devastating diabetes complication that reduces patients' quality of life. The risk of non-traumatic amputation in diabetic patients is 5 to 50 times higher than in non-diabetic patients. For this reason, unless diabetic feet are not treated properly and timely, they can go for amputation.[3]

According to the WHO, the risk of developing diabetic foot ulcers in patients with diabetes is 15%.[2,4] 25% of diabetic patients admitted to the hospital have foot problems.[5] Most diabetic foot amputations (62%) performed are below the knee level.[6] In the first three years following the amputation, re-amputation is required in 30-60% of the cases. Almost half of the (40-55%) amputated patients face the same scenario on the opposite side within 1-5 years. Death in the first three years has been reported in 35-50% of patients undergoing amputation.[7]

EGF was first isolated from mice sub-maxillary glands, and it is commonly found in the salivary glands.[8] EGF stimulates the growth and proliferation of fibroblasts, keratinocytes and vascular endothelial cells involved in forming wounded tissue. EGF binds to epidermal growth factor receptors on the cell surface with great affinity and stimulates the protein-tyrosine kinase activity of the receptor in the cell. This tyrosine kinase activity initiates the signal transduction cascade that causes many biochemical changes within the cell, such as an intracellular calcium level increase, glycolysis and protein synthesis increase, and an increase in the emergence of genes such as the epidermal growth factor receptor (EGFR) gene that causes DNA synthesis and cell growth.[9]

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The mitogenic and cell protective effects of EGF in wound healing stimulate the following mechanisms;-generative cells to the wound site-angiogenesis, accumulation and maturation of the extracellular matrix-like granulation tissue-wound contraction by myofibroblast activation, proliferation and growth-re-covering the surface of the wound area by migration, proliferation and growth of epithelial cells.[10]

In diabetic wounds, the constant presence of neutrophils, macrophages, and related cytokines in the environment predisposes to destruction in the microenvironment, and the balance between matrix synthesis and degradation is disturbed. Growth factors in diabetic wounds decrease due to increased enzymatic degradation in the wound area, thus significantly reducing diabetic wound healing.[11] Increased blood glucose and metabolites are toxic to EGF receptors, fibroblasts and endothelial cells and can be counted as a separate factor that delays wound healing.[12]

Particularly in ischemic-type diabetic foot ulcers, granulation rarely occurs because the proliferation phase is eliminated. Since the ultimate goal in treating such patients is to prevent the extremity from undergoing amputation, healing a wound without arterial blood perfusion emerges as a complex problem with a low chance of success.[13]

The biological activity of EGF occurs by binding to receptor molecules in mesenchymal and epithelial tissue. Fibroblast, endothelial cell-like cell types responsible for wound healing have EGF receptors, and it has been shown that the presence of EGF in the medium stimulates these cells and increases their proliferation.[11]

EGF is used to stimulate the formation of granulation tissue, which is beneficial in the treatment of diabetic foot in stage 3 and 4 Wagner classification of patients with neuropathic and ischemic ulcers in an area larger than 1 cm², and thus for secondary healing or closure of the wound with skin autograft with other conventional regimens.[11,14]

The primary aim of this research was to elucidate the effectiveness of intradermal EGF application on wound healing in diabetic foot ulcers regarding the fact that EGF can accelerate the formation of the skin cover layer (closing of the skin defect) on the infected surface, even in relatively more ischemic diabetic foot ulcers.

Additionally, we have tried to investigate and compare the patients who were followed up with wound debridement only in diabetic foot ulcers who had decreased blood supply in the wound area and those who underwent intradermal EGF in addition to debridement and to evaluate the effect of EGF on wound healing.

METHODS

The study was carried out with the permission of Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Researches Ethics Committee (Date: 05.04.2021, Decision No: 108/18). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Informed consent was obtained from all participants.

The data of 68 patients who applied to our institution's orthopedics and wound care outpatient clinic between 2018-2020 or were consulted by other departments with the diagnosis of diabetic foot ulcer, who underwent wound care, debridement and follow-up were retrospectively analyzed.

All patients included in this study were classified as Wagner Stage III and Stage IV diabetic foot ulcers (n=68). They were followed up with standard wound care methods and repetitive debridements, and the improvement of blood supply and wound healing was observed. If there were improvement in wound healing then we continued debridemend (n=28). If there was insufficient bleeding on the wound borders and defect floor after debridement, an EGF application was initiated (n=40), usually decided after the first two debridements. The same investigator has performed all EGF application decisions. As a result, debridement was applied to 28 of 68 patients, and debridement with intralesional epidermal EGF was applied to 40 of them.

Intralesional epidermal EGF 75 micrograms (every three days)1 were applied to patients with adequate wound healing. If there was ischemia (no improvement and granulation, insufficient blood supply) after treatment, the patients were evaluated with digital selective angiography (DSA). In patients with severe ischemia, if DSA did not show sufficient blood supply for wound healing, direct amputation was recommended before the patients underwent EGF application. Of the treatment groups, amputation was performed in 21.4% (n=6) of patients who received only debridement and 10% (n=4) of patients who received both debridement and EGF treatment.

Statistical Analysis

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 23.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage for categorical data and mean and standard deviation for continuous data were given as descriptive values. For comparisons between groups, the "Independent Sample T-test" was used for two groups, and the "Pearson Chi-Square Test" was used to compare categorical variables. The results were considered statistically significant when the p-value was less than 0.05.

RESULTS

Sixty-eight patients with Wagner Stage III and Stage IV diabetic foot ulcers (DFU) were evaluated. The distribution of demographic and clinical findings of the patients included in the evaluation is given in **Table 1**. Among the evaluation groups, 28 patients with relatively good circulation and satisfactory blood flow in classical wound debridement were followed up with standard wound care. In the second group, 40 patients who did not develop granulation with standard wound care, had insufficient blood supply and did not improve with classical wound debridement were followed up with intralesional treatment of 75 human-derived EGFs every three days. Complete granulation was observed in all patients after eight weeks (**Figure 1**). The mean time to complete granulation of the patients was 6.6 weeks in the standard treatment group and 4.9 weeks in the EGF group. This difference was statistically significant (p<0.05). In the first year after recovery, recurrence was seen in 42.9% (n=12) of the standard treatment group and 15% (n=6) of the EGF group (p<0.05).

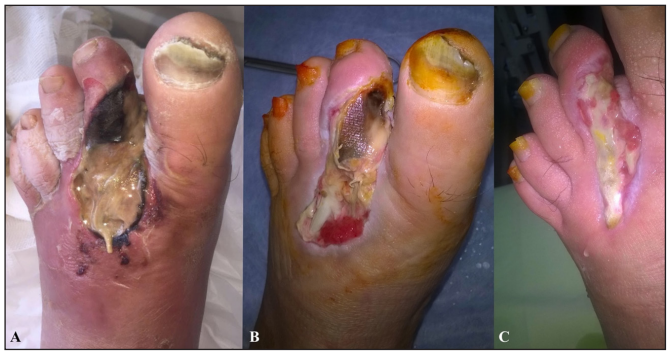

Figure 1.

There was no statistically significant relationship between the treatment groups and the gender of the patients (p>0.05). While there was a significant difference between the ages of the patients and the treatment groups, it was determined that the mean age of the patients who received standard wound care treatment was lower than that of the group that received EGF treatment (p<0.05).

There was a statistically significant difference between the treatment groups in terms of the mean lesion sizes of the patients (p<0.05). The mean lesion size of the EGF treatment group was higher than the standard treatment group.

While the rate of patients with 50% or more granulation in the second week of treatment in the groups was 35.7% (n=10) in the standard treatment group, it was 60% (n=24) in the EGF group (p<0.05). In the second week of treatment, complete granulation was observed in 7.1% (n=2) of the standard treatment group and 10% (n=4) of the EGF group, but this difference was not statistically significant (p>0.05).

Complete granulation rates at the fourth week of treatment in patients who did not show complete granulation in the second week of treatment were 30.8% (n=8) in the standard treatment and 61.1% (n=22) in the EGF treatment (p<0.05). Similarly, in patients who did not show complete granulation in the fourth week of treatment, complete granulation rates at the sixth week of treatment were found to be 44.4% (n=8) in standard treatment and 85.7% (n=12) in EGF treatment (p<0.05).

Complete granulation was observed at the eighth week in all 12 patients (10 who received standard wound therapy and two who received EGF therapy) without complete granulation at the end of the sixth week.

Of the treatment groups, amputation was performed in 21.4% (n=6) of patients who received standard wound treatment and 10% (n=4) of patients who received EGF treatment. There was no statistically significant relationship between treatment groups and amputation (p>0.05).

Table 1. Distribution of demographic and clinical findings of the treatment group

Characteristics	Total (n=68)	SWC (n=28)	SWC + EGF (n=40)	p value
	n/n (%) or median±SD	n/n (%) or median±SD	n/n (%) or median±SD	
Gender				1.000
Male	44/68 (64.7)	18/28 (64.3)	26/40 (65.0)	
Female	24/68 (35.3)	10/28 (35.7)	14/40 (35.0)	
Age, years	66±6	64±6	68±5	0.004
Lesion size, cm²	10.9±4.7	9.5±3.9	11.9±5	0.041
At least 50% granulation at 2 weeks	34/68 (50.0)	10/28 (35.7)	24/40 (60.0)	0.049
Complete granulation at 2 weeks	6/68 (8.8)	2/28 (7.1)	4/40 (10.0)	1.000
Complete granulation at 4 weeks	30/62 (48.4)	8/26(30.8)	22/36 (61.1)	0.023
Complete granulation at 6 weeks	20/32 (62.5)	8/18 (44.4)	12/14 (85.7)	0.028
Complete granulation at 8 weeks	12/12 (100)	10/10 (100)	2/2 (100)	NA
Time to complete granulation, weeks	5.6±1.8	6.6±1.5	4.9±1.7	<0.001
Recurrence in the first year after recovery	18/68 (26.5)	12/28 (42.9)	6/40 (15.0)	0.013
Amputation	10/68 (14.7)	6/28 (21.4)	4/40 (10.0)	0.297

DISCUSSION

The results of this study show that intradermal application of EGF significantly accelerates wound healing in diabetic foot ulcers compared to isolated debridement and significantly reduces the occurrence of recurrence and the likelihood of amputation. In addition, it can accelerate the formation of epithelial tissue even in more ischemic and infected diabetic foot ulcers.

The healing of the tissue depends on variables such as the age of the diabetic individual, the duration of diabetes, and the location of the lesion.[16,17] Although the patient may apply directly to the hospital with diabetic foot without knowing that he has diabetes, there is usually a relationship between the duration of diabetes and the development of diabetic foot.[18]

Singla et al.[19] compared 20 patients with standard wound dressings or EGF-impregnated bandages. In the study group, 80-90% granulation was observed in the first week, and 35% in the only debridement group. However, there was no statistically significant difference in granulation in the eighth-week results. The duration of hospital stay and wound closure time were found to be significantly shorter in the study group. In the topical use of EGF, the expected effect is more difficult to obtain due to proteases.[19] In our study, complete granulation was observed in all patients after eight weeks. The mean time to complete granulation of the patients was 6.6 weeks in the standard treatment group and 4.9 weeks in the EGF group, with statistical significance. In the first year after recovery, recurrence was seen in 42.9% of the standard treatment group and 15% of the EGF group, reaching statistical significance.

In the study of Fernández-Montequín et al.[20] consisting of 41 patients, group I was treated with 75 µg EGF, and group II was treated with 25 µg EGF. The EGF was administered 25 µg and 75 µg EGF intralesional three times a week. It was reported that the mean lesion area of the patients was more than 20 cm^2, and they were Wagner 3-4 group patients. Considering the response evaluation and granulation follow-up, 73.9% in group 1 and 50% response in group 2 were observed at the end of five weeks. The application was continued, and in the eighth week, 82.6% response was observed in group 1 and 61.1% in group 2. In more than 30% of the wound area, granulation tissue formation was achieved in most patients in both groups from the first week. More than 60% of these patients developed complete granulation after five weeks. These results were achieved despite Wagner grade 3 or 4 ulcers, often more significant than 20 cm^2, with ischemic and high amputation risk.[20] In our study, all of the patients were in the Wagner 3-4 group, and granulation occurred in 75% of patients and complete wound closure was achieved in 70%.

In a randomized, multicenter, placebo-controlled study by Montequin et al.[21] in 149 patients, group I was treated with 75 µg EGF, group II was treated with 25 µg EGF and group III was treated with a placebo. It was reported that the mean lesion area of the patients was more than 20 cm^2 and more than half of them were ischemic and were in the Wagner 3-4 stage. In the second week of the study, 83.1% response in group 1, 70.8% in group 2 and 39.6% in group 3 were observed. The time to recovery was found to be shorter in the high-dose group. EGF has been shown to accelerate healing. Amputation mainly occurs in ischemic patients.1

In another pilot study by Montequin et al.[21] in patients with Wagner Classification Grade 3-4, mean lesion area 16.3 cm^2, 20 patients received 75 µg EGF intralesional therapy three times a week. Complete granulation was seen in 100% of patients. The mean time to granulation was 23.6 days. Complete wound healing was reported in 75% of patients, and the amputation rate was 0%.21 In the study of Valezquez et al.[22] consisting of 32 patients, complete granulation was achieved in 90.62% of patients, amputation in 9.38% of patients, and a total treatment time was 46.5 days. In our research, while the rate of patients with 50% or more granulation in the second week of treatment was 35.7% in the standard treatment group, it was significantly higher (60%) in the EGF group. Complete granulation rates at the fourth week of treatment in patients who did not show complete granulation in the second week of treatment were 30.8% in the standard treatment and 61.1% in the EGF treatment ($p<0.05$). Similarly, in patients who did not show complete granulation in the fourth week of treatment, complete granulation rates at the sixth week of treatment were found to be 44.4% in standard treatment and 85.7% in EGF treatment ($p<0.05$). Complete granulation was observed at the eighth week in all patients, without complete granulation at the end of the sixth week.

In the study of Alos et al.[23] patients with diabetic foot ulcers from 41 hospitals were prospectively treated with 25 or 75 ug EGF three times a week for a maximum of eight weeks. EGF doses were determined by the physician who had diagnosed ulcers according to whether they were ischemic or not. There were 1788 patients, 43% of whom were ischemic, and 1835 diabetic foot ulcers. Complete granulation was seen in 76% of patients. Amputation was required in 12% of patients during treatment. Most of these cases consisted of those with ischemic and Wagner 3-5 group, and 5% relapse was seen. The most common side effects during application were pain, burning, chills, chills and palpitations at the application site.

In the study of Gonzalez-Acosta et al.[24] when intralesional EGF treatment was added to traditional standard care, the amputation rate decreased from 26.7% to 8.3%.[25] Garcia-Herrera et al.[25] have reported 43.1% to 8.1% in a similar design. Silva et al.[26] achieved 50% and 75% granulation responses in the second week after EGF treatment in patients with neuropathic ulcers. In our study, amputation was performed in 21.4% of patients who received standard wound treatment and 10% of patients who received EGF treatment.

In the study of Gomez et al.[27] 34 patients were treated with 75 ug EGF for a maximum of eight weeks. The placebo group and the EGF group were compared regarding the rate of reduction in ulcer size; 12.5 cm² was observed in the EGF group, and 5.2 cm² in the placebo group, and a statistically significant difference was found between the two groups. The difference between these two groups for newly formed epithelium was 3% and 28%.[27] In our study, the mean lesion size of the EGF treatment group was higher than the standard treatment group, with a statistically significant difference.

In the pilot study of twenty-nine patients by Acosta et al.[28] wounds over 20 cm² that were previously treated and did not heal were removed. EGF was applied to the patients three times a week, and the predicted amputation was prevented in 58.6% of patients who had an 80% granulation response in the eighth week.[28] In the histological examination of these patients, transformation, granulation and angiogenesis were observed in the matrix tissue. The quality of this healing tissue may be the reason for the decrease in recurrences in follow-up.

The current study had several limitations, primarily the retrospective design and the low number of patients. The general conditions of the patients were not standardized. Therefore, there was no randomization in patient selection. On the other hand, all the procedures were performed same senior surgeon with a standard protocol in place. The patients' DFUs were in different locations, and we could not establish a standard. The intralesional injection of EGF to the exact location might not be correct.

CONCLUSION

Regarding the results of this study, one could state that the effectiveness of intradermal EGF application on wound healing in diabetic foot ulcers has been elaborated. Intradermal EGF application significantly accelerates wound healing in diabetic foot ulcers and significantly reduces the occurrence of recurrence and the likelihood of amputation. Furthermore, EGF can accelerate the formation of a skin on the infected surface, even in relatively more ischemic diabetic foot ulcers.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Researches Ethics Committee (Date: 05.04.2021, Decision No: 108/18).

Informed Consent: Written informed consent form was obtained from all participants.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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Original Article

MEDICINE PALLIATIVE CARE

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Evaluation of the differences in sexual functions of women who underwent transobturatuar tape surgery

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ABSTRACT

Aims: The study aims to determine the changes in sexual function and life of patients with stress urinary incontinence (SUI) and mixed type urinary incontinence (MUI) with transobturator tape (TOT) operation.

Methods: 232 urinary incontinence patients who had only TOT surgery between the dates of May 2022- May 2023 were included in the study. Participants were similar in terms of demographic parameters. Participants completed several questionnaires, such as the Incontinence Impact Questionnaire (IIQ-7), Urogenital Distress Inventory (UDI-6), Female Sexual Function Index (FSFI), and the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12), both before surgery and six months post-operative.

Results: While IIQ-7 and UDI-6 values, which measure the adverse effects of urinary incontinence, were 13.06±3.74, 7.03±2.61 preoperatively, they were 2.14±2.12 and 2.92±1.77 postoperatively. The FSFI values for evaluating female sexual function were 22.58±1.91 preoperatively and 26.62±1.80 postoperatively, respectively. The total value of the PISQ-12 questionnaire, which also evaluated sexual function, was 39.77±14.19 preoperatively and 46.61±0.97 postoperatively. There was a significant difference between the results of the surveys conducted before and after the operation.(p values: 0.0001, 0.0001, 0.0001, and 0.0001, respectively).

Conclusion: Having a TOT operation affects the sexual function and life of patients suffering from SUI positively.

Keywords: Female sexual life, stress urinary incontinence, trans obturator tape

INTRODUCTION

Urinary incontinence in women negatively affects their emotional state, social life, and even sexual function and life.[1] Urinary incontinence is classified according to its physiopathology. Stress urinary incontinence (SUI) constitutes more than 50% of women suffering from urinary incontinence.[2] Mixed urinary incontinence (MUI) is the presence of detrusor overactivity and stress urinary incontinence (SUI) at different rates in the same case and has a prevalence of 7.5-25%. Almost two in three women suffer from either isolated stress urinary incontinence or mixed urinary incontinence.[3] When we consider the female sexual function with all its components, we understand that it is affected by multiple and combined situations. In addition to conditions that affect sexual function and sexual life related to gynecology, such as desire, arousal, lubrication, orgasm, satisfaction, and dyspareunia, coital incontinence, which is often ignored, also adversely affects sexual life and function.[4]

The incidence of all women suffering from SUI ranges from 28-70%. However, it is considered higher because women are ashamed to hide this situation.[5,6] The foul odor created by this situation adversely affects the sexual life of women and their partners with coital incontinence and may even end the sexual life ultimately.[7]

Sexual dysfunction due to stress urinary or mixed urinary incontinence can only be eliminated by treating the incontinence. Of the mid-urethral slings, trans obturator tape (TOT) is the procedure with the highest cure rate.[8]

The main subject we aim in this study is to find out the changes in sexual function and life before and after a TOT operation in terms of sexual function.

METHODS

The study was carried out with the permission of İstanbul Kanuni Sultan Süleyman Training and Research Hospital Clinical Researches Ethics Committee (Date: 26.05.2022, Decision No: KAEK/2022.05.117). All procedures were carried out in accordance with the ethical rules and the

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principles of the Declaration of Helsinki. We obtained informed consent from all patients and kept them in our archive.

We carried out this prospective study at a Training and Research Hospital between May 2022 and May 2023. The number of participants included in our study was 232, and the diagnosis of stress urinary incontinence (SUI) or stress-weighted mixed urinary incontinence (MUI) was made by specialist urogynecologists, and TOT operation was indicated. To diagnose SUI or MUI, we performed a cough test on the patients, conducted a bimanual examination, and took a detailed anamnesis. We used urodynamic tests only in cases where we had difficulty making a diagnosis. The demographic parameters of the patients were age, parity, mode of delivery, menopausal status, body mass index (BMI), smoking, coital incontinence, and incontinence types. We administered the incontinence impact questionnaire (IIQ-7), urogenital distress inventory (UDI-6), female sexual function index (FSFI), and pelvic organ prolapse/urinary incontinence sexual questionnaire (PISQ-12) questionnaires to all participants. We re-administered the same questionnaires to all participants in the sixth postoperative month. All the questionnaires we administered to the patients were completed in written form. We started the study with a total of 251 participants. Twelve of them did not want to come to follow-ups for various reasons. Four patients' operations were unsuccessful, and their incontinence continued. Two of the cases underwent gynecological surgery for benign reasons, and one for malignant reasons. (**Figure**).

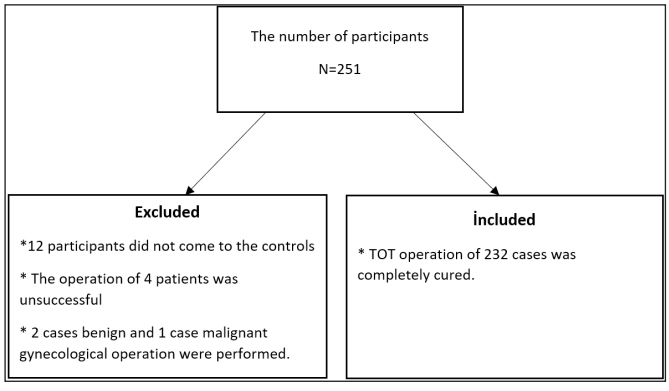

Figure. Flow diagram.

It was not combined with any additional operation during the TOT operation. Participants were operated with the same surgical team and using the same procedure. Preoperatively, 1 gram of cefezole was administered intravascularly to all patients. All operated patients were operated on under legionnaires anesthesia. The TOT operation was performed "from outside to inside" using a tension-free mesh. All cases were checked postoperatively on the 10th day, 30th day and 6th month. During the sixth month of control, all patients were asked to complete questionnaires about when they were sexually active. All patients were cured of SUI, as relapse, complications, and unsuccessful operations were exclusion criteria.

The incontinence impact questionnaire (IIQ-7) was created in 1995 to determine the impact of urinary incontinence on patients.[9] In this four-point Likert-type survey consisting of seven questions, the effects of urinary incontinence while performing daily activities are questioned. Each question is answered as not at all, a little bit, moderately, or greatly, and scores are given from 0 to 3, from none to many. The survey was validated from its original language into Turkish.[10]

We used the PISQ-12 questionnaire because it allows us to analyze sexual function from various aspects (partner, mental, and physical). The PISQ-12 scale consists of 12 questions, and the answers are rated on a 5-level Likert scale between "never" and "always." Scoring is between 0 and 4. In this scale, the total score is obtained by adding the points given to each question, and the maximum total score is 48. In this evaluation (PISQ-12), a low total score is considered to be an indicator of poor sexual function, and high scores are considered to be an indicator of less impairment of sexual function.[11] This questionnaire was validated from its original language into Turkish.[12]

We used the FSFI questionnaire to measure female sexual function because it contains nineteen questions and allows us to do the following. We evaluated parameters such as sexual desire, arousal, vaginal wetness, orgasm, pleasure, and dyspareunia. Female sexual function scale is an inquiry form consisting of 19 questions and six sub-dimensions.[13] As the scores from this five-point Likert scale decrease, sexual dysfunction increases, and a total score below 26.55 is interpreted in favor of female sexual dysfunction.[14] Language validation of the female sexual function scale was performed by Aygın et al.[14]

Inclusion criteria: Only people aged 35-50, suffering from SUI and stress-predominant MUI, and undergoing TOT surgery were included in the study. All cases were sexually active and heterosexual.

Exclusion criteria: In the study, individuals with pelvic organ prolapse (POP), mixed type incontinence with predominantly urge incontinence, detrusor overactivity, a history of surgery for SUI or POP, pelvic radiotherapy for oncological reasons, and those who were sexually inactive were excluded. Additionally, individuals under 35 years of age or over 50 years of age, those who experienced complications during the surgical procedure, and those with uncontrolled chronic diseases were excluded. The study also excluded individuals who did not want to participate, those who filled out the survey insufficiently, and those who did not take part in the controls.

Statistical Analysis

The gathered data has been analyzed using SPSS version 24.0 for Windows, developed in Chicago, IL, USA.We used the Shapiro-Wilk test to determine the normality of the distribution. As a result, we presented the normally distributed data as mean±standard deviation. We statistically compared the mean values of the parameters before and after the surgery using the Sample t-test. We considered the P value <0.05 significant at the 95% confidence level. In order to analyze the average values of dependent variables in a single population, we used G-power 3.1 software. An effect size of 0.5, a margin of error of 0.05 (α), and a power of 95% (1-β) were considered. It was concluded that the study results would only be statistically significant if a sample size of at least 45 was taken.

RESULTS

The Demographic data of the study participants are shown in Table 1. The mean age of the participants we included in the study was 42.39±2.34 years. The rates of live or stillbirth of the patients were 3.12±1.23. 79.74% of the participants gave birth by normal vaginal delivery. Considering the menopausal status, there were 114 participants in the reproductive period, 39 in the premenopausal period, and 79 in the postmenopausal period, respectively. The mean body mass index of the participants was 26.23 kg/m². The smoking rate of the patients was 17.67%. Urinary incontinence rate during intercourse was 70.69%. When the urinary incontinence types were examined, 74.32% were stress urinary incontinence.

Table 1. Demographic data

	N=232
Age (year)	42.39±2.34
Parity	3.12±1.23
Type of delivery (%)	
Abdominal birth	47 (20.26%)
Vaginal birth	185 (79.74%)
Menopause status, n (%)	
Reproductive	114 (49.14%)
Premenopausal	39 (16.81%)
Postmenopausal	79 (34.05%)
BMI (kg/m²)	26.23 kg/m²
Smoking, n (%)	41 (17.67%)
Coital incontinence, n (%)	164 (70.69%)
Types of incontinence (%)	
Stress type	74.32%
Mix type	25.68%

It is seen in Table 2 that while IIQ-7 and UDI-6 values, which show the adverse effects of urinary incontinence on women, were 13.06±3.74 and 7.03±2.61 preoperatively, we found 2.14±2.12 and 2.92±1.77 postoperatively. There was a statistically significant difference between these groups (p=0.0001, p=0.0001).

Table 2. The IIQ-7 and UDI-6 scores of the patients before and after surgery

	Before TOT operation (n=232)	After TOT operation (n=232)	p-value
IIQ-7	13.06±3.74	2.14±2.12	0.0001*
UDI-6	7.03±2.61	2.92±1.77	0.0001*

*: statistically significant, Sample t-test

The FSFI scores as a female sexual function scale in the participants we included in our study are shown in Table 3. There is a statistically significant improvement in all parameters except the pain in the scale (p values: 0.0001, 0.0001, 0.0001, 0.0001, and 0.0001, respectively). The mean values of Desire, Arousal, Lubrication, Orgasm, and Satisfaction were preoperative 3.02±0.62, 3.23±0.60, 4.05±0.66, 4.06±0.68 and 4.13±0.72, postoperative 3.55±0.690, 4.79±1.05, 4.57±0.51, 4.43±0.72, and 5.12±0.68.

Table 3. The FSFI score of patients before and after surgery

Domain	Before TOT operation (n=232)	After TOT operation (n=232)	p-value
Desire	3.02±0.62	3.55±0.690	0.0001*
Arousal	3.23±0.60	4.79±1.05	0.0001*
Lubrication	4.05±0.66	4.57±0.51	0.0001*
Orgasm	4.06±0.68	4.43±0.72	0.0001*
Satisfaction	4.13±0.72	5.12±0.68	0.0001*
Pain	4.09±0.71	4.16±0.78	0.097
Total FSFI	22.58±1.91	26.62±1.80	0.0001*

*: statistically significant, Sample t-test

PISQ-12 survey results showing sexual status in pelvic organ prolapse and urinary incontinence are shown in Table 4. According to the results of this survey, there is a statistically significant improvement in all scores (p values, respectively: 0.0001, 0.0001, 0.0001). The mean values of the Behavioral/emotive domain, Physical domain, and Partner-related domain were 9.37±11.22, 13.85±4.81 and 16.55±3.40 preoperatively, 14.43±0.70, 14.77±0.75, and 17.41±0.50 postoperatively, respectively.

Table 4. The pelvic organ prolapse/urinary incontinence sexual questionnaire (PISQ-12)

Domain	Before TOT operation (n=232)	After TOT operation (n=232)	p-value
Behavioral/emotive domain	9.37±11.22	14.43±0.70	0.0001*
Physical domain	13.85±4.81	14.77±0.75	0.0001*
Partner-related domain	16.55±3.40	17.41±0.50	0.0001*
Total score	39.77±14.19	46.61±0.97	0.0001*

*: statistically significant, Sample t-test

DISCUSSION

In our study, we aimed to measure the sexual function of 232 urinary incontinence patients with questionnaires before and after the TOT operation and to compare these results. Since all of the cases included in our study started to have regular sexual life in the sixth month, we asked them to complete our control questionnaires in the sixth month postoperatively. In all survey results, we discovered a significant improvement in sexual function and sexual life. Based on the flow diagram, our study showed that only 4 out of 251 cases failed. However, we were unable to determine the success of the TOT operation on 12 cases due to a lack of follow-up information. Out of the remaining 239 cases, 4 cases (1.67%) failed. It is noteworthy that we excluded complicated cases from the study. Hence, we don't know if our results are consistent with the literature. Our study found the TOT operation to be effective in all cases, and this supports the literature due to its low failure rate.[16] Urinary incontinence can cause women severe anxiety and self-confidence problems.[17] In this context, when we evaluated the anxiety and self-confidence due to urinary incontinence in women in the sixth month of our study with UDI-6 and IIQ-7, we found a promising improvement compared to the pre-TOT operation. Conditions such as coital incontinence and related odor and wetness that occur during the sexual intercourse of women with their partners affect the sexual function of both the woman and her partner.[17,18] Women's posture due to urinary incontinence badly affects their social standing, body image, and self-confidence. Our study supports this situation with the postoperative improvement of the Behavioral/emotive domain and Physical domain values, especially in the PISQ-12 questionnaire.

Many women who suffer from urinary incontinence experience leakage, particularly during sexual intercourse. Coital incontinence may occur during penetration or orgasm and may prevent effective orgasm.[4] In addition, the feeling of discomfort due to coital incontinence will reduce sexual satisfaction by decreasing interest. In the study, we found a radical improvement in the values related to orgasm, pleasure, and satisfaction in the FSFI questionnaire. TOT operation positively affects effective orgasm, satisfaction, and increased pleasure. It has also been proven in the literature that TOT operation significantly reduces coital incontinence.[19] Recent studies show that patients with coital incontinence benefit more from TOT operations than those without coital incontinence.[20] TOT operation does not only treat urinary incontinence. It also treats coital incontinence and sexual dysfunction. In conclusion, our study found that sexual desire, sexual arousal, vaginal lubrication, orgasm, satisfaction, behavioral and mental state, physical state, and partner-related situations changed positively with the FSFI and PISQ-12 questionnaires. In line with the literature, TOT operation positively affects all these parameters and radically improves female sexual function.

During sexual intercourse, in addition to emotional and mental stimulation, women secrete a lubricating mucus-like fluid from the Bartholin gland with anatomical and physical stimulation.[21] The primary nerve responsible for innervation controlling this condition is the pudendal nerve, and it has been proven that it is impossible to damage the pudendal nerve anatomically in TOT operations.[22] While some studies mentioned that clitoral blood flow is adversely affected in transvaginal tape (TVT) application, resulting in decreased pleasure and sensation, this has been proven not to be the case in TOT operation.[23] However, contrary to this, some studies have reported that the clitoral region swells and temporary edema occurs in 15.8% of the patients who underwent TOT operation.[24] To remove such contradictory situations impartially, studies that include all sections of the prospective society with prominent participants are needed. In the study of Elzevier et al.[24] who examined TOT operations, they suggested that dyspareunia increased in TOT operations performed from the outside, mainly due to the narrowing of the vaginal inlet. Addressing this situation, Serati et al.[25] revealed that changes in clitoral blood flow, injury to the clitoral innervation, decreased genital sensation, vaginal stricture, and dyspareunia in TOT surgeries are all due to errors in surgical technique and application. Again, examining this issue, Weber et al.[26] in their study, showed that when operations such as TOT operation are not combined with other procedures, vaginal narrowing is minimal and does not cause dyspareunia. In this context, we did not encounter the abovementioned conditions in our study, and dyspareunia was no change in one of our scales.

The cases were evaluated for dyspareunia using questions 17, 18, and 19 of the FSFI questionnaire. The results are presented in the pain row of **Table 4**. Furthermore, the presence of dyspareunia was also assessed using question 5 of the physical space questions of the PISQ-12 survey. There was a significant statistical difference in the physical field parameters' total values before and after the surgery. However, while there were no significant differences in the results of the 5th question before and after the surgery, the postoperative period showed a more significant numerical result in the Physical domain. In studies in the literature investigating the relationship between female sexual dysfunction and TOT, almost one out of

four patients had de novo dyspareunia, and the FSFI score was abysmal.[27] However, in the study of Narin et al.[28] it was observed that while dyspareunia did not change, the FSFI score also improved. In another recent study, it was observed that there was no change in pain scores due to TOT operation and even an increase in arousal scores.[29] The TOT procedure was only carried out for research purposes, which could explain why dyspareunia tends to improve in roughly 50% of cases, particularly before undergoing the TOT procedure, as per existing literature. The same study revealed that 4% of cases developed new dyspareunia.[30] In a recent study, in 94 cases, the mesh was removed after TOT due to dyspareunia. After the mesh was removed, there was a significant improvement in dyspareunia rates.[31] However, more comprehensive studies are needed to confirm the association between mesh-supported surgeries and dyspareunia after the procedure, as there are contradictory findings. In our study, however, no change was observed in our scores regarding dyspareunia. Many conflicting factors affect the outcome of the TOT operation, resulting in contradictory situations. To resolve this, we need to conduct extensive multi-center studies to gain a better understanding. Our study highlights that correcting coital incontinence caused by urinary incontinence can significantly improve self-confidence. At the same time, with the TOT operation, sexual pleasure will increase, and anxiety will be minimized. With the decrease in anxiety, libido and the rate of pleasure and orgasm will increase. During sexual intercourse, vaginal lubrication triggers both the partner and the woman emotionally and physically while preventing dyspareunia. However, the postoperative findings of our study belong to the postoperative sixth month of the cases. Therefore, we could not comment on the long-term results of the cases included in our study. Prospective studies covering long periods are required to illuminate all these dark spots.

CONCLUSION

The sexual lives of women suffering from urinary incontinence deteriorate both mentally and physically. Elimination of urinary incontinence with TOT operation significantly improves sexual dysfunctions in women. Our study showed dramatic improvements in the FSFI and PISQ-12 scores, which we use to reveal sexual dysfunction. Accordingly, it is crucial to evaluate sexual function in all women suffering from urinary incontinence, and these questionnaires should be used routinely in urogynecology outpatient clinics. Treating sexual dysfunction due to urinary incontinence is only possible by treating urinary incontinence.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul Kanuni Sultan Süleyman Training and Research Hospital Clinical Researches Ethics Committee (Date: 26.05.2022, Decision No: KAEK/2022.05.117).

Informed Consent: Since the study was designed prospectively, written informed consent was obtained from the patients. A copy with a wet signature was given to the participants and a copy is kept in my archive.

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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Original Article

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Comparison of low dose cytosine arabinoside, azacitidine and azacitidine venetoclax combination treatment as remission induction in elderly acute myeloid leukemia patients

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ABSTRACT

Aims: Low-intensity therapies are widely preferred in the treatment of advanced age, fragile acute myeloid leukemia (AML) patients. In this study, we aimed to compare hematological recovery rates after first cycle chemotherapy and overall survival for advanced aged AML patients treated with azacitidine (AZA) or low dose cytosine arabinoside (LDCA) or venetoclax (Ven) with AZA combination.

Methods: Ninety-one patients were retrospectively analyzed.

Results: Forty-one patients treated with LDCA, 30 patients treated with AZA and 20 patients treated with AZA+Ven were included in the study. Patients who received these three treatments and who achieved response and did not receive any other treatment during the follow-up period were included in the study. Median age at diagnosis was 70. The percentage of patients who achieved neutrophil recovery after the first cycle was 27%, 73% and 50% of the patients treated with LDCA, AZA and AZA+Ven respectively. The rate of patients who achieved platelet recovery was 60%, 80%, 70% respectively. Erythrocyte transfusion independency was 54% for LDCA patients, 73% for AZA patients and 60% for combination therapy. Overall survival was longer in patients receiving AZA+Ven than other treatment groups while grade 3-4 infections were more common in the first cycle of the treatment.

Conclusion: According to our study, patients treated with AZA had better platelet and neutrophil recovery rates with also longer overall survival than patients treated with LDCA, but total overall survival was superior in AZA+Ven combination. Hypomethylating agents with venetoclax is a preferable treatment option in elderly AML patients.

Keywords: Acute myeloid leukemia, azacitidine, low dose cytosine arabinoside, venetoclax, elderly patients

INTRODUCTION

Acute myeloid leukemia (AML) is a clonal malignant disease characterized by the presence of abnormal leukemic cells in the bone marrow or soft tissues. Median age is 68 and prevalence of the disease increases with age.[1] Premalignant clonal hematopoiesis can be observed in 2 % of normal healthy individuals, and 5-6 % of individuals older than 70 years. This may be an explanation for the increase in AML incidence in advanced age.[2] According to the SEER data; disease-related death in AML patients within first year is 80 % over the age of 65 and it is one of the lowest survival cancer types with a median survival of 2.7 months.[3]

Anti-leukemic therapy is essential for all AML cases regardless of age and treatment should be selected to the patients' performance status and comorbid conditions.[4] There are publications showing that treatment-related mortality in AML cases varies between 10-30%. It has been reported that one fourth of newly diagnosed AML cases who are not suitable for anti-leukemic treatment were treated with hypomethylating agents (HMA). In advanced age, this rate increases up to 60%.[5]

For nearly 30 years; LDCA has been used as a treatment option for acute leukemia patients with advanced age and/or comorbidities who are not suitable for intensive chemotherapy. For AML cases over 70 years old; studies comparing LDCA with the best supportive care approaches and hydroxyurea showed that LDCA was more beneficial.[6,7] After that, LDAC have remained the main therapy in AML patients with advanced

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age in comparison studies with new drugs. With the demonstration of the effectiveness of hypomethylating agents decitabine and azacitidine (AZA) in AML in the mid-2000s, these agents became a therapeutic option for AML treatment. AZA (75 mg / m² day, 7 days) was found to achieve a longer overall survival (OS) compared to LDAC, intensive induction therapy or best support care, although it was statistically insignificant.[5,8,9] After the use of HMA treatments alone, the addition of venetoclax (ven) to this treatment resulted in an improvement in OS in patients who were elderly, frail and unsuitable for intensive treatment.[10,11] In recent years, adding ven therapy to HMA has become the gold standard option in treatment for patients in this age group.[12,13] Unfortunately, ven+hypomethylating agent treatments, which are now recommended as gold standart therapy in many guidelines for older AML patients, can only be used with off-label approval in our country due to reimbursement institution restrictions.

Despite advances in treatment, disease-related and treatment-related delayed hematological recovery, febrile neutropenia, bacterial and viral infections are the main problem staying beyond the mortality for these patients. In this study we aimed to compare the clinical results of LDCA, AZA, AZA+Ven treatments in patients with advanced age AML followed in our center.

METHODS

The study was carried out with the permission of the Ankara Yıldırım Beyazıt University Ethics Committee (Date: 14/01/2021, Decision No: 67). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

Ninety-one patients diagnosed with de-novo AML were included in the study. AML cases 60 years and older who received the first induction chemotherapy and achieved a response were included. The diagnosis of AML was made according to World Health Organization (WHO) and European Leukemia Network (ELN) classifications.

Data Collection

Study was designed retrospectively by using file data records of patients whose diagnosis and treatment were performed in our center.

Age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, treatment groups, neutrophil and platelet recovery times, eritrocyte indepency status after first cycle, duration of induction therapy, hospitalization days, bone marrow pathological findings, hemogram, biochemical parametres were recorded.

The aim of the study was to evaluate to compare hematological recovery rates, infective complication rates after first cycle chemotherapy and overall survival so in order to prevent bias, patients who received one of the three treatment arms in the study and achieved a complete response, complete response with partial hematologic recovery, complete response with incomplete recovery, morphologic leukemia free state and partial remission according to the ELN 2022 response criteria at the end of the first cycle and continued their treatment with the same chemotherapy were enrolled. Again, in order to avoid bias, patients who did not respond to their first treatment and/or switched to another treatment were excluded from the evaluation. ELN 2022 response criteria was shown in **Table 1**.

Infection grading was based on the adverse events grading of the National Cancer Institute.[14] After the first chemotherapy cycle; the neutrophil recovery time was calculated as the day when the absolute neutrophil count was ≥500×10⁶/L for 3 consecutive days. For platelet count, recovery time was calculated as the day which platelet count was ≥50,000×10⁶/L in days for 3 consecutive days. Since these values are the hematological recovery values in ELN 2022, these numbers were taken as basis.[12] Since there was no clear limit for hemoglobin recovery, erythrocyte transfusion independence was evaluated at the end of the first cycle. Drug dose and days were compatible with the previous studies; low dose subcutaneous LDCA was administered as 20 mg twice daily for ten days; subcutaneous AZA was administered 75 mg/m²/day for seven days.[15,16] In AZA treatment

Table 1. ELN 2022 response criteria

Response	Criterias
Complete response (CR)	Bone marrow blasts <5%; no circulating blasts; no extramedullary disease; neutrophil count ≥1000×10⁶/L; platelet count ≥100,000×10⁶/L
Complete response with partial hematologic recovery (CRh)	Bone marrow blasts <5%; no circulating blasts; no extramedullary disease with neutrophil count 500-1000×10⁶/L and platelet count 50,000-100,000×10⁶/L
Complete response with incomplete recovery (CRi)	Bone marrow blasts <5%; no circulating blasts; no extramedullary disease with neutrophil count <1000×10⁶/L or platelet count <100,000×10⁶/L
Morphologic Leukemia Free State (MLFS)	Bone marrow blasts <5%; no circulating blasts; no extramedullary disease regardless of hematological recovery
Partial remission (PR)	Bone marrow blast 5-25 % and at least 50 % blast decrease in bone marrow after treatment with neutrophil count ≥1000×10⁶/L; platelet count ≥100,000×10⁶/L

group, the 5-2-2 scheme was widely used due to a two-day break at the weekend.[17] AZA and ven combination was administered as in the clinical trials.[10,11] Azacitidine 75 mg/m²/day were given for 7 days and ven 100 mg on the 1st day, 200 mg on the 2nd day and 400 mg on the 3rd day. Ven was given in all subsequent 28-day cycles. In patients given azole prophylaxis, the ven dose was given as 100 mg. Treatment cycles were scheduled every 4 weeks for all drugs until progression, relapse or intolerance.

Statistical Analysis

Statistical analysis "IBM SPSS Statistics for Windows. It was performed using Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). Descriptive statistics are presented as n and % for categorical variables and as Mean±SD and median (IQR) for continuous variables. Chi square test was used to compare mortality with various treatment parameters. The normal distribution assumptions of the data were examined by looking at the Kolmogorov-Smirnov values. One Way ANOVA test and Kruskal Wallis H test were used for comparisons between groups, and Paired Samples t test and Wilcoxon Signed Ranks Test were used for comparison of repeated measurements. In cases where significant differences were found as a result of One Way ANOVA test and Kruskal Wallis H test, Sidak Post-Hoc test was used to determine the direction of the difference. $p<0.05$ was considered statistically significant.

RESULTS

The data of 91 cases with denovo AML were evaluated. 41 patients were treated with LDCA, 30 patients with AZA, 20 patients with AZA+ven. There was no difference between the two treatment arms in terms of gender, age, hemogram parameters, bone marrow blast percentages at the time of diagnosis. The number of ECOG 3-4 patients was higher in the LDAC arm than in the AZA and combination therapy groups. In Table 2, clinical and laboratory findings at the time of diagnosis were shown according to the treatment protocol.

After the first month of the therapy, number of patients having an absolute neutrophil count above 500×10^6/L and platelet count above $50,000\times10^6$/L was significantly lower in LDCA therapy arm. Although the number of patients became erythrocyte transfusion independent was lower in LDCA group from the other therapy groups, this difference didn't have a statistically significance. Grade 3-4 infection during the first month of the therapies was significantly higher in LDAC and combination therapy groups than AZA treatment group. Percentages of patients with febrile neutropenia (FEN) was significantly higher in LDCA arm as well as duration of hospitalization and hospitalization days more than 1 week in first month of treatment. Comparison of treatment response and treatment-related complications at the first months of induction treatment were shown in Table 3.

Median OS of 91 patients was 7.1 months. Median OS of the patients who treated with LDCA treatment was 5.2 months, AZA was 9.3 months and AZA+Ven combination was 15.7 months. When stratified by age and ECOG performance status, overall survival was significantly better in patients under 70 years of age and in patients with ECOG 2 and below. This difference was statistically better in AZA+ven treatment patients. Similar to overall survival, survival in these subgroups was significantly longer in favor of AZA+ven combination therapy. Survival data are presented in Table 4.

Table 2. Clinical and laboratory findings of the patients at the time of diagnosis

	Total patients n: 91	Low dose cytosine arabinoside n:41 (45%)	Azacitidine n:30 (33%)	Azacitidine+ Venetoclax n:20 (22%)	p value	Post-hoc
Gender (F/M)	38 (42%)/53 (58%)	12 (29%)/29 (71%)	15 (50%)/15 (50%)	11 (55%)/9 (45%)	0.08	-
Age [Median (Min-Max)]	70 (60-88)	75 (65-88)	69 (65-74)	65 (60-75)	0.89	-
Hemoglobin level (Mean± SD) g/dl	9.6 (±2.03)	8.9 (±2.08)	10.3 (±1.6)	9.4 (±2.06)	0.43	-
Bone marrow blast percentage [Median (Min-Max)]	48 (20-94)	56 (24-94)	43 (20-89)	45 (30-90)	0.07	-
Leucocyte count [Median (Min-Max)]	5750×10^6/L ($200-291000$)	5780×10^6/L ($730-291000$)	6250×10^6/L ($730-113000$)	4860×10^6/L ($200-168000$)	0.08	-
Neutrophil count [Median (Min-Max)]	2580×10^6/L ($10-92800$)	2000×10^6/L ($0-92800$)	2600×10^6/L ($0-8700$)	2960×10^6/L ($20-130800$)	0.10	-
Platelet count ($x10^6$/L) [Median (Min-Max)]	58126×10^6/L ($5000-202000$)	48100×10^6/L ($7000-202000$)	52500×10^6/L ($5000-151000$)	62460×10^6/L ($8000-140000$)	0.09	-
ECOG, n (%)						
0-2	30 (33%)	5 (12%)	14 (47%)	11 (55%)	0.01	1>2,3
3-4	61 (67%)	36 (88%)	16 (53%)	9 (45%)		

F: Female, M: Male, Min: Minimum, Max: Maximum, SD: Standart Deviation, CRP: C-reactive protein, ANC: Absolute neutrophil count, ECOG: Eastern Cooperative Oncology Group

Table 3. Comparison of treatment response and treatment-related complications at the first month of induction treatment

	Total patients n: 91	Low-dose cytosine arabinoside treatment n: 41	Azacitidine treatment n: 30	Azacitidine+ venetoclax treatment n: 20	p value	Post-hoc
Patients having ANC >500×10^6/L after the first months of induction treatment	43 (47.2%)	11 (27%)	22 (73%)	10 (50%)	0.01	1<2,3
Patients who achieved transfusion independency after the first months of induction treatment	56 (61 %)	22 (54%)	22 (73%)	12 (60%)	0.13	-
Patients having >50000×10^6/L platelets count after the first months of induction treatment	62 (68%)	24 (60%)	24 (80%)	14 (70%)	0.04	1<2,3
Number of patients achieving recovery of neutrophil and platelet counts and transfusion independency after the first months of induction treatment	36 (39.5%)	8 (19.5%)	20 (66%)	8 (40%)	0.01	1<2,3
Grade 3-4 infection in first month of chemotherapy	23 (24%)	11 (27%)	5 (17%)	6 (30%)	0.02	1,3>2
Number of patients with FEN condition	36 (39.5%)	18 (44%)	10 (33%)	8 (40%)	0.04	1>2,3
Duration of hospitalization at the first chemotherapy cycle (Median)	16 days	18 days	8 days	16 days	0.04	1,3>2
Number of patients Hospitalized for more than 1 week at the first chemotherapy cycle	21 (23%)	12 (29%)	4 (13%)	5 (25%)	0.01	1,3>2

ANC: Absolute neutrophil count, FEN: Febrile neutropenia

Table 4. The comparisons of OS time according to Low dose cytosine arabinoside and 5-Azacitidine treatment of older aged AML patients

	Total patients n: 91	Low dose cytosine arabinoside n: 41	Azacitidine treatment n: 30	Azacitidine+venetoclax treatment n: 20	p value	Post-hoc
OS median (month)	7.1	5.2	9.3	15.7	0.04	3>2,1
Age adjustment OS (month)						
<70	7.4	4.1	11.9	16.3	0.02	3>2,1
≥70	5.3	5.2	5.8	12.1		
ECOG adjustment OS (month)						
0-2	12.1	8.3	12.3	17.8	0.04	3>2,1
3-4	5.8	4.2	6.1	11.3		

OS: Overall survival, ECOG: Eastern Cooperative Oncology Group

DISCUSSION

The goal in the treatment of acute leukemia is to achieve a complete response. However, the goal of achieving a complete response with intensive chemotherapies is not always a practical approach because of the comorbidities associated with AML patients and higher ECOG performance score. The treatment for these patients should be to provide survival advantage and increase in quality of life. Low-intensity protocols and supportive treatments should be personalized due to patient and disease-related factors. LDCA and HMA are frequently used low-intensity treatment options. The physical performance status of the elderly AML patients has a critical importance in their tolerance to treatment. It has been reported that treatment-related toxicity has been more common in patients with advanced age AML who have poor performance at the time of treatment and therefore treatment response has been lower from fit patients.[18] In this study including newly diagnosed de novo AML cases who had not received treatment before; it was aimed to compare the clinical and laboratory results of LDCA, AZA and AZA+Ven treatments. Of these three treatment types, HMA and ven combination can only be given to patients in our country with off-label approval. LDCA treatment was a treatment option for elderly frail AML patients for a long time until HMA treatments was developed. In comparative studies of HMA treatments with LDAC, HMA treatments were found to be more successful in this patient group.[8,9] In light of this information, in our country, HMA treatment has become the most frequently used treatment in the first line therapy of fragile AML patients who are suitable for intensive treatments. Subsequently, with the result of studies adding HMA treatments and LDCA ven, these combinations became the best choice in these patients.[10,19] In this study, which was conducted specifically to reveal the situation in our country, three treatments were compared.

Totally 91 patients; 41 treated with LDCA, 30 with AZA monotherapy and 20 with AZA+Ven therapy was analyzed. The median age of the patients is 70 and 67% of our patients had ECOG performance status 3-4, making it a suitable selected cohort for analysis.

Patients having neutrophil and platelet recovery after the first course of chemotherapy were higher in AZA monotherapy patients. This may be due to the low probability of LDCA treatment improving whole blood parameters in the first month, as expected. In terms of combination treatment, since the ven HMA combination is expected to be more successful than the single HMA treatment, the low cytopenia recovery rate at the end of the first cycle in the combined treatment may be due to ven-related cytopenia. As a matter of fact, in terms of overall

survival, it was seen that the AZA + Ven combination was more successful. It has been suggested that neutrophil recovery time is affected not only by chemotherapy but also by patient and treatment related factors.[20] In our cohort, patients who received LDCA had a higher rate of grade 3-4 infection with less neutrophil recovery rates. Another important data of the study is that grade 3-4 infections were more common in the combination arm, which is the most effective arm, and the duration of hospitalization for more than 1 week and the frequency of febrile neutropenia were found to be higher in the combination treatment than in the HMA monotherapy arm. The longest patient hospital stays in the LDCA arm may be due to the fact that this patient group received treatment for a longer period of time (7 days versus 10 days) and consisted of patients with higher ECOG. Again, prolonged cytopenias in this treatment arm may explain the higher rate of grade 3-4 infections and FEN. In combination therapy patient group, the longer hospital stay compared to monotherapy, due to follow-up for tumor lysis after rump up in the first cure, and the prolonged cytopenic state due to ven may explain the increased frequency of grade 3-4 infections and FEN compared to monotherapy. According to the data of comparing azacitidine and low dose cytarabine in terms of intravenous antibiotic requirement involving 131 patients; It was shown that less antibiotics were needed in the azacitidine group.[9] The hospitalization periods of the patients who received azacitidine and best supportive care, low dose cytarabine and intensive chemotherapy were compared; the average length of hospital stay in the azacitidine arm was 20.7 days per year, while in the others it was reported as 31.6 days. Also; the hospitalization time per year was significantly less in treated patients with azacitidine when it was compared with all three groups separately.[9] In our study, compatible with the literature; hospitalization periods longer than 1 week in the first month patients treated with AZA were found to be lower than other treatment groups and the rates of febrile neutropenia and grade 3-4 infection were also lower. Despite these side effects and long hospital stay, overall survival of patients receiving treatment with the combination was found to be better in the overall analysis. It has been reported that in patients over 65 years of age, azacitidine provides a survival advantage of 12.1 months versus 6.9 months compared to low dose cytarabine, intensive induction chemotherapy or best supportive chemotherapy.[8] Study in the literature that enabled the combination to be approved in world showed an approximately 5-month survival advantage with the addition of ven to azacitidine treatment 14.7 months vs 9.6 months.[10] In our study, combination therapy was shown to have an overall survival advantage of 10.3 months compared to LDCA treatment and 6.4 months compared to single azacitidine treatment.

Limitations of the study

The limitations of our study are that it has a relatively limited number of patients and it is a single center data.

CONCLUSION

Considering the difficulties of treatment for elderly and fragile AML patients, our study is important due to the evaluation of hospitalization, infection status and hematological recovery during/after the first course of low-dose chemotherapy, HMA and HMA ven combination therapy. Which is not yet covered by payment in our country and can be used with an off-label approval, but which is a standard treatment all over the world, ven+AZA treatment provided better survival to elderly frail patients than LDAC alone and AZA treatment alone.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Ankara Yıldırım Beyazıt University Ethics Committee (Date: 14.01.2021, Decision No: 67).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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Original Article

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Evaluation of ceftazidime-avibactam susceptibility in carbapenem resistant *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* isolates

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ABSTRACT

Aims: Carbapenem-resistant Gram-negative microorganisms are gradually increasing in hospitalized patients in intensive care units and causes increased morbidity, mortality, and cost. This study aims to investigate the susceptibility of ceftazidime-avibactam (caz-avi), which has recently started to be used for the treatment of infections caused by carbapenem-resistant (CR) Gram-negative bacteria isolated from various samples received from the intensive care unit (ICU) of our hospital.

Methods: Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) strains isolated from various clinical specimens that were sent to our laboratory between January 1st, 2021, and October 30th, 2022, were retrospectively evaluated in the study. The culture and antibiogram results of the samples were received over the laboratory information system (LIS) and evaluated using statistical analyses. Ceftazidime-avibactam susceptibility was studied using the disc diffusion method.

Results: Ceftazidime-avibactam antibiotic susceptibility test results of 352 (69.4%) CRKP and 155 (30.6%) CRPA strains isolated from various clinical samples from the ICU of our hospital were analyzed. Of the CRKP strains, 313 (88.9%) were found to be susceptible and 39 (11.1%) were found to be resistant to ceftazidime-avibactam. Of the CRPA strains, 131 (84.5%) were found to be susceptible and 24 (15.5%) were found to be resistant.

Conclusion: Determining the regional susceptibility of carbapenem-resistant strains isolated in our hospital to a new antimicrobial combination such as caz-avi will allow a better understanding of the spread of resistance.

Keywords: Ceftazidime-avibactam, antimicrobial resistance, Gram negative bacteria

INTRODUCTION

Today, carbapenems are used as a last step in the treatment of infections caused by multi-drug resistant (MDR) Gram-negative microorganisms. The frequency of carbapenem-resistant Gram-negative microorganisms in the ICU is increasing, causing higher morbidity and mortality rates.[1,2] In recent years, polymyxin group antibiotics have been widely used in the treatment of infections caused by CR Gram-negative microorganisms. Polymyxin group antibiotics have an optimal effect in treatment but they have inevitable toxic adverse effects.[3] Fosfomycin, tigecycline, and aminoglycoside antibiotics are also used in the treatment of CR.[4] In addition to the increasing carbapenem resistance, the limited number of currently available antibiotics and their toxic adverse effects have led to an increase in research on antibiotic options. In general, research has focused on caz-avi, meropenem-vaborbactam, ceftolozane-vaborbactam, imipenem/cilastatin-relebactam, eravacycline, plazomycin, and cefiderecol antibiotics.[1]

Avibactam is a diazobicyclooctane beta-lactamase inhibitor that has recently come into use in clinical practice and has expanded the spectrum of ceftazidime including many carbapenem-resistant *Enterobacteriaceae* members and *Pseudomonas aeruginosa (P. aeruginosa)*.[1] Its combination with ceftazidime was approved by the United States Food and Drug Administration (FDA) for intra-abdominal infections and complicated urinary tract infections in 2015 and it also began to be used for hospital-acquired and ventilator-associated pneumonia (VIP) in 2018.[5] Ceftazidime-avibactam is a potential new agent in the treatment of infections caused by MDR microorganisms.[6]

In general, antibiotic resistance rates show regional differences.[1] Ceftazidime-avibactam susceptibility rates of CR strains in the ICU of our hospital will contribute to regional data and will guide the planning of treatment. This study aimed to investigate the susceptibility rates of a new combination caz-avi in CR strains isolated from the ICU of our hospital.

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METHODS

The study was performed with the permission of Antalya Training and Research Hospital Ethics Committee (Date: 06.01.2022, Decision No: 1/8). All procedures were conducted in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Carbapenem-resistant *Klebsiella pneumoniae (K. pneumoniae)* (n=352) and carbapenem-resistant *P. aeruginosa* (n=155) strains isolated from various clinical specimens, sent from the ICU to our laboratory between January 1st, 2021, and October 30th, 2022, were included in the study. The culture and antibiogram results of the samples taken from the LIS were statistically evaluated. Gram staining was performed on each sample sent to the laboratory during routine culture procedures. Samples were inoculated onto 5% sheep blood agar (BA) (RTA, Turkey), chocolate agar (CA) (RTA, Turkey) and eosin methylene blue agar (EMB) (RTA, Turkey) and incubated at 37°C for 18-24 hours. Identification of isolates was performed using matrix-assisted laser desorption-ionization time-of-flight mass spectrometry (MALDI-TOF MS) (Biomerieux, France) in our routine studies and antibiotic susceptibility tests were performed using the VITEK 2 (Biomerieux, France) system in line with the recommendations of the manufacturers. The VITEK 2 system was used to determine carbapenem resistance. Ceftazidime-avibactam susceptibility was studied using the disc diffusion method. CRPA and CRKP colonies were inoculated onto Müller-Hinton agar (RTA, Turkey) at 0.5 McFarland dilution to detect caz-avi susceptibility. Ceftazidime-avibactam (30 µg/10 µg) discs were placed and incubated at 37°C for 18-24 hours. Diameters of the non-growth zone around the antibiotic discs were measured and sensitivities were evaluated according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria. *P. aeruginosa* ATCC 27853 and *K. pneumoniae* 700603 (ESBL) were used as control strains.

Statistical Analysis

The Statistical Packages for the Social Sciences (SPSS) software version 22.0 (SPSS Inc., Chicago, USA) was used for statistical analysis of the study.

RESULTS

In total, 352 CRKP and 155 CRPA strains were isolated from various clinical samples sent to the laboratory from the ICUs of our hospital. The age of the patients from whom the isolates were obtained was between 18 and 86 years. Two hundred four (58.0%) patients who had CRKP strains were male and 148 (42.0%) were female. One hundred four (67.0%) patients who had CRPA isolates were male and 51 (33.0%) were female. Carbapenem-resistant *K. pneumoniae* isolates were received from the general ICU (n=278, 79.0%), the surgical ICU (n=32, 9.0%), the neurologic ICU (n=29, 8.0%), and the coronary ICU (n=13, 4.0%), respectively. Carbapenem-resistant *P. aeruginosa* isolates were received from the general ICU (n=123, 79.3%), the surgical ICU (n=20, 13.0%), the neurologic ICU (n=10, 6.4%), and the coronary ICU (n=2, 1.3%), respectively. Three-hundred-fifty-two CRKP strains were isolated from blood (46%), sputum/BAL (41.5%), urine (7.7%), and tissue/abscess/wound samples (4.8%). One-hundred-fifty-five CRPA strains were isolated from blood (12.3%), sputum/BAL (69.0%), urine (16.1%), tissue/abscess/wound samples (2.6%) (Table 1).

Susceptibilities to amikacin, gentamicin, ciprofloxacin, meropenem and imipenem in CRKP isolates were determined as follows: 41 (11.6%), 32 (9.1%), 1 (0.3%), 5 (1.5%) and 3 (0.9%), respectively. All CRKP isolates showed resistance to amoxicillin clavulonic acid, cefepime, levofloxacin, phosphomycin, and ertapenem. Amikacin, meropenem and imipenem susceptibilities in CRPA isolates were determined as 95 (61.3%), 58 (37.5%) and 2 (1.3%), respectively. All CRPA isolates were found to be resistant to aztreonam, gentamicin, piperacillin, cefepime and ciprofloxacin (Table 2).

Of the CRKP strains, 313 (88.9%) were found to be susceptible and 39 (11.1%) were found to be resistant to ceftazidime-avibactam. Of the CRPA strains, 131 (84.5%) were found to be susceptible and 24 (15.5%) were found to be resistant. The caz-avi resistance rates of CRKP and CRPA strains isolated from tissue/abscess/wound samples were determined as 29.4% and 25.0%, respectively. It was statistically significantly higher than all other samples (CRKP p=0.05 and CRPA p=0.005).

Table 1. Sample distribution and caz-avi susceptibility results in CRKP and CRPA isolates

Sample	CRKP (n:352)			CRPA (n:155)		
	Sensitive n (%)	Resistant n (%)	P value	Sensitive n (%)	Resistant n (%)	P value
Blood	147 (89.8)	15 (10.2)	<0.05	16 (84.2)	3 (15.8)	<0.005
Sputum/BAL	132 (90.5)	14 (9.5)		91 (85.1)	16 (14.9)	
Urine	22 (81.5)	5 (18.5)		21 (84.0)	4 (16.0)	
Tissue/abscess/wound	12 (70.6)	5 (29.4)		3 (75.0)	1 (25.0)	
Total	313 (88.9)	39 (11.1)		131 (84.7)	24 (15.3)	

CRKP: Carbapenem-resistant *Klebsiella pneumoniae*. CRPA: Carbapenem-resistant *Pseudomonas aeruginosa*.

Table 2. Antibiotic susceptibility rates in CRKP and CRPA isolates

Anti-Bacterial Agent	CRKP (69.4%) n: 352		CRPA (30.6%) n: 155	
	Sensitive n (%)	Resistant n (%)	Sensitive n (%)	Resistant n (%)
Amikacin	41 (11.6)	311 (88.4)	95 (61.3)	60 (38.7)
Aztreonam	N*	N*	-	155 (100)
Gentamicin	32 (9.1)	320 (90.9)	-	155 (100)
Piperacillin	N*	N*	-	155 (100)
Amoxicillin Clavulonic Acid	-	352 (100)	N*	N*
Cefepime	-	352 (100)	-	155 (100)
Ceftazidime Avibactam	313 (88.9)	39 (11.1)	131 (84.5)	24 (15.5)
Ciprofloxacin	1 (0.3)	351 (99.7)	-	155 (100)
Levofloxacin	-	352 (100)	N*	N*
Fosfomycin	-	352 (100)	N*	N*
Meropenem	5 (1.5)	347 (98.5)	58 (37.5)	97 (62.5)
İmipenem	3 (0.9)	349 (99.1)	2 (1.3)	153 (98.7)
Ertapenem	-	352 (100)	N*	N*
Trimethoprim/Sulfomethoxazole	43 (12.2)	309 (87.8)	N*	N*

N*: Not worked, CRKP: Carbapenem-resistant *Klebsiella pneumoniae*. CRPA: Carbapenem-resistant *Pseudomonas aeruginosa*.

DISCUSSION

In the ICU, carbapenem-resistant Gram-negative bacteria infections have limited treatment options and high morbidity and mortality rates.[7,8] Ceftazidime is a third-generation cephalosporin with a broad spectrum of antimicrobial activity. The usefulness of cephalosporin in treating infections has been limited due to the spread of cephalosporin resistance through mechanisms such as ESBL production. Combining ceftazidime with avibactam, a novel β-lactamase inhibitor in diazobicyclooctane structure has increased its in vitro activity against several β-lactamase-producing aerobic Gram-negative pathogens. On the other hand, the addition of avibactam has been shown to restore the in vitro activity of ceftazidime against many extended spectrum β-lactamase, AmpC, KPC, and OXA-48-producing *Enterobacteriaceae* and CRPA isolates. In the INFORM global surveillance program from 2012-2014, 99.5% of *Enterobacteriaceae* and 92.0% of *P. aeruginosa* isolates were susceptible to caz-avi.[9] With the recent approval of its use in our country, concordant with global data, resistance to caz-avi antibiotherapy has begun to be reported in many studies and case reports.[10,11] In this study, caz-avi and other antibiotic susceptibilities of CRKP and CRPA strains in patients hospitalized in ICUs are presented to reveal regional data.

Recent global observations indicate an increase in resistance to ceftazidime avibactam for *K. pneumoniae* and *P. aeruginosa* isolates, despite previous studies abroad showing high susceptibility (95%-99%).[11,12] Sader et al.[13] evaluated the antimicrobial susceptibility of 623 Gram-negative organism-caused infections in patients with cancer in 52 hospitals in the United States of America as part of the INFORM program between 2013 and 2014 and found all *Enterobacteriaceae* 100% susceptible to caz-avi. In the same study, caz-avi sensitivities in *P. aeruginosa* strains were reported as 96.6%. Different from Sader et al.[13] carbapenem-resistant *P. aeruginosa* strains (n=131) were included in our study and caz-avi susceptibility was 84.5% in CRPA strains. Kempf et al.[14] found caz-avi resistance rate of 19.6% in carbapenem resistant *K. pneumoniae* isolates from respiratory tract specimens, while in the study conducted by Ramadan et al.[15] the resistance rate reached 79% in *K. pneumoniae* isolates. In a study by Torrens et al.16 with *P. aeruginosa* obtained from ICU of 11 different countries, including Turkey, it was observed that caz-avi resistance increased to 83% in MDR strains.

Livermore et al.[17] found the caz-avi susceptibility rate as 95% in *Enterobacteriaceae*. In their study, *Enterobacteriaceae* strains containing the most OXA-48 (36.7%), KPC, and NDM were isolated and almost all isolates with metallo beta-lactamase were reported as resistant to caz-avi. In the same study, caz-avi was found to be effective against *P. aeruginosa* in which AmpC was not suppressed and no effect was detected against strains with efflux-mediated resistance. In a multicenter study covering Europe, Latin America, and Asian-Pacific countries, Castenheria et al.[18] found caz-avi susceptibility rates of 78.7% in 286 CR strains. In the same study, non-metallo beta-lactamase CR strains were reported as 100% susceptible. Although carbapenemase resistance genes were not identified in our study, it is important in terms of reporting the first resistance data for caz-avi from our region.

Sensitivity studies started to be reported in our country with the license of caz-avi in 2019. In a multicenter study conducted in our country, İşler et al.[19] determined that 71% of OXA–48–like CRKP strains isolated from 200 blood cultures were susceptible to caz-avi. Mirza et al.[20] reported caz-avi susceptibility as 83.3% in 102 CRPA strains isolated from various clinical samples. Öztaş et al.[10] reported caz-

avi susceptibility as 77.5% in CRKP strains isolated from various clinical samples between 2017 and 2021. These susceptibility rates were low when compared with our data. In Öztaş et al.[10] study, the highest sensitivity was reported for colistin (83.26%) but it was recommended to be considered as a last option due to its nephrotoxicity. In another study, caz-avi and colistin susceptibilities of CRPA strains were determined as 90% and 100%, respectively, between 2016 and 2021.21 Arıcı et al.[11] investigated the invitro efficacy of caz-avi against CRKP and CRPA isolates isolated from ICUs as the causative agents of VIP and found the resistance rates to be 22.2% and 86.4%, respectively. The results of this study, in which high resistance rates were reported from our country, are alarming. The authors of this study emphasized the significance of performing regular surveillance cultures to control infections in the ICU. They also highlighted the need for frequent monitoring of resistance to ensure the timely and effective use of ceftazidime-avibactam, which is one of the last-resort antibiotics for severe infections in the ICU. It is expected that patients who have been hospitalized in the ICU for a long period of time and those with poor general condition will be expected to show resistance to newly introduced antibiotics. Our study revealed that caz-avi sensitivity was relatively high, despite selecting CRPA and CRKP isolates from ICU units.

In our study, we found that the rates of resistance to CRKP and CRPA in abscess and wound cultures were 29.4% and 25.0%, respectively, which was statistically significantly higher than in all other samples (CRKP p=0.05 and CRPA p=0.005). In certain clinical studies, the effectiveness of treating caz-avi susceptible strains was evaluated based on the diversity of the samples. Unlike other samples, some studies found that tissue and abscess cultures had response rates to treatment as low as 50.0%.[22,23]

Yang et al.[24] reported a caz-avi sensitivity of 65.5% in a total of 133 isolated CRKP strains. The authors emphasized that the disc diffusion method was a good alternative as an economical and practical method to detect the antibacterial activity of caz-avi against *Enterobacteriaceae* because automatic antimicrobial susceptibility test cards were not available in 2019 for caz-avi. Likewise, İşler et al.[19] studied caz-avi sensitivities in vitro using Sensititre, Etest, and 10/4 µg disc methods and found the results to be compatible. Also, they stated that the disc diffusion method was recommendable.

Our study has some limitations. The small number of patients and isolates that underwent susceptibility testing with ceftazidime-avibactam and the lack of investigation of resistance genes can be counted among these limitations. In addition, it could not be determined whether the patients with resistance strains in our study had previously used caz avi. It should also be taken into consideration that our results regarding caz-avi resistance may not reflect the whole region since our study was single-centered. One of the critical steps in preventing resistance to antibiotics is monitoring the resistance. Therefore, data collected from similar studies at a local and regional level will aid in understanding the spread of resistance.

CONCLUSION

Antimicrobial resistance is a dynamic and rapidly developing field. The treatment of resistant patients will increasingly be a challenge for physicians.[25] In our country, the use of caz-avi has only been authorized for complicated cases hospitalized in the ICU since 2019.[26] It is important to evaluate clinical success for appropriate patient groups in randomized controlled studies, based on in vitro studies conducted in our country for resistant infections. Maintaining active surveillance studies together with the meticulous implementation of appropriate antibiotic use policies will allow to ensure control of antibiotic resistance.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Antalya Training and Research Hospital Ethics Committee (Date: 01.012022, Decision No: 2022-006- 1/8).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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Predictive factors for acute pancreatic and peripancreatic fluid development in patients with acute pancreatitis

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ABSTRACT

Aims: Acute fluid collections after acute pancreatitis carries risk of serious complications as infected pseudocyst and Wall off Necrose development. Hence, it is important to predict the development of acute fluid collections for treatment and management of acute pancreatitis. In this study, it is aimed to investigate predictive factors for development of acute fluid collections in patients with acute pancreatitis.

Methods: Total of 438 patients diagnosed with acute pancreatitis were screened. According to the Revised Atlanta Classification fluid development after acute pancreatitis was determined and the relationship between fluid development and the hematological/biochemical parameters of the patients at the time of admission was investigated. The best cut-off point of laboratory measurements for fluid development was determined by ROC analysis and the factors that may be most decisive in distinguishing between the patients with and without fluid development were determined by multivariate forward stepwise logistic regression analysis.

Results: It is found that developing acute fluid collections after acute pancreatitis was higher in patients with younger age and male gender. Also the risk of developing acute fluid collections after acute pancreatitis was found to be 6.2 times higher in patients with CRP/Albumin ratio greater than 1.09; 2.5 times higher in patients with ALP below 199.5 U/L; 1.9 times higher in patients with WBC greater than 11,6 $\times 10^9$/L and 1.5 times higher in patients with PLR above 197.1. Also the risk of developing acute necrotic collections after acute pancreatitis was 3 times higher in patients with serum calcium level below 8,6 mg/dl.

Conclusion: It has been determined that, presence of high CRP/albumin ratio, high NLR and low serum ALP level can be used as an indicator in predicting acute pancreatic and peripancreatic fluid development.

Keywords: Acute fluid collections, acute necrotic collection, acute pancreatitis, acute peripancreatic fluid collections

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INTRODUCTION

Acute pancreatitis (AP) is an important disease that can progress to multiple organ failure and have a high health cost all over the world. While the annual incidence of AP is reported as 33-74 per 100000 and its mortality is 1-8.9% in the world-wide studies, it is stated that it cost over 2.6 billion dollars per year.[1-3] Pancreatic and peripancreatic fluid collection development is seen in 30-60% of patients in AP, and it has been reported that hospital stay and morbidity are higher in patients with fluid development.[3,4] The data on predicting pancreatic and peripancreatic fluid development in AP is limited, and most of them based on out dated studies and defined by the old Atlanta Classification terminologies. Due to these studies, alcoholic etiology, low serum alkaline phosphatase level, presence of ascite, presence of pleural efusion, male gender, palpable mass on physical examination and presence of a high computed tomography severity index (CTSI) shown to be associated with pseudocyst formation.[5,6]

According to the recently updated Revised Atlanta Classification, fluid collections developing after AP were divided into 4 groups and defined in detail. Fluid collections present for less than 4 weeks are classified as acute peripancreatic fluid collection (APFC) and acute necrotic collection (ANC). Collections that persist for more than 4 weeks have been identified as pseudocysts and walled-off necrosis (WON).[7]

Fluid collections developping in acute period have an important place in the prognosis of AP in terms of their ability to evolve into chronic fluid collections and become

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infected.[8] In this regard, predicting the formation of acute pancreatic and peripancreatic fluid collections after AP will contribute the treatment and follow-up of AP.

METHODS

Ethical approval for the study was received from Ankara City Hospital Ethics Committee (Date: 22.12.2021, Decision No: E2-21-1104). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Population

Adult patients aged over 18 years old applyed to Ankara City Hospital and diagnosed with AP by emergency internal medicine clinic between January 2020 and November 2021 included in the study. The data of 438 patients were evaluated retrospectively through the hospital information processing system (HICAMP®). Patients with a history of chronic pancreatitis, malignancy, abdominal surgery and pregnancy were not included in the study. The relationship between acute fluid development after AP and hematological/biochemical parameters was investigated.

Definitions

The diagnosis of AP was confirmed for all patients by emergency internal medicine clinic doctor according to the Revised Atlanta Classification Criteria. For the AP diagnosis; at least two of the following criteria were required: presence of a typical abdominal pain, presence of more than 3-fold increase in serum amylase or lipase levels and characteristic radiological imaging findings.[7]

Complete blood count was performed with Sysmex XE-2100 (SysmexCorp.®Kobe, Japan) automated hematology analyzer, CRP test was performed with BN II analyzer (DadeBehring/Siemens®, Germany), other parameters were measured with a modular analyzer (Cobas 8000 Roche®, Mannheim, Germany).

Data Collection

Demographic information, AP etiologies, co-morbidities, medications, hematological and biochemical parameters at the time of admission to the hospital (WBC, Hb, RDW, NEU, LYM, PLT, total and direct bilirubin, albumin, uric acid, triglyceride, LDL cholesterol, calcium, ALP, GGT, AST, ALT, amylase, lipase, CRP, procalcitonin) were recorded from HICAMP®.

The contrast-enhanced abdominal computed tomography (CACT) imaging reports of the patients taken at the time of admission and within 48-72 hours of follow-up were checked from hospital imaging system for invastigating whether patients have acute pancreatic/peripancreatic fluid or not.

Statistical Analysis

To investigate whether biochemical and hematological measurements were statistically significant in distinguishing between the patients with and without fluid development, calculating the area under the ROC curve (AUC) and 95% confidence intervals (CI) was used. If the AUC were found to be significant, the points where the sum of the sensitivity and selectivity levels reached the maximum were accepted as the best (optimal) cut-off points. Then, sensitivity, selectivity, positive and negative predictive values, and diagnostic accuracy rates at optimal cut-off points were calculated.

The factors that may be most decisive in distinguishing between the patients with and without fluid development were determined by multivariate forward stepwise logistic regression analysis. All variables detected as $p<0.10$ as a result of univariate statistical analysis were included in the regression model as candidate risk factors. Variables that were not considered clinically important and those with multicollinearity problems were excluded from the model. Additionally, odds ratios, 95% CI and Wald statistics were calculated for each variable included in the final model.

For data analysis IBM SPSS Statistics 25.0 (IBM Corporation, Armonk, NY, USA) package program was used. Results were considered statistically significant for $p<0.05$.

RESULTS

Of the 438 patients included in the study, 220 (50.2%) were male and 218 (49.8%) were female. The age of the patients ranged between 19 and 96 years (56.73±29.6). While AP was most commonly due to biliary causes (74.2%), the second most common reason was idiopathic causes (13%). When classified according to severity, 380 (84.9%) of the patients were evaluated as acute interstitial edematous pancreatitis (AIOP) and 58 (15.1%) as necrotizing pancreatitis (NP). It was observed that 8 (1.82%) of the patients included in the study died after follow-up due to AP.

It was determined that patients with fluid development after AP were younger and mostly in male gender ($p=0.045$; $p=0.003$, respectively). The rate of hypertriglyceridemic etiology was statistically significantly higher in the patients with fluid development ($p=0.014$). There was no statistically significant difference between the groups in terms of comorbidities and medication use ($p>0.05$).

Table 1. Biochemical and hematological values according to patients with and without fluid development

	Without fluid	With fluid	p-value
Total bilirubin (mg/dl)	0.98 (0.65-2.72)	1.19 (0.68-2.43)	0.918
Direct bilirubin (mg/dl)	0.53 (0.25-1.90)	0.60 (0.25-1.40)	0.869
Albumin (g/L)	41.00 (38.00-44.20)	41.62 (37.24-44.77)	0.961
Uric acid (mg/dl)	5.20 (4.20-6.23)	5.50 (4.50-7.00)	0.038
Triglyceride (mg/dl)	105.50 (83.25-154.75)	102.00 (79.00-144.75)	0.346
LDL cholesterol (mg/dl)	93.00 (71.00-120.00)	92.00 (71.00-113.00)	0.498
Calcium (mg/dl)	9.20 (8.80-9.50)	9.00 (8.55-9.40)	0.010
ALP (U/L)	126.00 (86.00-233.00)	111.00 (81.00-172.00)	0.007
GGT (U/L)	164.00 (59.00-423.25)	154.00 (49.00-408.50)	0.618
AST (U/L)	115.00 (37.00-239.00)	74.00 (28.00-212.00)	0.104
ALT (U/L)	132.00 (35.00-305.00)	93.00 (31.00-262.00)	0.212
Amylase (U/L)	697.00 (290.00-1468.00)	952.00 (311.00-1774.00)	0.168
Lipase (U/L)	983.00 (365.00-2078.00)	1149.00 (375.00-2552.00)	0.243
CRP (mg/dl)	16.50 (7.00-40.25)	63.50 (23.50-132.75)	<0.001
Procalcitonin (µg/L)	0.08 (0.03-0.20)	0.11 (0.04-0.42)	0.016
WBC ($\times10^9$/L)	9.85 (7.69-12.80)	12.19 (9.00-15.39)	<0.001†
Neutrophil ($\times10^9$/L)	7.59 (4.97-10.36)	9.80 (6.62-13.43)	<0.001†
Lymphocyte ($\times10^9$/L)	1.47 (1.00-1.93)	1.25 (0.83-1.77)	0.029†
Hemoglobin (g/dl)	13.36±1.70	13.84±2.02	0.008‡
Platelet ($\times10^9$/L)	253.00 (209.50-302.50)	250.00 (208.00-309.00)	0.966†
RDW (%)	14.00 (13.30-14.70)	14.00 (13.40-14.90)	0.546†

Descriptive statistics; They are shown as median (25^{th} percentile-75^{th} percentile) or mean ± standard deviation. † Mann Whitney U test, ‡ Student's t test.

Compared to laboratory measurements it was found that WBC, neutrophil, CRP and procalcitonin levels were statistically significantly higher (p<0.001; p=0.008; p=0.038 and p=0.016 respectively) and calcium, ALP levels were statistically significantly lower (p=0.010 and p=0.007) in patients with fluid development (Table 1).

Compared to other laboratory measurements it was also detected that CRP/Albumin, neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) levels were higher (p<0.001; p<0.001 and p=0.033) in patients with fluid development (Table 2).

Table 2. Other proportional values according to patients with and without fluid development

	Without fluid	With fluid	p value
Albumin/bilirubin	38.94 (12.87-63.08)	31.93 (13.01-57.75)	0.686
Albumin/platelet	0.16 (0.13-0.19)	0.16 (0.13-0.19)	0.622
RDW/platelet	0.06 (0.05-0.07)	0.06 (0.05-0.07)	0.945
CRP/albumin	0.46 (0.18-1.04)	1.70 (0.60-3.81)	<0.001
Neutrophil/ lymphocyte	4.98 (2.61-8.84)	7.55 (3.96-14.30)	<0.001
Platelet/ lymphocyte	178.34 (131.34-253.27)	205.45 (137.50-297.87)	0.033

Descriptive statistics; Shown as median (25th percentile-75th percentile). † Mann Whitney U test.

To distinguish the patients with and without fluid development the area under the ROC curve was found to be statistically significant for WBC, uric acid, calcium, ALP, CRP, procalcitonin, CRP/Albumin, NLR and PLR measurements respectively (Table 3). The ROC curve for WBC, CRP, and CRP/Albumin ratio is shown in Figure 1.

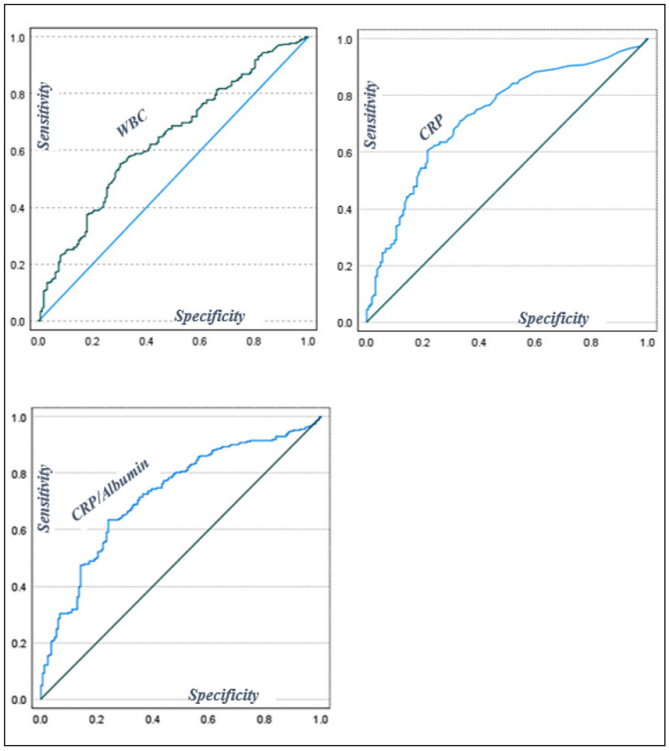

Figure 1. ROC curves for WBC, CRP, and CRP/Albumin respectively.

Table 3. ROC analysis results for laboratory values in distinguishing patients with and without fluid development

	AUC	95% CI	p-value
White blood cell	0.639	0.586-0.692	<0.001
Uric acid	0.559	0.504-0.614	0.034
Calcium	0.574	0.520-0.628	0.008
ALP	0.577	0.520-0.633	0.008
CRP	0.730	0.681-0.778	<0.001
Procalcitonin	0.568	0.514-0.623	0.014
Albumin/bilirubin	0.512	0.455-0.568	0.688
Albumin/platelet	0.514	0.458-0.570	0.621
RDW/platelet	0.502	0.446-0.558	0.945
CRP/albumin	0.724	0.676-0.773	<0.001
Neutrophil/lymphocyte	0.631	0.577-0.685	<0.001
Platelet/lymphocyte	0.561	0.506-0.616	0.029

AUC: Area under the curve, CI: Confidence Interval

The most predictive factors in distinguishing the patients with and without fluid development were examined with multivariate logistic regression analysis. According to the forward stepwise elimination method, the most determining factors in distinguishing groups with and without fluid development were CRP/Albumin ratio, ALP, age, WBC and PLR (Table 4).

Regardless of other factors, CRP/Albumin ratio greater than 1.04 increased the risk of fluid development 6.2 times (95% Cl: 3.808-10.366 and p<0.001) while ALP below 199.5 U/L incrased 2.5 times (95% Cl: 1.505-4.226 and p<0.001) and younger age incrased 0.9 times (95% Cl: 0.965-0.991 and p<0.001) (Table 5).

Table 5. The most predictive factors in differentiating patients with and without fluid development

	Odds ratio	95% Cl	Wald	p value
CRP/albumin >1.0482	6.282	3.808-10.366	51.737	<0.001
ALP <199.5 U/L	2.522	1.505-4.226	12.332	<0.001
WBC >11.685×10^9/L	1.938	1.210-3.103	7.592	0.006
Age	0.978	0.965-0.991	11.507	<0.001
Platelet/lymphocyte >197.146	1.596	1.012-2.519	4.044	0.044

CI: Confidence Interval

Evaluating separately the patients with APFC and ANC, it was found that while the most determining factors in distinguishing the patients with APFC were CRP/Albumin ratio, ALP, age and WBC, they were CRP/Albumin ratio, WBC, ALP, calcium and age in patients with ANC.

Regardless of other factors, CRP/Albumin ratio greater than 1.04 significantly increased the risk of ANC 10.9 times (95% Cl: 4.813-24.770 and p<0.001) when ALP below 199.5 U/L increased 4.4 times (95% Cl: 1.676-12.031 and p=0.003). Also there was a statistically significant inverse association between age and ANC development (Odds ratio=0.974; 95% CI: 0.955-0.993 and p=0.008). On the other hand, it is found that calcium level below 8.6 mg/dl increased developing ANC 3 times (95% CI: 1.424-6.331 and p = 0.004).

DISCUSSION

Acute pancreatitis is still an important disease that causes serious morbidity and mortality all over the world.[2,3] When the incidence of AP is between 13-45/100,000, its mortality is reported to be approximately 1%. However, in cases of severe pancratitis with organ failure and infection, mortality may vary between 20-40%.[8,9]

In several studies, it was observed that 70-80% of AP cases were AIOP and approximately 20-30% were ANP.[3,4] In our study it was found that 84.9% of the patients were AIOP and 15.1% were ANP. Our results were close to the rates obtained from the literature.

In the literature, the incidence of fluid development after AP was observed as 30-50% and it was found that 50% of cases with fluid development regressed spontaneously within the first week, while 30-50% turned into pseudocyst.[10] While the rate of ANC development after AP was observed as 20-40% and the rate of WON development as 1-9%, Manrai et al.[11] showed that 57.8% of AP cases developed ANC and progressed to WON.[12,13]

Table 4. The best cut-off points of ROC analysis in distinguishing patients with and without fluid development and the diagnostic performance indicators at these points

	Best cut	Sensitivity	Selectivity	PTD	NTD	Accuracy
White blood cell	>11.685×10^9/L	152/275 (55.3%)	113/162 (69.8%)	152/201 (75.6%)	113/236 (47.9%)	265/437 (60.7%)
Uric acid	>6.45 mg/dl	95/275 (34.5%)	131/162 (80.9%)	95/126 (75.4%)	131/311 (42.1%)	226/437 (51.7%)
Calcium	<8.695 mg/dl	86/275 (31.3%)	136/163 (83.4%)	86/113 (76.1%)	136/325 (41.8%)	222/438 (50.7%)
ALP	<199.5 U/L	225/275 (81.8)	53/163 (32.5%)	225/335 (67.2%)	53/103 (51.5%)	278/438 (63.5%)
CRP	>44.5 mg/dl	166/274 (60.6%)	127/35 (78.4%)	166/201 (82.6%)	127/235 (54.0%)	293/436 (67.2%)
procalcitonin	>0.255 µg/L	96/274 (35.0%)	131/162 (80.9%)	96/127 (75.6%)	131/309 (42.4%)	227/436 (52.0%)
CRP/Albumin	>1.0482	174/274 (63.5%)	123/162 (75.9%)	174/213 (81.7%)	123/223 (55.2%)	297/436 (68.1%)
Neutrophil/lymphocyte	>6.428	159/275 (57.8%)	102/162 (63.0%)	159/219 (72.6%)	102/218 (46.8%)	261/437 (59.7%)
Platelet/lymphocyte	>197.146	145/275 (52.7%)	100/162 (61.7%)	145/207 (70.0%)	100/230 (43.5%)	245/437 (56.1%)

GP: True Positive, FN: False Negative, GN: True Negative, FC: False Positive, N: Total number of cases, PTD: Positive predictive value, NTD: Negative estimated value.

Compared to the literature data, in our study WON development was higher and pseudocyst development was lower. It was thought it is due to the difference in the interpretation of imaging examinations and in the demographic and clinical characteristics of the patients.

There are few studies in the literature on predictive factors for fluid developments after AP. Most of these studies include old terminologies used before Revised Atlanta Classification such as pancreatic abscess and also the hematologic/biochemical parameters examined were limited.[5,6,14]

In a study conducted by Cui et al.[1] in China with 302 patients, younger age and alcoholic etiology were found to be statistically significant for development of pancreatic fluid collection. In a another study conducted by Diculescu et al.[5] in Romania with 62 patients was observed that presence of ascites in the patient was associated with acute fluid collection and alcoholic etiology and low serum ALP level were associated with pseudocyst formation.

Also in a study conducted by Poornachandra et al.6 in India with 65 patients observed that male gender, presence of ascites at at the time of admission, presence of palpable mass in the abdomen and high CTSI were significant predictive values for pseudocyst formation. Additionally, Manrai et al.[11] stated a relationship between high BUN, serum creatinine ratio, BISAP, APACHE score and presence of organ failure in fluid development after AP, but did not find a statistically significant evidence in terms of age and gender.

In our study it was found that fluid development was statistically significantly higher in male gender and younger patients. Our results are similar with the data obtained by Cui et al.[1] and Poornachandra et al.[6] regarding fluid and pseudocyst formation after AP.

When our study was evaluated according to the etiology of AP, it was found that patients with AP due to hyperthyroglyceridemia had more fluid development compared to other etiologic reasons. Our results were consistent with literature data showing AP cases due to hypertriglyceridemia are more severe.[15,16] Accordingly, our study differs from the studies of Cui et al.[1] and Diculescu et al.[5] found a relationship between fluid and pseudocyst development after AP with alcoholic etiology. It was thought that the reason of the difference was due to alcohol was the most common etiologic cause of AP in both studies while it was in limited number of cases in our study (4.1%).

Hypercalcemia plays a role in the etiology of AP by disrupting intracellular defense mechanisms with increased cytosolic calcium level in pancreatic acinar cells and causing early trypsinogen activation.[17] However, hypocalcemia develops in patients with AP. The development of hypocalcemia in AP is attributed to calcium salts, hypomagnesemia and transient hypoparathyroidism caused by free fatty acids released after digestion of mesenteric adipose tissue by pancreatic enzymes in the early phase, while it is attributed to inflammatory response and sepsis in the late phase. It has shown that low serum calcium level indicates severe inflammatory response and organ failure and is a predictive parameter for severe AP.[14] So that, serum calcium level is also used in Ranson and Glasgow-Imrie scoring.[18]

Studies investigating the relationship between serum calcium level and fluid development after AP are very limited in the literature. In a study conducted in by Akgül et al.[14] scanned total of 102 patients diagnosed with AP and found that low serum calcium level (<8 mg/dl) was a significant predictive factor in pseudocyst development.

In our study, serum calcium level was statistically significantly lower in the patients with fluid development but the predictive value was found to be low ($p>0.001$). However it was found that calcium level below 8.6 mg/dl increased the risk of developing ANC by 3-fold. This result supports that low serum calcium level can be used as an important predictive factor to indicate the development of ANC after AP.

Alkaline phosphatases are a group of glycoproteins in the liver, kidney, intestines, bone, placenta, pancreas and WBC and there are many studies in the literature indicating that high serum ALP levels can be used as a predictive factor in the diagnosis and severity of AP.[19] However, recent studies have also shown that serum intestinal ALP level decreases in inflammatory and septic conditions and may be used in the treatment of some inflammatory diseases.[20]

Diculescu et al.[5] observed that serum ALP level was lower in patients with pseudocyst formation after AP. They stated that serum ALP level below 185 U/L could be used as a predictive factor with 90% specificity in pseudocyst formation after AP, but they did not report any opinion to explain about the relationship between low serum ALP level and developing pseudocyst.

In our study, serum ALP level was statistically significantly lower in patients with fluid development after AP. It was found that ALP levels below 199.5 U/L significantly increased fluid developpent by 2.5 times after AP. However it was seen that, excluding the group developed APFC, ALP levels below 199.5 U/L significantly increased developing ANC by 4.5 times.

According to our results, low serum ALP level can be used as a predictive factor especially in ANC formation. However, we think that the relationship between developing fluid/pseudocyst after AP and low ALP level should be supported by more comprehensive studies and the reasons should be discussed.

There are many studies about hematologic parameters as acute inflammation parameters in the literature.[21] In recent years NLR has been studied extensively in various diseases as a new inflammation parameter. It was also shown that NLR has a high predictive value in predicting the severity of AP, but there is no study on the prediction of fluid development after AP.[22]

Kaplan et al.[23] investigated the relationship between the prognosis and mortality of AP with NLR-PLR combination and they found that NLR-PLR combination had superior predictivity in terms of prediction of mortality compared to Ranson, Atlanta, and Bisaps scoring system. In another study, Dancu et al.[24] showed that NLR examined at 48 hours had a high predictive value in predicting the severity of AP but was not superior to BISAP.

In our study, NLR was found to be higher in patients with fluid development and was statistically significant in differentiating the patients. Considering NLR is an indicator of inflammation, it was related to the patients with fluid development were classified into moderate and severe AP according to the Revised Atlanta Classification.

There are several studies showed that PLR can be used as an effective predictive factor in demonstrating severity in AP.[25,26] But there is no study in the literature investigating the relationship between PLR and fluid development after AP.

We found that PLR above 197.146 increased fluid development by 1.5 times but it had a lower sensitivity than NLR and CRP/albumin values. However it is important to state that, PLR can be used as a predictive value in the fluid development after AP.

PCT is an acute phase reactant increases in bacterial infections and non-bacterial systemic inflammatory responses. Also it can be used in predicting severity in AP, organ failure after AP and infected necrosis.[27] There is no study in the literature investigating the relationship between serum PCT levels and fluid development after AP. In our study, PCT levels were found to be higher in patients with fluid development and can be used in differentiating the patients with fluid development.

CRP is one of the most widely used acute phase reactants to demonstrate infective and non-infective inflammation with the advantages of being easy to study and inexpensive all over the world.[28] In addition to its use as a parameter in the Ranson criteria, there are many studies in the literature regarding the prediction of severity of AP by CRP. According to these studies, it has been shown that CRP levels at 48 hours after admission, has a high predictive value in the determination of severity in AP.[29]

In a prospective study, Vinish et al.[30] found that serum CRP level >150 mg/dl can be used as a predictive factor in the development of pancreatic fluid. Also Cui et al.[1] stated that the presence of high serum CRP level at 48 hours along with young age and alcoholic etiology to be significant as a predictive factor for the development of pancreatic fluid collection after AP.

In our study, CRP level was found to be significant in differentiating patients with and without fluid development after AP, but its sensitivity and specificity were low.

CRP/albumin ratio can be used as an inflammatory marker in various diseases and AP.[31,32] In a retrospective study it was shown that the mortality risk was 19.3 times higher in patients with a CRP/albumin ratio ≥16.28 and in another study CRP/albumin ratio was found to be 90% sensitive (cut-off value of 8.51) in determining the severity of AP.[33,34]

In our study, it was found that CRP/albumin ratio greater than 1.04 increased the risk of fluid development by 6.2-fold and increased the risk of ANC itself by 10.9-fold. According to our results, CRP/albumin ratio can be used in predicting fluid development after AP with high predictive value.

There are several limitations in this study. Although it has a higher sample size compared to similar limited studies in the literature, it is a retrospective, single-center study. So that a selection bias may be existed, even though the clinical data were derived from a prospectively maintained database. Hence, randomized, multicenter prospective studies are needed.

CONCLUSION

It has been determined that male gender and younger age may be a risk factor for development of acute fluid collections after AP. Also presence of high CRP/albumin ratio, high NLR and low serum ALP level can be used as an indicator in predicting of acute pancreatic and peripancreatic fluid development. Additionally, the presence of hypocalcemia has a high predictive value in predicting the development of ANC itself.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital Ethics Committee (Date: 22.12.2021, Decision No: E2-21-1104).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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Original Article

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Prognostic accuracy of radiological scoring systems in acute pancreatitis: CTSI vs. mCTSI

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ABSTRACT

Aims: Acute pancreatitis (AP) is a complex and unpredictable clinical condition with variable outcomes. Early risk assessment is vital for tailored interventions and improved patient outcomes. The computed tomography severity index (CTSI) and modified computed tomography severity index (mCTSI) are radiological scoring systems used to evaluate AP severity.

Methods: We conducted a single-center retrospective study spanning from January 1, 2018, to December 31, 2022, to compare CTSI and mCTSI in predicting mortality in AP. Data were retrieved from our institution's electronic records for 266 eligible adult patients. Statistical analysis assessed the relationship between scoring systems, patient demographics, etiology, and mortality.

Results: Among the 266 patients, 9.4% died. Mortal patients were older (mean age: 72.09±15.12) than survivors (mean age: 59.93±16.93). The most common etiology was biliary pancreatitis (58.64%). mCTSI showed significant differences between the mortality and non-mortality groups (p=0.026), whereas CTSI did not (p=0.112). The ROC analysis for mCTSI yielded an area under the curve of 0.629, with a Youden index of 0.193 (p=0.044). A mCTSI cut-off of 3 had a sensitivity of 59.1% and specificity of 60.2%.

Conclusion: Advanced age and biliary etiology were associated with increased mortality. mCTSI demonstrated superiority in predicting mortality compared to CTSI.

Keywords: Acute pancreatitis, scoring systems, mortality

INTRODUCTION

Acute pancreatitis (AP) is a multifaceted and often unpredictable clinical condition that manifests with varying degrees of severity and clinical courses. Timely risk assessment is paramount for tailoring precise interventions and optimizing patient outcomes. To address this challenge, numerous scoring systems have emerged for the evaluation of AP severity, with the computed tomography severity index (CTSI) and its modified counterpart, the modified computed tomography severity index (mCTSI), gaining significant prominence.

The CTSI, originally introduced by Balthazar et al. in 1990, stands as a comprehensive radiological tool for assessing pancreatic inflammation extent and complications through contrast-enhanced computed tomography (CECT) scans.[1] In subsequent years, the mCTSI was devised as a streamlined alternative with the aim of preserving predictive accuracy while enhancing user-friendliness.[2]

In this study, we embark on an in-depth analysis to compare the effectiveness of CTSI and mCTSI in predicting mortality among patients diagnosed with acute pancreatitis. Our investigation is based on data collected from a single institution, which bolsters the internal validity of our findings while reducing potential variations linked to multi-institutional disparities.[3-6]

The primary outcome of this research is to evaluate and juxtapose the prognostic utility of CTSI and mCTSI in predicting Mortality in patients diagnosed with acute pancreatitis. By leveraging data gathered within our institution over a specified period, we endeavor to provide valuable insights into the clinical applicability of these radiological scoring systems within a specific patient population.

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METHODS

Study Design

The study was carried out with the permission of Kartal Dr. Lütfi Kırdar City Hospital Clinical Researches Ethics Committee (Date: 27.04.2023, Decision No: 2023/514/248/7). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study is a single-center retrospective analysis conducted at Kartal Dr. Lütfi Kırdar City Hospital, spanning the period from January 1, 2018, to December 31, 2022. The primary objective of this investigation is to compare the prognostic accuracy of the computed tomography severity index (CTSI) and the modified computed tomography severity index (mCTSI) in predicting mortality among patients diagnosed with acute pancreatitis.

Data Collection

Patient data were retrieved from our institution's electronic medical records (EMR) and radiology databases. A comprehensive search was conducted to identify all patients admitted to our institution with a confirmed diagnosis of acute pancreatitis during the specified study period.

Inclusion Criteria

- Patients diagnosed with acute pancreatitis according to established diagnostic criteria, including clinical, biochemical, and radiological findings.
- Adult patients aged 18 years or older.
- Availability of contrast-enhanced computed tomography (CECT) scans performed within 48 hours of admission for the calculation of both CTSI and mCTSI.
- Complete medical records, including clinical, laboratory, and radiological data.

Exclusion Criteria

- Patients with incomplete medical records or missing relevant data.
- Pediatric patients (aged below 18 years).
- Patients with chronic pancreatitis or other chronic pancreatic diseases.
- Patients with a history of pancreas surgery or trauma.
- Patients with incomplete CECT scans for the calculation of CTSI or mCTSI.

Data Extraction

Data extraction was performed by trained medical personnel using standardized data collection forms. The following information was extracted:

- Demographic information (age, sex).
- Etiology of acute pancreatitis (e.g., gallstone, alcohol-induced, idiopathic).
- Clinical parameters on admission (e.g., vital signs, laboratory values).
- Radiological findings, including CECT scans.
- Computed Tomography Severity Index (CTSI) and Modified Computed Tomography Severity Index (mCTSI) scores calculated based on CECT scans.
- Clinical outcomes, including mortality during hospitalization.

CTSI and mCTSI Scoring Systems

The severity of pancreatitis was assessed using both the CT severity index and the modified CT severity index, and then categorized into mild, moderate, and severe classifications. Computed tomography (CT) with intravenous contrast medium injection is accepted as the imaging procedure of choice: first to document the extent of pancreatic and extrapancreatic acute fluid collections and, second, to detect pancreatic necrosis. These two parameters have been identified as prognostic indicators of the severity of AP. CTSI, based on combined assessment of peripancreatic fluid collections, and the degree of pancreatic necrosis were developed to improve prognostic accuracy. The CT Severity Index includes an assessment of the patient's imagination. A normal pancreas is assigned a score of 0, whereas a focal or diffuse enlargement is assigned a score of 1, peripancreatic inflammation is assigned 2 points, a single fluid collection is assigned 3 points, and several fluid collections and/or gas are assigned 4 points. The scoring system for necrosis assessment is as follows: absence of necrosis is assigned 0 points, 30% necrosis of the pancreas is assigned 2 points, 30%–50% necrosis of the pancreas is assigned 4 points, and 50% necrosis of the pancreas is assigned 6 points. Modified computed tomography severity index (mCTSI) differs from the CTSI by the presence of extra pancreatic complications and grading of the peripancreatic fluid collection by their presence or absence, instead of the number of fluid collections.

Statistical Analysis

Statistical analyses were performed using SPSS 22.0 for Windows. Descriptive criteria were presented as mean and standard deviation values and percentage distribution. The Kolmogorov-Smirnov test was used to examine the conformance of the data to the normal distribution. The ROC analysis was performed to establish the cutoff values of risk scores for predicting mortality. The significance threshold was determined to be $p<0.05$.

RESULTS

A total of 290 acute pancreatitis patients were admitted to the emergency department of Kartal Dr. Lütfi Kırdar City Hospital during the study period. After excluding 21 patients with incomplete data and 3 patients transferred to other hospitals, 266 patients were included in the study. Of these, 158 (59.4%) were male, and 108 (40.3%) were female. Twenty-two (9.4%) patients died during the course of their illness.

One notable finding was the significant difference in mean age between the survivor and non-survivor groups. Patients who succumbed to acute pancreatitis had a notably higher mean age (72.09±15.12) compared to survivors (59.93±16.93). This observation underscores the well-established association between advanced age and increased mortality in AP.[7] Age-related factors such as decreased physiological reserves and comorbidities may contribute to the vulnerability of older patients to severe outcomes in acute pancreatitis.[6,7] Tomographic findings of the survivor and non-survivor groups have been determined in Table 1.

Table 1. Data shows tomographic findings and gender distribution between the non-survivor and survivor group

	Non-survivor grup (n=22)	Survivor grup (n=244)
2 or more regions with fluid collections	6 (27.3%)	26 (10.7%)
Cyst	3 (13.6%)	6 (2.5%)
Abscess	0	1 (0.4%)
More than %50 necrosis	1 (4.5%)	3 (1.2%)
%30-50 necrosis	1 (4.5%)	0
Up to %30 necrosis	2 (9.1%)	3 (1.2%)
Extrapancreatic complications	14 (63.6%)	107 (43.9%)
Ascites	10 (45.5%)	33 (13.5%)
Vascular complications	0	1 (0.4%)
Gastrointestinal complications	15 (68.2%)	82 (33.6%)
Pleural effusion	12 (54.5%)	26 (10.7%)
Parenchymal necrosis	3 (13.6%)	6 (2.5%)
Peripancreatic necrosis	0	0
Peripancreatic and parenchymal necrosis	2 (9.1%)	1 (0.4%)
Male	16 (72.7%)	142 (58.2%)
Female	6 (27.3%)	102 (41.8%)

The etiological heterogeneity of acute pancreatitis is a well-recognized challenge in clinical management. In our study, biliary pancreatitis was the most common etiological factor (58.64%), followed by idiopathic pancreatitis (25.2%). Identifying the underlying cause of acute pancreatitis is imperative, as it can influence both disease severity and patient outcomes.6

Regarding the radiological scoring systems, our analysis revealed that mCTSI showed a significant difference between the survivor group and the non-survivor group, whereas CTSI did not demonstrate such discrimination (Table 2). This finding suggests that mCTSI may have an advantage over the traditional CTSI in predicting Mortality in acute pancreatitis within our specific patient population.

Table 2. Data shows Mann Whitney test results for MCTSI and CTSI

	Non-Survivor group median (range)	Survivor group median (range)	p value
MCTSI	4 (0-10)	2 (0-10)	0,026
CTSI	2 (0-10)	2 (0-10)	0,112

In our receiver operating characteristic (ROC) analysis for mCTSI, the area under the curve (AUC) was 0.629, indicating moderate accuracy in predicting mortality (Figure 1). The Youden index, sensitivity, and specificity values suggest that an mCTSI cut-off level of 3 may have clinical relevance for risk stratification. However, it is important to note that while mCTSI demonstrated statistical significance, the predictive accuracy remains moderate, emphasizing the multifactorial nature of mortality prediction in acute pancreatitis.[8,9]

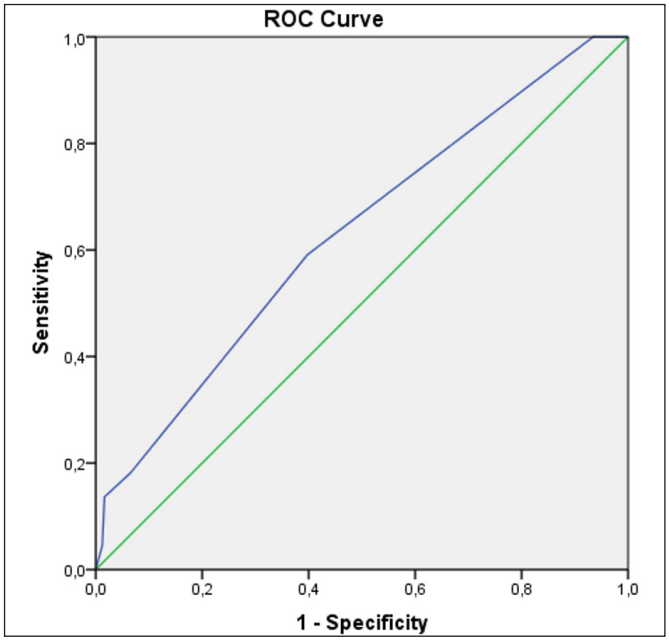

Figure 1. Figure shows the ROC Curve analysis for MCTSI. AUC=0.629 (95% CI:0.506-0.752)

DISCUSSION

Acute pancreatitis (AP) is a multifaceted clinical condition with a broad spectrum of severity and outcomes. The accurate assessment of disease severity plays a pivotal role in guiding clinical decisions and optimizing patient care.[10,11] In this single-center retrospective study spanning from 2018 to 2022, we endeavored to compare the predictive efficacy of the

computed tomography severity index (CTSI) and the modified computed tomography severity index (mCTSI) in forecasting Mortality among patients diagnosed with acute pancreatitis.

Our study population consisted of 266 patients admitted to the emergency department Kartal Dr. Lütfi Kırdar City Hospital, who met the inclusion criteria for the analysis. Notably, our cohort was characterized by a slightly higher proportion of males (59.4%) than females (40.3%), reflecting a trend reported in various epidemiological studies.[12] The overall Mortality rate in our study was 9.4%, consistent with the range of mortality rates reported in the literature.[8]

One of the key findings of our investigation was the significant difference in mean age between the mortality and non-mortality groups. Patients who succumbed to acute pancreatitis had a notably higher mean age (72.09±15.12) compared to survivors (59.93±16.93). This observation underscores the well-established association between advanced age and increased mortality in AP.[7] Age-related factors such as decreased physiological reserves and comorbidities may contribute to the vulnerability of older patients to severe outcomes in acute pancreatitis.[7]

The etiological heterogeneity of acute pancreatitis is a well-recognized challenge in clinical management. In our study, biliary pancreatitis was the most common etiological factor (58.64%), followed by idiopathic pancreatitis (25.2%). The etiological distribution in our cohort aligns with previously reported patterns, where gallstone-related etiology frequently dominates the clinical landscape.[13-16] Identifying the underlying cause of acute pancreatitis is imperative, as it can influence both disease severity and patient outcomes.[6]

Regarding the radiological scoring systems, our analysis revealed that mCTSI showed a significant difference between the mortality group and the non-mortality group, whereas CTSI did not demonstrate such discrimination. This finding suggests that mCTSI may have an advantage over the traditional CTSI in predicting mortality in acute pancreatitis within our specific patient population. This observation is consistent with other studies that have highlighted the utility of mCTSI as a simplified yet effective tool for risk assessment in acute pancreatitis.[11,17]

Numerous scoring systems for acute pancreatitis continue to be utilized in clinical practice.[18] Additional criteria, such as pancreatic volume, have also started to be incorporated into scoring systems.[19] Blood gas characteristics, which encompass many scoring systems, are widely utilized in the diagnosis and management of numerous disorders in medical practice.[20,21] The optimal scoring system should possess characteristics of simplicity, cost-effectiveness, and efficacy, while also avoiding any additional burden on standard clinical examination protocols.

In our receiver operating characteristic (ROC) analysis for mCTSI, the area under the curve (AUC) was 0.629, indicating moderate accuracy in predicting mortality. The Youden index, sensitivity, and specificity values suggest that an mCTSI cut-off level of 3 may have clinical relevance for risk stratification. However, it is important to note that while mCTSI demonstrated statistical significance, the predictive accuracy remains moderate, emphasizing the multifactorial nature of mortality prediction in acute pancreatitis.[9]

CONCLUSION

In conclusion, our study contributes to the growing body of literature on radiological scoring systems in acute pancreatitis. Our findings suggest that mCTSI may have advantages over CTSI in predicting mortality in our specific patient population. However, further prospective studies with larger cohorts are warranted to validate and refine the utility of mCTSI as a prognostic tool in acute pancreatitis. Comprehensive risk assessment in acute pancreatitis should consider multiple factors, including age, etiology, and radiological findings, to facilitate individualized patient management and optimize outcomes.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kartal Dr. Lütfi Kırdar City Hospital Clinical Researches Ethics Committee (Date: 27.04.2023, Decision No: 2023/514/248/7).

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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Original Article

MEDICINE PALLIATIVE CARE

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How does mortality affect sustainable development goals?

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ABSTRACT

Aims: The aim of this study was to reveal the relationship between the sustainable development indicators index score and mortality, including maternal deaths, deaths under the age of five (u5mortality) traffic deaths, and death of non-communicable disease (NCD mortality).

Methods: Panel data method was used in the analyses, mortality rates independent variables belonging to 11 OECD countries with regular data between 2000-2020; sustainable development indicators index score was considered as the dependent variable.

Results: According to the results of the least squares analysis, a 1% increase in maternal mortality reduced the sustainable development index score by 0.021%; a 1% increase in under five years mortality reduced the sustainable development index score by 0.037%; a 1% increase in NCD mortality reduced the sustainable development index score by 0.044%; a 1% increase in trafficmortality reduced the sustainable development index score by 0.016% ($p<0.01$). A Granger-type causality relationship was identified in different directions between the Sustainable Development Index score and various types of mortality. Additionally, it has been observed that the variables exhibit a long-term relationship. The results of this research explain that long-term mortality rates account for approximately 10% of all sustainable development-related indicators, emphasizing that a healthy social structure is a fundamental requirement for the sustainable development of countries.

Conclusion: Therefore, according to the empirical evidence obtained from the research, the increase in mortality negatively affects the SDG index score in the countries under analysis.

Keywords: Econometric evaluation, sustainable development goals, mortality

INTRODUCTION

The science of economics, expressed as ensuring the effective management of scarce resources in the context of needs and dealing with effects quantitatively, has begun to address economic efficiency within the framework of sustainability. This is a result of the decrease in resources on a global scale and the increase in consumption due to changes in needs. In this context, the literature attempts to explain the quantitative evaluation that deals with the framework of economic growth using the concept of Economic Development within the socioeconomic structure shaped and transformed by the economy.

Development is a dynamic concept that entails a positive change from the current situation. Progress in the world cannot be solely addressed through quantitative growth. The term 'sustainable' was first introduced in the 1972 report titled 'Limits to Growth,' emphasizing the importance of qualitative growth by considering the environment, nature, and ecology. The primary goal of the report is to establish a global equilibrium. It has been seen as essential to prevent sudden and uncontrolled collapses, to ensure that the material needs of the people are met, and to build a development that will provide continuity. In the report, sustainability is defined as a process in which depleted resources in nature are endowed with the ability to renew themselves continuously.[1,2]

Sustainable Development in the Brundtland Report published in 1987; it has been defined and accepted as "meeting the needs of the present while allowing future generations to meet their needs".[3]

Transforming Our World; 17 Sustainable Development Goals and 169 targets of these goals were determined within the scope of the 2030 Agenda for Sustainable Development. In this context, the aim is to realize human rights, empower women, and ensure gender equality in the light of economic, social, and environmental dimensions on a global scale.[4] The report (SDR) on objectives and targets prepared in an up-to-date manner for sustainable development includes yearly data for all countries; the spread score is presented in the form of a report that includes raw values, normalized scores, board ratings, trends, and target scores. With this report,

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the SDG Index score, along with all target and indicator scores, is calculated retrospectively over time using time series data that include missing values from previous years. The report also provides detailed information about the main goals and objectives of the SDG Index score.[5] In this index, "SDG 3: Healthy and Quality Life Goals", the goal for 2030 is to ensure a healthy and quality life for all ages. This includes reducing the mortality rates of children under the age of five, the maternal mortality rate below 70 per 100,000 live births, and the premature death rate from non-communicable diseases by one-third. This goal was covered under 17 sub-headings in the SDG index score. The aim of this study was to reveal the relationship between the Sustainable Development Indicators Index score of the member countries of the Organization for Economic Cooperation and Development and various types of mortality including maternal deaths, deaths under the age of five, traffic deaths, and NCD mortality.

Within the scope of the analysis, 1 (one) main hypothesis was determined and 2 (two) sub-questions were proposed to explain the main hypothesis.

- **H1:** Sustainable development goals are related to mortality.
- **Q1:** What was the level of impact of mortality on sustainable development goals?
- **Q2:** How did mortality affect sustainable development goals?

Studies evaluating the relationship between sustainable development goals and health are frequently carried out in the literature. These studies generally focus on projections, scenarios and relational assessments.[6-8] In this study, from a different perspective, econometric (panel data analysis) methods were used to examine the mortality data, which is one of the Sustainable Development Goals and health indicators. Therefore, it is thought that the findings obtained by empirical econometric methods in this study will enrich the literature on health from a methodological point of view.

METHODS

The study was designed retrospectively with using secondary data so ethical approval was not required. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In the analysis, the relationship between the mortality and the SDGScores was analyzed by panel data method. Panel data analysis is a method that allows the evaluation of cross-section data and time series data in a common area.[9] Since the study was considered within the scope of countries with data in a certain year range, this analysis method was considered suitable for the study. In the analysis, an econometric model was established in which the mortality was considered as the independent variable and the SDGScores the dependent variable. This study was designed as a descriptive cross-sectional type. The significance tests of the model were evaluated with the least squares method, and the Granger causality test, cointegration tests and variance decomposition models were applied to determine the causality and long-term relationships between the variables. For this study, 11 countries with regular mortality data under the heading "SDG3: Good Health and Well-Being" were used between 2000-2020. These countries were Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Hungary, Spain, and Türkiye. In Table 1, the analysis includes the variables, their abbreviations, source information for the data, and detailed explanations for each variable under the corresponding sub-headings. It should also be noted here that in this research, in order to obtain more reliable results from the analysis results and to meet the assumption of normal distribution, log transformation was applied to the variables and analyzes were carried out on the variables whose logarithm was taken.

Statistical Analysis

Statistical analyzes were performed using the Eviews 10 program (Eviews 10, IHS Global Inc., 4521 Campus Drive, #336, Irvine, CA 92612).

Table 1. Definition of variables*

Variables	Definition	Unit	Source	Abbreviation
SDG index score	The SDG Index Score, and all goal and indicator scores, retroactively calculated across time using time series data that was carried forward in years with missing data in period t	Score Point	sdgindex.org	SDGScore
Maternal mortality	Maternal mortality rate in period t	per 100000 live births	sdgindex.org	Matmort
Under five years mortality	Mortality rate, under-5 in period t	per 1000 live births	sdgindex.org	u5Mort
Traffic deaths	Traffic deaths in period t	per 100000 population	sdgindex.org	Trafficmort
Non communicable diseases mortality	Age-standardized death rate due to cardiovascular disease, cancer, diabetes, or chronic respiratory disease in period t	% in adults aged 30–70 years	sdgindex.org	NCDmort

*The data were included in the analyzes by taking logarithmic transformations.

RESULTS

According to the descriptive information of the variables in to the analysis;

- SDG Score Index mean was 77.55±4.63 (min: 66.20, max: 86.40)
- Maternal mortality mean was 8.89±5.42 (min: 2.94, max: 31.70)
- Under five years mortality mean was 6.05± 5.28 (min: 2.22, max: 37.88).
- NCD mortality mean was 13.75±4.24 (min: 8.46, max: 29.09).
- Traffic mortality mean was 7.49±2.93 (min: 3.07, max: 16.65).

The representation of the variables according to countries and year ranges was given in Figure 1. Figure 1 shows a negative correlation between the SDG Index score and the mortality that were the subject of the study.

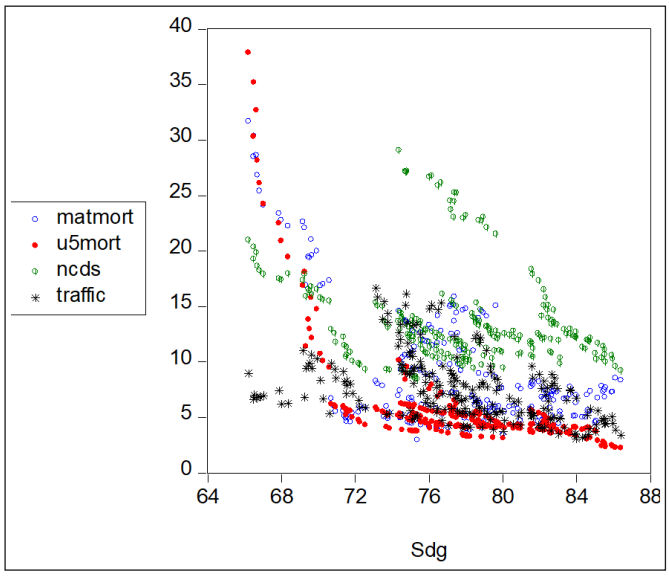

Figure 1. Relationship between SDG scores and mortality variables, 11 countries, 2000-2020.
Source: Prepared by the author.

Econometric Model

At this stage of the study, the mathematical function of the model to be used in econometric analysis was given.

$$SDGScore = f\,(Matmort, U5Mort, NCDmort, Trafficmort\,)$$

The econometric model to be estimated from this equation was established as follows:

$$SDGScore_{it} = \beta_0 + \beta_1 Matmort_{it} + \beta_2 u5Mort_{it} + \beta_3 NCDmort_{it} + \beta_4 Trafficmort_{it} + u_{it}$$

In the model in the equation; the "β_0" coefficient constant expresses the SDGScore that occur independently of the explanatory variables. While "β_1" for Matmort, "β_2" for u5Mort, "β_3" for NCDmort, "β_4" for represents the parameters to be estimated for Trafficmort, "u" represents the error term; "i" denotes the cross-sectional dimension of the panel data, and "t" denotes the time dimension. "SDGScore" was taken as the dependent variable.

Least Squares Test

The least squares test (LS) method is one of the methods used to measure the significance of an econometric model.[10] In the analysis it was observed that the fixed-effect model gave more consistent results compared to the Hausman test result in estimating the SDGScore and the number of independent variables, which are the dependent variables of the analysis ($p<0.00$). According to these results, our model was analyzed under fixed effects and it was determined that the power of the independent variables to explain the dependent variables was consistent (R2 99%, adjusted R2 99%). It has been determined that there was no multicollinearity problem in the model (VIF: between 0-10), there was no cross-sectional dependence (Peseran CD: 0.3761), there was no correlation between variables (Durbin Watson: 1.5), and there was no heteroscedasticity problem (Breusch Pagan: 1.0000). These tests confirmed the significance of the econometric model established in the research. According to the least squares analysis results in Table 2, a 1% increase in maternal mortality reduced the sustainable development index score by 0.021%; a 1% increase in u5mortality reduced the sustainable development index score by 0.037%; a 1% increase in NCDmortality reduced the sustainable development index score by 0.044%; a 1% increase in trafficmortality reduced the sustainable development index score by 0.016% ($p<0.01$).

Table 2. Least square test results

Dependent variable	Independent variables	Coefficient	Prob.	R2	Adjusted R2	F-Statistic	Prob (F-statistic)
SDGScore				0.99	0.99	5252.747	0.0000*
	Matmort	-0.021517	0.0000*				
	u5Mort	-0.037982	0.0000*				
	Trafficmort	-0.016846	0.0000*				
	NCDmort	-0.044602	0.0000*				
	C	4.603150	0.0000*				
Hausman Tests cross section/period: 0.0000; Peseran Test:0.3761; Breusch PagaN LM Test: 1.0000; JB Normality Test: 0.476877; Skewness: 0.115125; Kurtosis: 2.682425; VIF:1.281404-6.793452; Durbin Watson: 1.51							
*,**,*** significance at %1,%5,%10 level respectively. Source: Prepared by the author.							

Cointegration and Granger Casuality/Block Exogeneity Wald Tests

Granger causality analysis is a method that evaluates the contribution of the lagged values of the other variable (sample Xt variable) in explaining the current value of one of the variables (sample Yt variable).[11] It is frequently applied in panel data analysis to determine the direction of the relationship between variables. The most important assumption of this analysis was to ensure the stationarity of the variables. Unit root tests are a widely used method for testing stationarity. Generally, variables are stationary if their mean and variance do not change over time. The most commonly used unit root tests in the literature are ADF tests, PP tests, Im-Pesaran-Shin (IPS) tests, Levin-Lin-Chu (LLC) tests.[9,11-13] For this reason, unit root tests were applied to the variables in order to determine the stationarity status of the variables subject to the research. The results and significance values of these tests were given in Table 3.

Table 3. Unit root tests results

Variables	Level	Levin, Lin and Chu	Breitung t-stat	IM, Pesaran and Shin W-stat	ADF	PP
SDGScore						
	Level					
	Invidual effects	0.9914	-	1.0000	1.0000	1.0000
	Invidual effects and trends	0.4668	0.4305	0.6164	0.7216	0.2915
	None	1.0000	-	-	1.0000	1.0000
	1.diff.					
	Invidual effects	0.0000*	-	0.0000*	0.0000*	0.0000*
	Invidual effects and trends	0.0000*	0.0000*	0.0000*	0.0000*	0.0000*
	None	0.0000*	-	-	0.0004*	0.0000*
Matmort						
	Level					
	Invidual effects	0.0705***	-	0.8749	0.9198	0.2950
	Invidual effects and trends	0.3861	0.3700	0.5514	0.5860	0.0196**
	None	0.0000*	-	-	0.0000*	0.0000*
	1.diff.					
	Invidual effects	0.0038*		0.0000*	0.0000*	0.0000*
	Invidual effects and trends	0.0000*	0.0054	0.0000*	0.0000*	0.0000*
	None	0.0000*	-	-	0.0000*	0.0000*
u5Mort						
	Level					
	Invidual effects	0.0000*	-	0.0029*	0.0007*	0.0000*
	Invidual effects and trends	0.0000*	1.0000	0.0000*	0.0000*	0.9994
	None	0.0155*	-	-	0.0192**	0.0000*
	1.diff.					
	Invidual effects	0.0000*	-	0.0000*	0.0000*	0.9969
	Invidual effects and trends	0.0000*	0.0028*	0.0000*	0.0000*	0.9988
	None	0.0000*	-	-	0.0009*	0.0812***
Trafficmort						
	Level					
	Invidual effects	0.0004*	-	0.6969	0.6625	0.0265**
	Invidual effects and trends	0.8998	0.6413	0.9839	0.9947	0.9473
	None	0.0000*	-	-	0.0000*	0.0000*
	1.diff.					
	Invidual effects	0.0000*	-	0.0000*	0.0000*	0.0000*
	Invidual effects and trends	0.0000*	0.0679***	0.0000*	0.0001*	0.0000*
	None	0.0000*	-	-	0.0000*	0.0000*
NCDmort						
	Level					
	Invidual effects	0.0015*	-	0.9255	0.5996	0.0000*
	Invidual effects and trends	0.6112	0.5240	0.8660	0.9235	0.4281
	None	0.0000*	-	-	0.0000*	0.0000*
	1.diff.					
	Invidual effects	0.0000*	-	0.0000*	0.0000*	0.0000*
	Invidual effects and trends	0.0002*	0.0080**	0.0000*	0.0000*	0.0000*
	None	0.0000*	-	-	0.0143**	0.0000*

*,**,*** significance at %1,%5,%10 level respectively.

According to the unit root test results, the variables become stationary at different levels when the level values and first differences were taken. It was determined that the variables were stationary in common at the I(1) level. For this reason, in the Causality and Co-Integration analyzes conducted in the study, the variables were studied at the I(1) level. The second step after this results was to determine the lag length. According to **Table 4**, the lag lengths of the variables were at the 3rd lag according to the AIC, SC, HQ, LR and FPE. Thus, the lag length of the model was determined as 3rd lag length according to the information criteria.

In **Table 4**, after evaluating that all of the variables were stationary at the I(1) level by the unit root test, the lag length of the model was determined in the VAR model, and the long-term relationships were investigated by Johansen Fisher cointegration analysis between the variables. To test whether there was a long-term relationship between the variables, eigenvalue (max-eigen value) and trace statistics were used. While investigating the long-term relationship between the variables with the Johansen Fisher cointegration test, the 3rd length was applied to determine the lag length of the VAR model. According to the results of Johansen's (1988) cointegration tests; the trace test statistic of the H0 hypothesis (r=0), which states that there was no cointegration between SDGScore and mortality, was found to be 168.80 since this value was greater than the critical value of 69.81 at the 1% significance level, the null hypothesis was rejected. Trace test indicated 5 cointegrating eqn(s) at the 0.05 level.

In the Granger casualty analysis, the lag length of the model was determined as 3rd lag length in VAR model and the results was given in **Table 5**. The results obtained from the diagnostic tests of Granger causality tests showed that there was no heteroscasticity, serial correlation, cross-sectional dependence in the model and that the model did not contain a unit root, and supported the accuracy of the results obtained. According to the Granger causality analysis results, four different causal relationships were identified between the variables subject to the research.

As a result of the causality analysis made after the determination of long-term relationships, variance decomposition was performed in the research model in order to show how much of the SDGScore Index of mortality variables was explained. Variance decomposition investigates the percentage of change in a variable attributable to itself and the percentage attributable to other variables.[14] As can be seen in **Table 6**, SDGscore index variable was determined by its own shocks in the short run under the 100.000 monte carlo simulation. According to this test results; at the end of the 10th period, 90.79% of the SDGscore variable was explained by itself, 1.46% by Matmort, 0.39% by u5Mort variable, 3.41% by Trafficmort variable, and 3.93% by NCDmort variable.

Table 4. Laglength criteria and cointegration test results

A. VAR Lag Order Selection Criteria

Lag	LogL	LR	FPE	AIC	SC	HQ
0	1747.243	NA	1.03e-16	-22.62653	-22.52792	-22.58648
1	1990.503	467.5651	6.03e-18	-25.46108	-24.86946	-25.22076
2	2099.697	202.7889	2.02e-18	-26.55450	-25.46988	-26.11393
3	2168.260	122.8787*	1.15e-18*	-27.12025*	-25.54262*	-26.47942*
4	2186.953	32.28868	1.26e-18	-27.03835	-24.96770	-26.19726
5	2197.244	17.10659	1.53e-18	-26.84732	-24.28366	-25.80597
6	2215.464	29.10588	1.69e-18	-26.75928	-23.70261	-25.51767

B . Cointegration Test

	Eigenvalue	Trace Statistic	0.05 Critical Value	Prob.
None *	0.340430	168.8080	69.81889	0.0000
At most 1 *	0.193681	95.56254	47.85613	0.0000
At most 2 *	0.184009	57.67404	29.79707	0.0000
At most 3 *	0.095212	21.88414	15.49471	0.0047
At most 4 *	0.023995	4.274528	3.841466	0.0387

Trace test indicates 5 cointegrating eqn(s) at the 0.05 level; * Denotes rejection of the hypothesis at the 0.05 level; Roots of Characteristic Polynomial:0.956986-0.098292.

Source: Prepared by the author.

Table 5: Granger casuality/block exogeneity wald tests

Hipotesis	Probability	Result	Interpretation of the result
SDGScore ≠> Matmort	0.2155	Received	
SDGScore ≠> u5Mort	0.0967***	Rejected	
SDGScore ≠> Trafficmort	0.8352	Received	
SDGScore ≠> NCDmort	0.4022	Received	
Matmort ≠> SDGScore	0.4277	Received	SDGScore → u5Mort
Matmort ≠> u5Mort	0.9404	Received	
Matmort ≠> Trafficmort	0.4798	Received	
Matmort ≠> NCDmort	0.0441**	Rejected	
u5Mort ≠> SDGScore	0.8769	Received	Matmort → NCDmort
u5Mort ≠> Matmort	0.6314	Received	
u5Mort ≠> Trafficmort	0.9660	Received	
u5Mort ≠> NCDmort	0.7631	Received	NCDmort → SDGScore
Trafficmort ≠> SDGScore	0.1276	Received	
Trafficmort ≠> Matmort	0.9140	Received	
Trafficmort ≠> u5Mort	0.8046	Received	NCDmort → Trafficmort
Trafficmort ≠> NCDmort	0.1863	Received	
NCDmort ≠> SDGScore	0.0104**	Rejected	
NCDmort ≠> Matmort	0.4059	Received	
NCDmort ≠> u5Mort	0.3519	Received	
NCDmort ≠> Trafficmort	0.0851***	Rejected	

Roots of Characteristic Polynomial:0.956986-0.098292; Serial Correlation LM Tests:0.2332; Residual Portmanteau Tests for Autocorrelations:0.0441; Residual Heteroskedasticity Tests (Levels and Squares): 0.6109; Residual Heteroskedasticity Tests (Includes Cross Terms):0.1850; *,**,*** significance at %1,%5,%10 level respectively. Source: Prepared by the authors.

Table 6. Variance decomposition analysis results of SDGScore variable*

	SDGScore	Matmort	u5Mort	Trafficmort	NCDmort
1	100.00	0.00	0.00	0.00	0.00
2	95.50	0.75	0.16	0.75	2.81
3	93.97	1.02	0.36	1.26	3.36
4	91.19	1.34	0.35	3.26	3.83
5	91.04	1.35	0.36	3.39	3.84
6	90.94	1.44	0.37	3.39	3.84
7	90.84	1.44	0.37	3.40	3.92
8	90.82	1.45	0.37	3.42	3.93
9	90.81	1.46	0.38	3.41	3.93
10	90.79	1.46	0.39	3.41	3.93

*Estimated under 100.000 monte carlo simulation. Source: Prepared by the author.

Impulse-response functions reveal the effects of shocks on variables and their effects at what time, with the help of tables or graphics. With this process, it is understood in which variable the shocks occur and how the variables will react to these shocks. In order to determine how the shocks will occur, the movements of the variables within 10 periods were examined first under the 100.000 monte carlo simulation. The reactions of the other series against a 1-unit change in the shocks occurring in the variables were revealed with the help of graphs.[14] As seen in **Figure 2**; a standard deviation shock given to the Matmort variable negatively affected the SDG score index until the middle of the 4th period; while it turned positive halfway through the 5th period; it turned negative till the 7th period; then turned positive starting from the 7th period, and was continued until the end of the period. While a standard deviation shock given to the u5mort variable affected the SDGScore variable positively from the 1st period to at the end of the 10 period. A standard deviation shock given to the NCDmort variable negatively affects the SDG score variable till the beginning of the second period. However, it had a positive effect on the SDG score variable from the 2nd period to the beginning of the 5th period then the negative effect, was seen between the 5th and 6th periods, and from the 6th periods it turned positive at the end of the 10 periods. A standard deviation shock given to the Trafficmort variable negatively affects the SDG score variable till the beginning of the second period, and from the 2nd periods it turned positive at the end of the 10 periods.

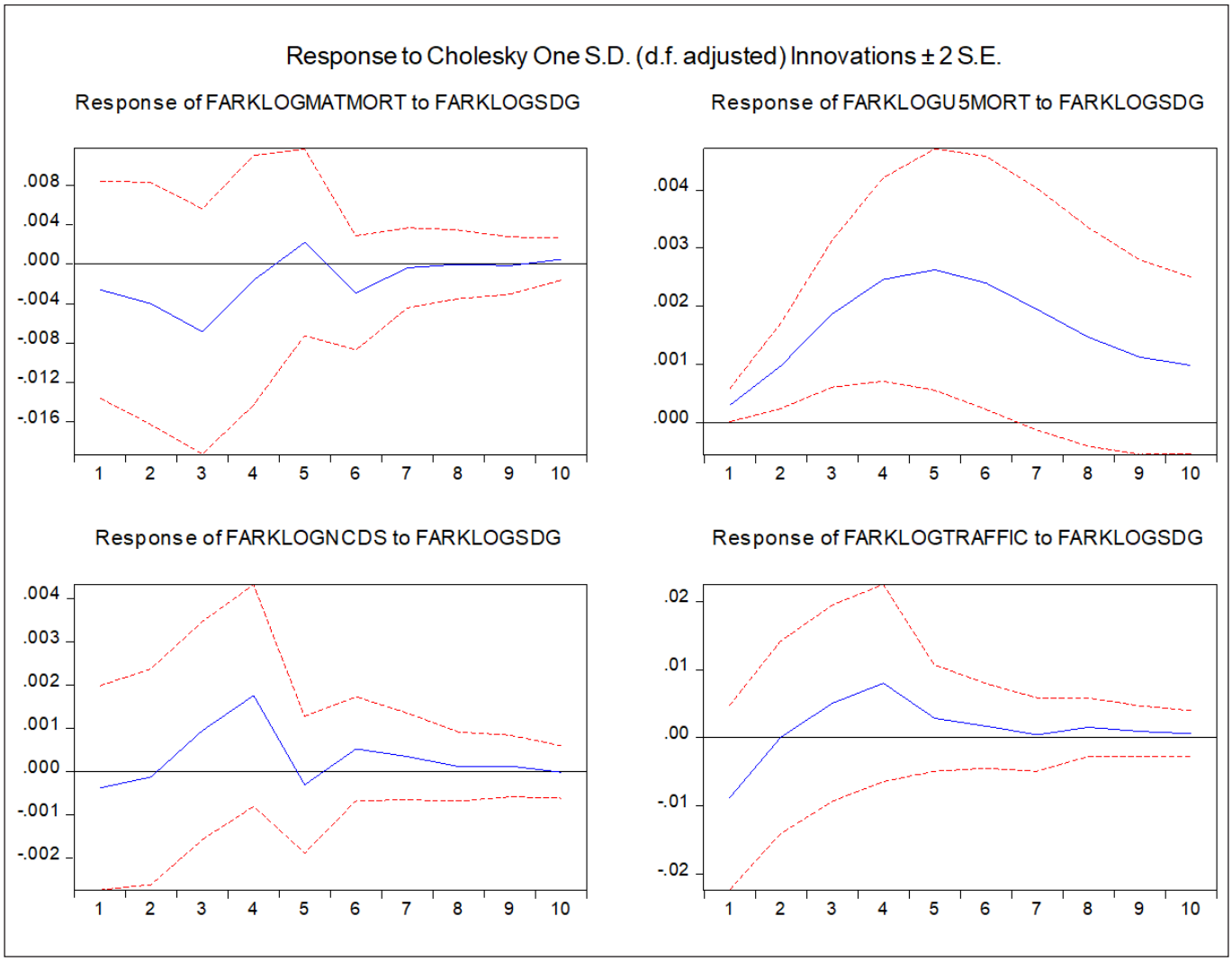

Figure 2. Effect of shock in mortality variables on SDGScore variable*
*Estimated under 100.000 monte carlo simulation.

DISCUSSION

Within the scope of this research, the relationship between health and development was investigated. In this context, the relationship between health indicators such as maternal mortality, mortality under the age of five, traffic mortality, NCD mortality, and the Sustainable Development Indicators Index score was examined. According to the questions determined in the study;

- **Q1:** What was the level of impact of mortality on sustainable development goals?

According to the results of the least squares analysis, a 1% increase in maternal mortality reduced the sustainable development index score by 0.021%; a 1% increase in u5mortality reduced the sustainable development index score by 0.037%; a 1% increase in NCD mortality reduced the sustainable development index score by 0.044%; a 1% increase in traffic mortality reduced the sustainable development index score by 0.016% ($p<0.01$).

- Q2: How did mortality affect sustainable development goals?

Co-integration tests, in which the long-term relationships between the variables were examined in the study, revealed that there was a long-term relationship between mortality and development indicators. Besides these results unidirectional Granger-type causality was determined i) from SDG score index towards u5 mortality ii) from NCD mortality towards SDG Score Index iii) from Maternal mortality towards NCD mortality iv) from NCD mortality towards Traffic mortality.

Additionally the variance decomposition results mortality explained the SDG score in the long term, and shocks in mortality affected the SDG score negatively. In light of these results, the main hypothesis of the study was accepted as "Sustainable development goals were related to mortality" and this effect was negative. Therefore, according to the empirical evidence obtained from the research, the increase in mortality decreased the SDG index score in the countries subject to the analysis.

SDG index score means development in a country and is related to the per capita income, education level, and improvements in the health status of the people of that country. Health is a factor that contributes to the development of human capital and directly affects economic growth. Good health indicates a high-value source of well-being around the world. Health is not only the absence of disease but also the capacity of the individual to develop his abilities and skills. Health reduces production losses due to diseases, reduces absenteeism from school, improves learning, and enables the use of financial resources allocated for treatment in different ways.[15] Ensuring the productivity of a healthy individual with a good education provides important contributions to the economic growth of that country and therefore to its development. In a healthy society, productivity increases, and economic growth is positively affected due to the good quality of human capital.[16] For example, malnutrition in the newborn and infancy periods negatively affects the child's chances of survival and social development. In the long term, this situation negatively affects the economic and cultural development of countries.[17] In the development of societies, premature deaths due to mother-infant-traffic accidents and chronic diseases affect the economies of the countries negatively and this situation has a negative impact on economic development. The literature stated that maternal–child health should be associated with the emerging issues of long-term development, human capital, and economic growth.[18] Also NCDs have a negative impact on individual health, family budgets, and national employment. It should also be noted that NCDs are closely linked to other SDGs.[6] For example, in the relationship between country income and child mortality, it is mentioned that child deaths are lower in high-income countries than in low-income countries, so the effect of country income on mortality rates is reduced. In other words, it is claimed that rich countries have longer and higher quality life expectancies and lower mortality rates.[19] Poverty was increasingly associated with poor health outcomes that include maternal mortality.[20] In a study evaluating the relationship between socio-demographic, maternal, obstetric, and neonatal factors associated with neonatal deaths, it was determined that reducing inequalities in maternal and newborn care will also reduce the mortality rate among the poorest families. If the current trend continues, it will take another 50 years for families in the poorest group to reach the 2030 Every Newborn Action Plan (ENAP) target.[7] In one study, since 1990, progress has been made toward SDG targets in Somalia (such as prolonging life expectancy, reduction in maternal and infant mortality), but it has also been emphasized that more improvements are needed in health systems to achieve better results.[21] Research from 33 Western Pacific countries demonstrates the importance of public health law in supporting the achievement of health-related SDGs.[22] From this perspective it is stated that reaching the goals determined by the sustainable development goals was effective on the health of individuals and the death rate was reduced and literature generally accepted that there was a sustainable greater effort needed to be improving health SDG.[21,23-25] Efforts for healthcare systems to reduce mortality include i) increasing the education of the society on healthy aging, prevention from accidents, protecting and improving maternal and child health, ii) providing individuals with healthy life skills to reduce chronic disease burdens, iii) ensuring universal health coverage globally, iv) strengthening health financing, v) reducing poverty, vi) evaluating indicator results with transparency, vii) health supporting and developing related public and private partnerships.

Limitations

In addition, the limitations of this study were the time dimension of this research (2000-2020), the countries covered in the research, the variables determined as the research subject, the type of indicator taken into account in the calculation of the variables (maternal mortality rate, under-five child mortality, NCD mortality, deaths coused from traffic).The method used was also evaluated as its limitations. It is thought that the results obtained from this research can be used for comparison purposes in future studies, and analysis with different countries, time periods, variables, and different methods will contribute to the literature.

CONCLUSION

According to the empirical evidence obtained from the research, the increase in mortality affects the SDG Index score in the countries subject to the analysis negatively. Mortality rates were a significant problem in all countries. A well-educated and healthy human capital structure is a basic requirement for the sustainable development of countries. The results of this research explain that long-term mortality rates account for approximately 10% of all sustainable development-related indicators, emphasizing that a healthy social structure is a fundamental requirement for the sustainable development of countries. Therefore, within the framework of the results obtained from this research, countries can prioritize health-related indicators among the targets to be prioritized in their evaluations of development goals.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was designed retrospectively with using secondary data so ethical approval was not required.

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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Original Article

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Pelvic incidence effects pars interarticularis defect and spondylolisthesis

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ABSTRACT

Aims: Pars interarticularis defect (PID) is a common problem in society and may be accompanied with low back pain and radiculopathy. Magnetic resonance imaging (MRI) can detect it with high sensitivity. If left untreated, it may progress to spondylolisthesis. In this study, we wanted to emphasize the importance of the pelvic incidence (PI) angle in terms of following the development of spondylolisthesis after PID by examining the relationship between PID and spondylolisthesis and PI.

Methods: 118 patients who applied to Şanlıurfa Training and Research Hospital between 2021-2022 and underwent lumbar MRI were included in the study. The criteria for inclusion of patients in the study were the detection of a pars interarticularis defect on MRI, the ability to be evaluated by direct radiography or CT, and the ability to monitor the femoral head and sacrum in a way that PI could be measured. PI angle measurement was performed, confirmed by CT. The relationship between PID, spondylolisthesis and PI was examined.

Results: Of the 118 patients participating in the study, 77 (65.3%) were women and 41 (34.7%) were men. Pars defect was most commonly seen at the L5 level (67.8%). The average pelvic incidence angle is 64.2±8.6. Half of the patients were calculated as Meyerding grade 0 and 95.8% were treated medically. The median pelvic incidence angle value of patients without spondylolisthesis was found to be 58.0, the median pelvic incidence angle value of patients with a Meyerding grading of one was found to be 68.0, and the median value of the pelvic incidence angle of patients with a Meyerding grading of one was found to be 78.0 ($p<0.001$).

Conclusion: In this study, we detected patients with PID with MRI and revealed that there is a significant relationship between high PI degree and PID and spondylolisthesis. When high PI is detected in patients with PID, predicting that spondylolisthesis may develop in these patients is an important finding that will shape follow-up and treatment.

Keywords: Pars interarticularis, spondylolisthesis, pelvic incidence

INTRODUCTION

Pars interarticularis is located between the superior and inferior articular facet. Pars interarticularis defect (PID) is a problem that is seen in 3-10% of the population and frequently causes low back pain and radiculopathy.[1] Its incidence varies with age, gender, genetic factors and activity. Its incidence increases with age, and it is 2-3 times more common in men than in women. While its incidence in the Eskimo population can reach 50%, it can be seen in 47% of athletes presenting with back pain.[2] It can be unilateral or bilateral. In studies, it was most frequently detected at the L5 level.[1] Microtraumas during repetitive lumbar extension have an important place in its pathophysiology.[3]

Radiography, computed tomography (CT) and magnetic resonance imaging (MRI) are radiological methods frequently used to detect PID. Anteroposterior and lateral radiographs have lower sensitivity than CT. MRI has similar sensitivity to CT.[1,4] The fact that CT does not show radiation exposure and soft tissues as well as MRI is one of the reasons why MRI is preferred more frequently in patients presenting with low back pain and radiculopathy. In addition, MRI shows bone marrow edema better in the early stages.[5,6]

While PID does not cause listhesis in 30-50% of patients, isthmic spondylolisthesis can be seen in 50-70% of patients.[3] Many pelvic parameters have been investigated, but strong evidence has been presented that there is a relationship between pelvic incidence (PI) and PID and spondylolisthesis. PI is a personal and fixed pelvic parameter that determines lumbar lordosis and pelvic orientation.[7] In those with high PI degrees, it is expected that the force on the pars interarticularis during extension will increase due to hyperlordosis and more PID will

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occur. This causes isthmic spondylolisthesis to be more common.[8] The relationship between spondylolisthesis and pelvic parameters has been examined in many publications in the literature, but there are few studies examining PID and spondylolisthesis and pelvic parameters. With this study, we wanted to contribute to the literature by examining PID and spondylolisthesis detected by MRI and the relationship between these findings and PI in patients presenting with low back pain and radiculopathy.

METHODS

The study was approved by the Harran University Clinical Researches Ethics Committee (Date: 13.11.2023, Decision No: HRÜ/23.21.16) and because the study was designed retrospectively, no written informed consent form was obtained from patients. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study was planned as a retrospective cohort study. The data of the patients who applied to the Neurosurgery outpatient clinic of Şanlıurfa Training and Research Hospital between 2021-2022 and who underwent lumbar MRI due to complaints of low back pain and radiculopathy were examined, and patients whose data were suitable were included in the study. 118 patients who applied to the outpatient clinic between 2021-2022 were included in our study. The criteria for inclusion of patients in the study were the detection of a pars interarticularis defect on MRI, the ability to be evaluated by direct radiography or CT, and the ability to monitor the femoral head and sacrum in a way that PI could be measured. Patients over the age of 18 were included in the study and the pediatric population was excluded.

Three stages were taken into account when investigating PID; early, progressive and terminal stages. Although there are different classifications, in this study the classifications were taken into account only when examining the images to prevent the pars defect from being overlooked, and no statistical information was created regarding this condition. In CT images, a thin fissure line and sharp boundaries were observed in the early stage, a wider fissure line was observed in the progressive stage, while the appearance of pseudoarthrosis was taken into account in the terminal stage. MRI is more effective in showing defects that cannot be detected by CT at a very early stage, but since STIR sequence or fat-suppressed sequence was not performed in all patients in our study, information on this subject could not be provided. In the early stages of the defect, low signal intensity is observed in the T1 sequence and higher signal intensity in the T2 sequence, while as fracture healing progresses, low signal intensity is observed in both sequences.

PI (the angle between the line drawn from the center of the femoral head to the midpoint of the sacral endplate and the line drawn perpendicularly from the midpoint of the sacrum) was evaluated by lateral radiography. If the femoral head could not be evaluated clearly and appeared bilateral, the midpoint of the line drawn from the midpoint of both femoral heads was taken into account. Meyerding grading was used in the grading of spondylolisthesis. Since no Meyerding grade 4 patients were identified, they were examined by grouping them as Meyerding 0 (no spondylolisthesis), 1, 2-3.

SPSS 29.0 program was used in statistical analysis. Descriptive analyzes were performed and continuous variables were presented as mean, standard deviation, median and 25-75th percentile values. Normal distribution analyzes of continuous variables were evaluated with Shapiro-Wilk analysis and it was determined that all of them did not comply with normal distribution. Three patients with pars defects detected in both L4 and L5 were included in the L5 group in statistical analysis. For statistical comparisons, the chi-square test was used for categorical variables and the Mann-Whitney U test was used for continuous variables. The change between pelvic incidence angle and Meyerding grading is shown with a boxplot graph. The limit of statistical significance was accepted as a p value of less than 0.05.

RESULTS

77 women (65.3%) and 41 men (34.7%) were included in the study. The average age of the participants is 46.5±13.7. Pars defect was most commonly seen at the L5 level (67.8%). The average pelvic incidence angle is 64.2±8.6. Half of the patients were calculated as Meyerding grade 0 and 95.8% were treated medically. The defect was found to be unilateral in only 4 of the patients participating in the study (**Table 1**).

No relationship was found between gender, pelvic incidence angle and pars defect level. The median age of patients with pars defects at the L3-L4 level was 56.0, while the median age of those with pars defects at the L5 level was 41.0. The detected difference is statistically significant ($p<0.001$). Meyerding grade 2 or higher was detected in 5.7% of the patients with pars defects at the L3-4 level and 20.5% of the patients with the L5 level ($p=0.046$) (**Table 2**).

The median pelvic incidence angle value of patients without spondylolisthesis was found to be 58.0, the median pelvic incidence angle value of patients with Meyerding grading 1 was 68.0, and the median value of the pelvic incidence angle was found to be 78.0 in patients with Meyerding grading 2 and above ($p<0.001$) (**Table 3**). The change in pelvic incidence angle with the Meyerding grade is shown in **Figure 1**.

Table 1. Descriptive analyzes of the variables included in the study

Variables	n	%
Gender		
Female	77	65.3
Male	41	34.7
Age, years		
Mean±SD	46.5±13.7	
Median (25-75 p)	48.0 (36.0-58.25)	
Pars defect level		
L3	4	3.4
L4	31	26.3
L4 L5	3	2.5
L5	80	67.8
Pelvic incidence		
Mean±SS	64.2±8.6	
Median (25-75 p)	63.0 (58.0-70.0)	
Meyerding grade		
0	60	50.8
1	39	33.1
2	15	12.7
3	4	3.4
Treatment		
Surgical	5	4.2
Medical	113	95.8
Side		
Unilateral	4	3.4
Bilateral	114	96.6

Table 2. Comparison of variables with pars defect level

Pars defect level	L3-4		L5		p
	n	%	n	%	
Gender					0.946
Female	23	65.7	54	65.1	
Male	12	34.3	29	34.9	
Age, years Median (25-75 p)	56.0 (44.0-60.0)		41.0 (33.0-57.0)		<0.001
Pelvic incidence Median (25-75 p)	61.0 (56.0-67.0)		64.0 (58.0-72.0)		0.105
Meyerding grade					0.046
0-1	33	94.3	66	79.5	
2-3	2	5.7	17	20.5	
Meyerding grade					0.091
0	18	51.4	42	50.6	
1	15	42.9	24	28.9	
2-3	2	5.7	17	20.5	

Table 3. Relationship between pelvic incidence score and meyerding grade

Pelvic incidance	Median	25-75 p	p
Meyerding grade			<0.001
0	58.0	54.0-60.75	
1	68.0	65.0-70.0	
2-3	78.0	78.0-80.0	

Mann-Whitney U Test was used.

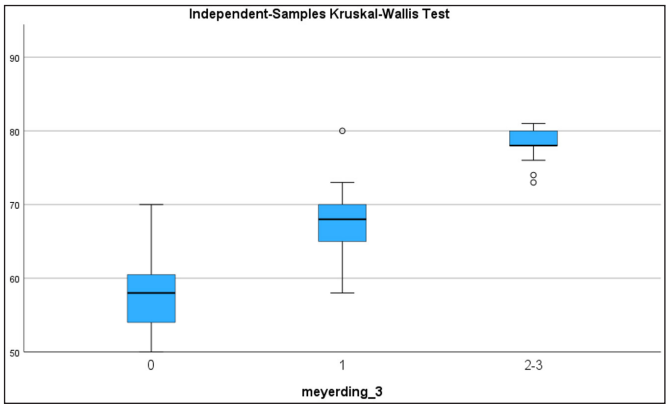

Figure 1. Pelvic incidence angle change with Meyerding grade

DISCUSSION

Pars interarticularis defect and spondylolisthesis is a problem whose prevalence in the population varies between 3-10%, and its frequency can reach 78% depending on activity participation. Although it is more common in men than women in studies, this is entirely related to activity, and in our study, the incidence was found to be higher in women (65.3%).[1,9] Micheli et al.[10] They recorded a 47% incidence rate in their study of athletes with back pain. Similar studies have shown that the incidence of pars defects increases with activity participation.[1] In the region where we conducted this study, women work as agricultural workers and, accordingly, it is detected more frequently in female gender. It is thought to have been done. Although the rate was higher in Sairyo et al.'s[6] studies on CT, in a study they conducted on MRI, they detected a defect at the L5 level in 66.3% of the patients.[5,11] In our study, similar to the literature, 67.8% of the patients had a defect. PID was detected at the L5 level in 32.2% of patients, and at L3 or L4 levels in 32.2%. The rate of unilateral PID was found to be 3.4%, which is similar to the literature.[12]

Many radiological methods are used in the diagnosis of PID. Although CT is better at showing bone tissue, it is not as sensitive as MRI in showing the processes of the nerve root, intervertebral disc and pars defect. However, there is high radiation exposure.[6,13] Rush et al.[14] In their study on 26 patients, they detected 36 PIDs with MRI, but they could not detect 3 PIDs that could be detected with CT. Saifuddin et al.[15] found the sensitivities of MRI and CT to be similar in their study. Masci et al.16 in their study, the sensitivity of MRI; They found it to be 80% when compared with scintigraphy and 94.74% when compared to CT. When all these studies were examined; MRI has similar but lower sensitivity than CT and scintigraphy in diagnosing PID. In addition, it is an imaging method frequently used in polyclinics because it does not emit radiation and is successful in revealing other pathologies. We did not aim to reveal the sensitivity

of MRI or its differences with other imaging methods in our study. We wanted to diagnose a common problem in society with an imaging method that we frequently use and examine its relationship with PI. Therefore, only MRI examinations were examined, patients with PID were confirmed with CT, and their relationship with Meyerding grading and PI were examined through imaging.

PID, which occurs due to recurrent microtrauma or another reason, progresses naturally with pseudoarthrosis if there is no recovery. This condition causes instability and may progress to isthmic spondylolisthesis. Since high Meyerding grades are associated with mechanical instability, they increase the likelihood of symptoms and the need for surgery in the patient.[17,18] Predicting which patients will develop spondylolisthesis after PID develops can play an important role in the follow-up and treatment of patients. Studies have been conducted on pelvic parameters, but no parameter other than PI has been shown to be related to PID and spondylolisthesis.[19,20] In their study, Legaye et al.[21] found that there was a relationship between spinal sagittal alignment and PI. Hanson et al.[22] in their study, the mean PI was found to be 47.4° in the pediatric control group, 57° in the adult control group, 68.5° in the low-grade isthmic spondylolisthesis group, and 79.0° in the high-grade isthmic spondylolisthesis group. Significantly higher pelvic incidence values were detected in both the low-grade and high-grade isthmic spondylolisthesis groups than in the adult or pediatric control groups (P=0.001). The pelvic incidence of the high-grade group was found to be significantly higher than the low-grade group (P=0.007). In this study, spondylolisthesis was not detected in 50.8% of the patients. In our study, we found the mean PI value to be 64°. The average PI was 58° in patients without spondylolisthesis, 68° in low-grade listhesis patients, and 78° in high-grade listhesis patients. PI value was found to be significantly higher in patients with high-grade spondylolisthesis (P=<0.001). PI values were found to be significantly lower in the patient group without spondylolisthesis (P=<0.001). The rate of patients to whom we applied surgical treatment was found to be 4.2%.

The fact that we planned to study only by evaluating MRI is one of the limiting points of our study. However, we found this to be negligible, considering that it has similar sensitivity to CT and is a more frequently used method. The fact that thin-section MRI and fat-suppressed sequence were not performed in all patients may have caused patients with early-stage PID to be overlooked. To overcome this limitation, we included only the adult patient population in our study.

CONCLUSION

PID is a condition that is frequently detected incidentally in the population and can cause low back pain and radiculopathy. Most patients do not require surgical treatment. It can be detected with high sensitivity by CT and MRI. Sagittal spinopelvic balance directly affects all anatomical segments it is associated with. In this study, we demonstrated that there is a significant relationship between high PI degree and PID and spondylolisthesis. When high PI is detected in patients with PID, predicting that spondylolisthesis may develop in these patients is an important finding that will shape follow-up and treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Harran University Clinical Researches Ethics Committee (Date: 13.11.2023, Decision No: HRÜ/23.21.16).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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Original Article

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The effects of smartphone addiction on sleep quality and obesity level in obese men

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ABSTRACT

Aims: To investigate the effects of smartphone addiction on sleep quality and body mass index (BMI) values in obese men.

Methods: During the study period, 90 men aged 18 to 45 years who were monitored for obesity, presented to the hospital, and agreed to participate in the study were recruited. The study statistically evaluated sleep quality and factors affecting it using patient demographic characteristics, the Pittsburgh Sleep Quality Index (PSQI), the Smart Phone Addiction Scale (SPAS), and the Hospital Anxiety-Depression Scale (HADS).

Results: Patients were divided into two groups according to PSQI score: PSQI ≥5 n:51 (56.7%) and PSQI <5 n:39 (43.3%). The association between PSQI scores and age, body mass index (BMI), educational status, HADS-A, and HADS-D, SPAS, was examined. HADS-A, and HADS-D, SPAS scores were higher in the group with poor sleep quality ($p<0.001$). In addition, a high smartphone addiction score was found to increase the presence of PSQI ≥5 12-fold. It was shown that BMI values were higher in patients with high SPAS ($p< 0.030$).

Conclusion: Poor sleep quality and smartphone addiction appear to influence BMI in obese individuals. Studies to improve sleep quality are very important to identify modifiable risk factors, improve the design of prevention programs, and reduce the prevalence of obesity in the young population.

Keywords: Sleep quality, obesity, smartphone addiction, depression, anxiety

INTRODUCTION

Obesity is global public health problem is estimated to be largely responsible for increased mortality from cardiovascular disease and cancer. Obesity is a multifactorial disease in which many behavioral, environmental, genetic, metabolic and sociocultural factors play a role.[1,2]

Recent studies have shown that the development of sleep problems parallels the development of obesity.[3,4] Adequate and quality sleep is very important for overall health. Lack of sleep contributes to obesity by triggering metabolic, hormonal and behavioral steps that increase dietary energy intake and decrease energy expenditure.[4-6] Meta-analyzes confirm that poor sleep quality and duration are associated with higher positive energy balance, leading to higher body mass index (BMI).[7-9]

Many factors affect sleep quality and duration, and one of the rapidly evolving factors may be the increasing use of technology, particularly smartphone addiction.

Cell phone addiction is a rapidly growing factor that affects physical and mental health. There are several reasons why cell phone addiction leads to shorter sleep duration or less sleep.[10] Cell phones are now used not only to make phone calls, but also to text, surf the internet, play mobile games, or use social networks. These behaviors can lead to short nights' sleep and disturbed sleep patterns in cell phone addicts.

Thank you to the capabilities offered by smartphones; our daily lives have become very convenient and easy. However, this leads to significant changes in people's lifestyles. As conditions such as a changing diet and lack of exercise increase daily, the incidence of obesity continues to rise. This is a widespread and important health problem, not only in our country but worldwide.

The aim of our study was to investigate the effects of smartphone addiction on BMI values and sleep quality in obese individuals. In the literature, studies on the relationship between smartphones, which we frequently

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use today, obesity and sleep quality are limited. For this reason, the subject of the research can be a pioneer for other researches in the future.

METHODS

The study was carried out with the permission of Ethics Committee of the Ministry of Health and Scientific Research of Haydarpaşa Numune Training and Research Hospital (Date: 18.04.2022, Decision No: HNEAH-KAEK 2022/85). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Consecutive obese individuals aged 18 to 45 years who used a smartphone during the study period (May-September 2022), who agreed to participate were included. The study's participants gave their written informed consent. The World Health Organization (WHO) defines obesity as excessive fat accumulation in the body to a degree that adversely affects health.[11] Obesity was described by a BMI of 30 or more.[12]

Participants were informed about the study in advance. Individuals with a BMI of 30 or more who agreed to participate in the study and were cooperative were included. Individuals with a known sleep disorder diagnosis, individuals on medication to treat a sleep disorder any other psychiatric and endocrine disorder, and individuals working shift work were excluded from the study. To measure smartphone addiction, an interview-based semi structured questionnaire, which asked for sociodemographic characteristics of patients (age, gender, height, weight, educational status, comorbidity, etc.), and the smart phone addiction scale were used. The Pittsburgh sleep quality index (PSQI) scale was used to assess patients' sleep quality, and the hospital anxiety and depression scale (HADS) was completed to assess emotional state.

Assessment Scales

Sociodemographic questionnaire: Patients were asked about age, gender, educational status, marital status, additional disease, height, and weight. Values were recorded by calculating BMI.

Smart phone addiction scale: The Smart Phone Addiction Scale (SPAS) is a scale developed by Kwon et al.[13] based on Young's Internet Addiction Scale and characteristics of smartphone use. The Smart Phone Addiction Scale consists of 33 items. It is a Likert scale. Demirci's research and studies were used to determine its translation from English to Turkish and its validity and reliability.[14] In this study, the mean SPAS score of smartphone users was found to be greater than or equal to 76. Individuals with high scores are considered risky smartphone users (high smartphone users), whereas individuals with low scores are not considered risky smartphone users (low smartphone users).

Pittsburgh sleep quality index (PSQI): The PSQI, a reliable and consistent test, was used to determine patients' sleep quality during the past month (α= 0.77).[15] The PSQI, which includes 19 questions and allows us to assess sleep quality, amount of sleep, presence and severity of sleep disorders, was completed by the same physician during individual patient interviews. The PSQI consists of seven questions assessing subjective sleep quality, sleep duration, sleep efficiency, sleep delay, sleep disorder, use of sleeping pills, and interference with daytime work. Each response is assigned a score between 0 and 3 according to symptom frequency. The total score ranges from 0 to 21, with high scores indicating poor sleep quality and high levels of sleep disorder. A total score of 5 or more clinically indicates significantly poorer sleep quality. Diagnostic sensitivity is 89.6% and specificity is 86.5%. Agargün et al.[16] adapted the PSQI questionnaire to Turkish patients.

Hospital anxiety and depression scale (HADS): This scale was developed by Snaith and Zigmond.[17] The reliability and validity of the Turkish version was confirmed by Aydemir et al.[18] It is easy to use because it is short and understandable. There are 14 items in total. Seven of the 14 questions (odd numbers) measure anxiety and seven (even numbers) measure depression. Responses are rated on a four-point Likert scale ranging from 0-3. The lowest score patients can achieve on both subscales is 0 and the highest is 21. The cut-off points of the Turkish version of the HADS were set at 7 for the depression subscale (HAD-D) and 10 for the anxiety subscale (HAD-A). Accordingly, those who score above these levels are considered to be at risk.

Statistical Analysis

Statistical analyzes were performed using the SPSS version 25.0 program. Histogram plots and the Kolmogorov-Smirnov test were applied to examine the fit of the variables to the normal distribution. Mean, median, standard deviation, and min-max values were used to present descriptive analyzes. Categorical variables were compared using the chi-square test. The Mann-Whitney U test was implemented to evaluate nonnormally distributed (nonparametric) variables between two groups. The Kruskal-Wallis test was implemented when more than two groups were to be compared. The Spearman correlation test was performed to analyze the measurement data between groups. Binary logistic regression analysis was used to examine the factors affecting the presence of poor sleep on the PSQI. Cases with a P-value less than 0.05 were considered statistically significant results.

RESULTS

Ninety men aged 19-33 years (mean 24.36±3.03) were included in our study.

10% (n=9) of participants had a secondary school degree, 53.3% (n=48) had a high school degree, and 36.6% (n=33) had a university degree.

No additional disease was present in 86.6% (n=78) of the study participants. The mean BMI of the participants was 39.79±3.99, and 48 (53.3%) of the participants had a SPAS score of 76 or more. Patients were assessed for anxiety and depression using the HAD scale. 28 (31.1%) individuals were above the HADS scale threshold for anxiety (HADS-A) and 42 (46.7%) for depression (HADS-D) (Table 1).

Table 1. Demographic characteristics of participants

	n	%
Age	24.36±3.03	24 (19-33)
BMI	39.79±3.99	39.65 (31.4-50.6)
Educational Status		
Middle school	9	(10)
High school	48	(53.33)
University	33	(36.67)
Additional Disease		
Absent	78	(86.67)
Present	12	(13.33)
Marital Status		
Single	64	(71.11)
Married	26	(28.89)
Employment Status		
Unemployed	41	(45.5)
Employed	49	(54.5)
PSQI	6.11±3.62	5 (0-14)
<5	39	(43.33)
≥5	51	(56.67)
SPAS	78.98±28.11	76 (36-153)
<76	42	(46.67)
≥76	48	(53.33)
HADS-A	8.03±4.08	7.5 (0-16)
Anxiety		
Below the threshold (0-10 points)	62	(68.89)
Above the threshold (11-21 points)	28	(31.11)
HADS-D	7.02±4.09	6 (0-16)
Depression		
Below the threshold (0-7 points)	48	(53.33)
Above the threshold (8-21 points)	42	(46.67)

Patients were divided into two categories according to PSQI scores: PSQI ≥5 n=51 (56.7%) and PUKI <5 n=39 (43.3%). The association between PSQI scores and age, BMI, educational status, marital status, employment status, SPAS, HADS-A, and HADS-D was examined. Those with high SPAS and those with HAD anxiety and depression scores above threshold had higher rates of PSQI ≥5. In addition, those with a PSQI ≥5 had higher SPAS, HADS-A, and HADS-D scores (p< 0.01, p< 0.01, p=0.02) (Table 2).

Table 2. Comparative assessment of groups in terms of demographic characteristics according to sleep quality

	PSQI		p
	<5 median±SD/n	≥5 median±SD/n	
Age	24.23±2.92	24.45±3.14	0.740[1]
BMI	38.93±3.7	40.45±4.12	0.072[1]
Educational Status			0.258[2]
Middle school	2	7	
High school	24	24	
University	13	20	
Additional Disease			0.009[2]
Absent	38	40	
Present	1	11	
Marital Status			0.416
Single	25	38	
Married	13	13	
Employment Status			0.042[2]
Unemployed	13	28	
Employed	26	23	
SPAS	61.23±17.93	92.55±26.98	<0.001[1]
<76	31	11	<0.001[2]
≥76	8	40	
HADS-A (Mean ± SD)	5.97±3.2	9.61±4	<0.001[1]
Anxiety			<0.001[2]
Below the threshold (0-10 points)	36	26	
Above the threshold (11-21 points)	3	25	
HADS-D (Mean ± SD)	5.46±3.63	8.22±4.06	0.002[1]
Depression			<0.001[2]
Below the threshold (0-7 points)	29	19	
Above the threshold (8-21 points)	10	32	

[1]Mann-Whitney U Test [2] Chi-Square Test

The correlation between age, BMI, SPAS, HADS-D and HADS-A scores, and PSQI score was examined. Accordingly, there was a statistically significant relationship has been identified between PSQI and BMI, SPAS, HADS-A, and HADS-D scores (p<0.05) (Table 3).

Table 3. Sleep quality correlation

	Age	BMI	SPAS	HADS-A	HADS-D
PSQI					
r	0.117	0.279	0.603	0.516	0.400
P	0.271	0.008	<0.001	<0.001	<0.001

Spearman Correlation Test

When examining the factors that affect poor sleep quality on PSQI, a SPAS≥76 was found to increase the presence of PSQI ≥5 12.4 fold (p<0.001) (Table 4).

Table 4. The factors that affect poor sleep quality

	B	S.E.	p	Exp(B)	95% C.I. for EXP(B)	
					Lower	Upper
Additional disease	0.984	1.202	0.413	2.674	0.254	28.187
SPAS	2.520	0.580	<0.001	12.428	3.986	38.749
Anxiety	1.492	0.916	0.103	4.447	0.739	26.758
Depression	0.731	0.709	0.302	2.078	0.518	8.336

Binary Logistic Regresyon

Significant results were obtained when comparing between SPAS groups. Accordingly, to convey that the number of individuals who were single in terms of 'marital status', BMI, PSQI, and HADS-A scores were significantly higher in those with SPAS≥76 (p=0.001, p=0.030, p<0.001, p=0.017) (Table 5).

Table 5. Comparative assessment of groups in terms of demographic characteristics according to smarthphone addiction

	SPAS		p
	<76 median±SD/n	≥76 median±SD/n	
Age	24.57±2.98	24.17±3.09	0.338[1]
BMI	38.85±3.97	40.61±3.87	0.030[1]
Educational status			
Middle school	5	4	0.758[2]
High school	23	25	
University	14	19	
Marital status			
Single	23	41	0.001[2]
Married	19	7	
Employment status			
Unemployed	14	27	0.029[2]
Employed	28	21	
PSQI	3.86±2.27	8.08±3.43	<0.001[1]
<5	31	8	<0.001[2]
≥5	11	40	
HADS-A	6.81±3.47	9.1±4.3	0.017[1]
Anxiety			0.006[2]
Below the threshold (0-10 points)	35	27	
Above the threshold (11-21 points)	7	21	

[1]Mann-Whitney U Test [2] Chi-Square Test

In the analysis of SPAS and PSQI scores according to the working status of the participants, a statistically significant difference was found between the working status variable (p<0.05) (Table 2-5).

DISCUSSION

In our study, 51 of 90 obese patients were found to have poor sleep quality. It was determined that the frequency of anxiety and depression was high in the group with poor sleep quality. Body mass index was higher in those with high cell phone addiction. Poor sleep quality, BMI, cell phone addiction, anxiety, and depression were found to be correlated in the same direction.

Obesity is a global public health problem that is estimated to be primarily responsible for increased mortality from cardiovascular disease and cancer.[1,2] Recent estimates indicate that the prevalence of obesity has doubled worldwide since 1980.[19] This obesity epidemic is accompanied by a trend toward shorter sleep duration and poorer sleep quality in modern society.[20] Poor sleep quality and length are associated with obesity, according to an increasing corpus of research.[20,21] A key regulator of hormonal activity is sleep. Glucose metabolism and sleep loss have led to metabolic and endocrine changes, including decreased glucose tolerance and alterations in appetite-regulating hormones.[22,23] Sleep quality affects energy balance via appetite, gut peptide concentrations, hypothalamic-pituitary-adrenal axis activity, and substrate oxidation. Poor quality sleep results in hormonal shifts like lower leptin and greater ghrelin concentrations, which improve positive energy balance, leading to excessive food intake and weight gain.[24] High BMI and waist circumference were significantly correlated with poor sleep quality, according to Jennings, Muldoon, and Hall's 2007 study.[25] Rahe et al.[26] found a significant connection between obesity and a poor quality sleep. Sleep problem is a significant risk factor for obesity, according to a research involving almost 140,000 participants.[27] Defined poor sleep quality as a risk factor for obesity and found that 100% of the morbidly obese people who participated in their study had poor sleep quality.[26] In a study conducted by Vargas et al.[9] with university students, it was found that being slightly overweight increased the risk of sleep disorders by 1.66 times. Our study showed that 56.7% of obese individuals had poor sleep quality and there was a positive correlation with BMI.

In our study, a statistically significant difference was observed between the sleep quality of those with and without chronic diseases. The sleep quality of those with chronic disease was found to be worse than the sleep quality of those without the diseases. In a study conducted in Nigeria on this subject, it was reported that the presence of a chronic disease affected sleep quality poorly,[28] while in some studies conducted in our country, it was found that chronic diseases decreased sleep quality.[29,30]

Ankara et al.[31] conducted a study with 144 participants and found that there was no significant difference between employees and non-employees in terms of SPAS.

In the study of Obuz,[32] no significant difference was found between employees and non-employees in SPAS

scale scores and diagnoses. In our study, in the analysis of SPAS and PSQI scores according to the working status of the participants, there was no statistical difference between SPAS and the working status variable significant difference was found.

When we examined the literature on the effect of marital status on SPAS, we found that there were few studies on this subject. Alosaimi et al.[33] with 2367 participants marital status and problematic smartphone use scale scores between the two groups was not found to be significantly different. In Obuz's[32] study, the mean SPAS score of singles was significantly higher than the mean score of married individuals. In our study, according to the marital status of the participants, there was a statistically significant difference between SPAS and marital status.

Sleep quality and daytime sleepiness have been reported to be significantly associated with mood disorders (depression and anxiety). A British study examining the association between sleep disorders, quality of life, anxiety, and depression found that these variables were particularly prevalent in extremely obese individuals, more than two-thirds of whom reported poor sleep quality.[35] Our study was consistent with the studies conducted and found that the incidence of anxiety and depression was significantly higher in obese individuals with poor sleep quality.

Many factors affect a person's sleep quality and duration, and one of the rapidly evolving factors may be the increasing use of technology, particularly cell phone addiction. There are several reasons why cell phone addiction causes shorter sleep duration or less sleep.[10] The smartphone can support social networking, gaming, and perform various functions such as phone, multimedia player, camera, navigation system, Internet browser, and e-mail service. These behaviors can cause short night's rest and disturbed sleep patterns in cell phone addicts. Cell phone addiction can lead to less and poorer sleep. Many studies show that cell phone use is associated with inadequate sleep duration.[10,36]

In a study conducted by Zhang et al.[37] with 427 university students in China, sleep latency, short sleep duration and poor sleep quality variables were found to have significant positive correlations with smartphone addiction. Sleep latency was significantly and positively associated with smartphone addiction. 32.3% of students subjectively reported having poor sleep quality. Researchers have found that excessive cell phone use and use in the dark are related to poor sleep.[38,39] Loughran et al.[40] reported the adverse effects of cell phone electromagnetic fields on electroencephalograms during sleep.

Similarly, Huber et al.[41] reported that exposure to electromagnetic fields (cell phone use) in the evening affects physiological factors such as sleep quality and melatonin rhythm and may affect brain activity, especially the pineal gland. They also stated that they could cause changes in brain electrical activity and cerebral blood flow. In addition, it has been reported that long-term use of cell phones may cause physical disorders such as muscle pain and headache, which may negatively affect sleep.[38]

In a 2004 study of university students, Thomée et al.[42] found that those classified as heavy computer, social media and cell phone users reported higher levels of long-term stress, depression and sleep disturbances. Furthermore, in another study of young adults, after excluding participants with baseline mental health problems, high cell phone use was associated with stress, sleep disturbances and depression following a one-year follow-up.[38]

When our study examined the factors that influence poor sleep quality (anxiety, depression, chronic diseases and smarthphone addiction), it showed that it was increased 12-fold in individuals with high smartphone addiction. There was a similar correlation was found between PSQI and BMI, rates of smarthphone use.

Several recent studies have found that problematic smartphone use is associated with certain health risks, ranging from psychosocial disorders such as depression, anxiety, and sleep problems[43-45] to possibly fatal injuries in traffic accidents.[46]

Excessive use of the calling and texting features of cell phones has been associated with depression, anxiety, and stress.[47] The results of a study conducted by Ithnain et al.[48] with 369 university students in Malaysia showed a significant positive relationship between smartphone addiction and anxiety and depression. Smartphone addiction has a significant impact on anxiety and depression is a was found to be a predictor.

Specifically, prolonged screen use leads to decreased physical activity, altered sleep schedules, and increased consumption of junk food, which increases the risk of obesity through decreased activity and increased energy intake.[49]

Our study found that individuals with high rates of smartphone use had higher BMI, poorer sleep quality, and higher anxiety scores.

In line with this information in the literature and our study based on the results, the risk of smartphone addiction, poor sleep quality, obesity and there is a relationship between psychological symptoms.

The rapid development of technology is leading to significant changes in people's lifestyles. As conditions such as dietary changes and lack of exercise increase, so does the incidence of obesity. In addition, excessive smartphone use leads to mood disorders and sleep problems, increasing the risk of developing obesity. Obesity is a widespread health problem, not only in our country but worldwide. Obesity is a major contributor to increasing disease rates and shortening life expectancy, and it significantly affects an individual's quality of life. Although the impact of behavioral addictions, including smartphone addiction, on our lives is increasing, little research has been conducted on these topics.

The limitations of our study are that it was conducted with a small sample and only males. The scales used are subjective assessments, and sleep problems should be confirmed by objective tests. Studies with large groups of patients are needed to verify the results.

CONCLUSION

Obese people's BMI seems to be impacted by poor sleep quality and smartphone addiction. Therefore, identifying potentially modifiable risk factors and underlying causes is critical to improve the design of prevention programs and reduce the prevalence of obesity in the young population.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ethics Committee of the Ministry of Health and Scientific Research of Haydarpaşa Numune Training and Research Hospital (Date:18.04.2022, Decision No: HNEAH-KAEK 2022/85).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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Original Article

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Morphometric analysis of chondromalacia patella and patella types

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ABSTRACT

Aims: The present study was conducted to determine patella types, chondromalacia patella finding in the Turkish society, and to evaluate the differences between gender and age groups to with Magnetic Resonance Imaging (MRI).

Methods: The study had a retrospective design, and included 256 people (122 females, 134 male) who were between the ages of 18 and 81 admitting to the Orthopedic Clinic of Kozan State Hospital with various complaints in knee joints and different preliminary diagnoses between January 2015 and December 2017. The evaluations made on MR images in the study. We evaluated in our study were patella types, chondromalacia classification and comparison according to age and gender.

Results: Patella types did not differ between the genders at significant levels; however, significant differences were detected between the genders in the chondromalacia patella (p=0.03). Patella types were classified, and it was found that Type II Patella was the most common patella type, and Type IV was identified as the least common.

Conclusion: We believe that the data obtained in our study will be useful in understanding morphometry of patella in anatomy, radiology and orthopedics fields. Based on our findings, we concluded that the anatomical shape of the patella is an important anatomic parameter, which may reflect the development of defects in the patellofemoral region It is also clinically important in terms of identifying knee pathologies more clearly in the aging process, and revealing the differences between societies, and in many pathologies that involve patella.

Keywords: Chondromalacia patella, knee, morphometry, patella types

INTRODUCTION

The knee joint, which plays major role in the stabilization of the lower extremity, is the largest and most complex joint in the body. The knee joint, which has a wide range of motion, is also subject to overloads. An important part of the knee joint is the patellofemoral joint. Patella, which is an integral component of the extensor mechanism of the knee joint, helps to feed the patellofemoral joint cartilage of the femur by protecting the knee joint against direct impacts with its placement in the anterior part of the knee joint.[1] Also, the anatomical features of the patella and the femur and their compatibility with each other are very important in performing the flexion and extension movements of the knee. If the leverage of patella is increased, the effectiveness of the musculus quadriceps femoris is also increased. For this reason, patella joint movement width increases the extension moment arm. If abnormalities develop in the position of patella, problems such as chondromalacia patella, recurrent subluxations, and dislocation of patella develop in patellofemoral joint function.[2] Anatomical disorders in the patella and femur and the deterioration of the harmony between these two bones may cause uneven distribution of the load on the patellofemoral joint, cartilage lesions and knee pain in the joint.[3] Knee pain is the second most prevailing disorder of knee and patellofemoral pain being considered one of the most common forms of knee pain, with incidence ranging between 15 and 45%. Patellofemoral pain is described as nontraumatic diffuse anterior knee pain during load bearing activities of the joint such as squatting, running, climbing, and descending stairs. Chondromalacia patella is an important cause of patellofemoral knee pain. Chondromalacia patella, also known as runner's knee, typically occurs in young patients, which is characterized by anterior knee pain that is associated with visible changes in patellar cartilage.[4] Patella type is considered to be an important factor in the etiology of chondromalacia patella. Although there were very few studies investigating the relations between chondromalacia patella and patella types, which is defined as the softening and ulceration of the patella back cartilage, which accompanies knee pain, no

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studies were detected in the literature investigating the distribution of these studies according to age groups. Although studies were detected on the distribution of patella types inour population, no studies were detected patella types in different age ranges.[5] Therefore, patella types and chondromalacia patella parameters were included in our study and their correlation with each other was examined. Wiberg et al.[6] classified patella types into 3 types, and Baumgartl et al.[7] divided them into 4 types. It was reported that medial and lateral facets are equal in Type I patella, medial facet remains smaller in Type II than the lateral, medial facet is small and close to convex and vertical in Type III, and there is no "middle corner" in medial facet, and the appearance is similar to a "Jockey hat" in Type IV.[8,9] Computed Tomography (CT) and Direct Graphic are used in pathologies regarding the knee joint, these methods do not provide as much detailed information as Magnetic Resonance Imaging (MRI).10 Therefore, in our study, measurements were made on MRI images.

We thought that such a study could give an idea about the morphology of the patella and chondromalacia patella which are common in our population. So, our purpose was to determine the distribution of patella types in our population in which knee pathologies are most common between the ages of 18-81, the distribution of patella types in different age groups and in 7 different age ranges in both genders, patella types, and to determine the relations between them. Furthermore, this study will have significant clinical impact on the production of specific prostheses belonging to our population with similar anthropological patella shape.

METHODS

The study was carried out with the permission of Çukurova University Non-interventional Clinical Researches Ethics Committee (Date: 02.06.2017, Decision No: 38). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Selection and Study Procedure

Retrospective MRI analysis was performed on patients who were hospitalized between January 2015 and December 2017. Our study included 256 people (122 women, 134 men) between the ages of 18 and 81, who applied to Kozan State Hospital between January 2015 and December 2017 with various complaints in the knee joint and were referred from clinics to the Radiodiagnostic Department for MRI examination with different preliminary diagnoses. Criteria for participating in the study;

(1) Not having had any surgery on the lower extremity
(2) No history of fractures of the lower extremities or columna vertebralis and no neurological disorder
(3) Not having real short legs
(4) Not having congenital hip dislocation
(5) Not having a benign or malignant mass in the knee joint
(6) Not having arthritis and rheumatological findings in the knee joint
(7) MRI images appear clear
(8) Having consented to the use of MRI images

Our study design is to analyze the distribution of knee MRIs with and without chondromalacia according to age, gender and patella types. In addition, this study also includes the analysis of chondromalacia degrees of images with chondromalacia according to age, gender and patella types. This study is a retrospective study and not an experimental study on participants. It involves the anonymized use of MRI images on a voluntary basis. For this reason, anonymous analysis and images that do not contain personal information were used. Voluntary consent forms were obtained from the people whose MRI images we would use, and only the gender and age information of the patients were recorded.

Magnetic Resonance Imaging And Measurements

Magnetic resonance imaging (MRI) is a radiation-free imaging technique that can be used to examine all soft tissues in the body. After the nervous system, the second most common area of use is the musculoskeletal system, especially the knee joint. In MRI, images can be obtained in many planes without moving the patient. MRI is a diagnostic method with high accuracy that can be routinely chosen for imaging articular cartilage. If 3D SPGR and FSE PD-weighted sequences are used with fat suppression technique, it will be possible to obtain valuable information about cartilage pathologies. In our study, the MRI examination of 256 patients was performed with Tesla MRI Device. In all cases, the images were obtained as T1-A SE in coronal plain, PD FSE in axial plain, and PD FSE in sagittal plan. MRI parameters were obtained in PD in sagittal plain (FSE:3800/19), in axial plain (FSE:3000/19), and coronal plain (FSE:2800/8).

All images included in this study consist of axial patella radiographs. Patella morphology was evaluated according to the Wiberg classification by two authors (E.Ö. and H.S.). Intraobserver comparisons have been made. Type 1, patellar tilt angle and patellar thickness/width were evaluated from the axial view of the patella; Type 2 was interpreted as lateral patellar displacement measured in the axial view of the patella; Type 3 was evaluated as the patellar compliance angle and patellar facet angle measured in the axial view of the patella; Type 4 was evaluated by interpreting the patellar height measured on the lateral of the knee.

The evaluations made on MR images in the study are as follows;

Patella types: The classification was made according to Wiberg and Baumgartl (1964), and patella was divided into 4 types (Figure 1).[6,7]

Type I: Medial - lateral facet shows equal and slightly concave appearance.
Type II: Medial facet is smaller, straighter, and convex compared to lateral.
Type III: Medial facet is small, convex, and close to the vertical.
Type IV: There is no medial facet and middle corner.

Patellar chondromalacia classification: The classification was made according to Outerbridge (1964) (Figure 2).[11] The classification was made according to Outerbridge (1964).[11] This classification is used as a simple, easy-to-use and reproducible grading system of articular cartilage lesions. Chondromalacia classification was made based on MRI images.

Chondromalacia was divided into 4 grades;

Grade 1: Softening and swelling.
Grade 2: Fragmentation and fissuring (<0.5 cm).
Grade 3: Fragmentation and fissuring (>0.5 cm).
Grade 4: Cartilage erosion in subchondral bone.

Age Decades: The analyzed images were divided into 7 groups according to age ranges;

Group I (1st decade): 18-20 years,
Group II (2nd decade): 21-30 years,
Group III (3rd decade): 31-40 years,
Group IV (4th decade): 41-50 years,
Group V (5th decade): 51-60 years,
Group VI (6th decade): 61-70 years
Group VII (7th decade): 71 and over years.

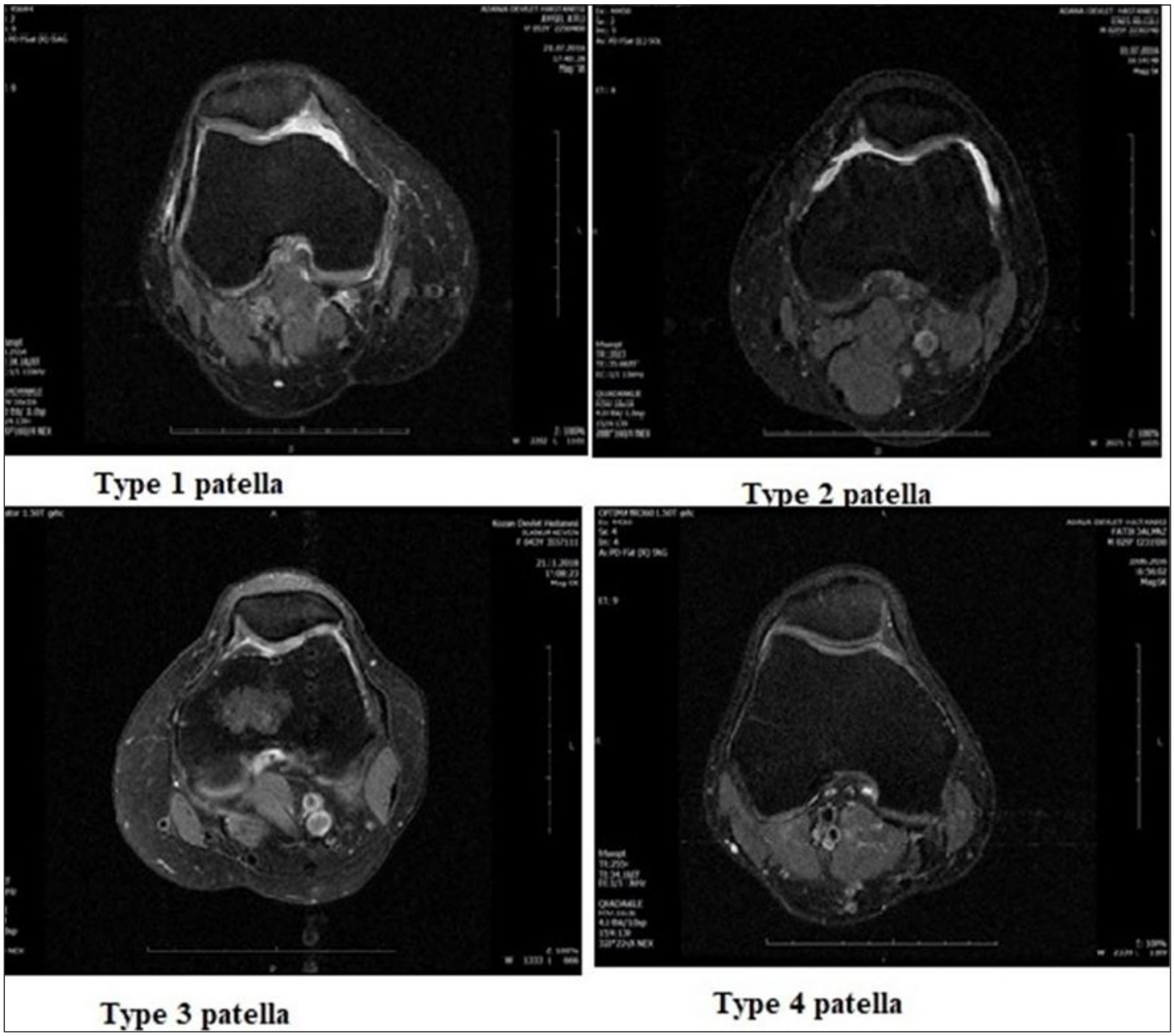

Figure 1. Patella types

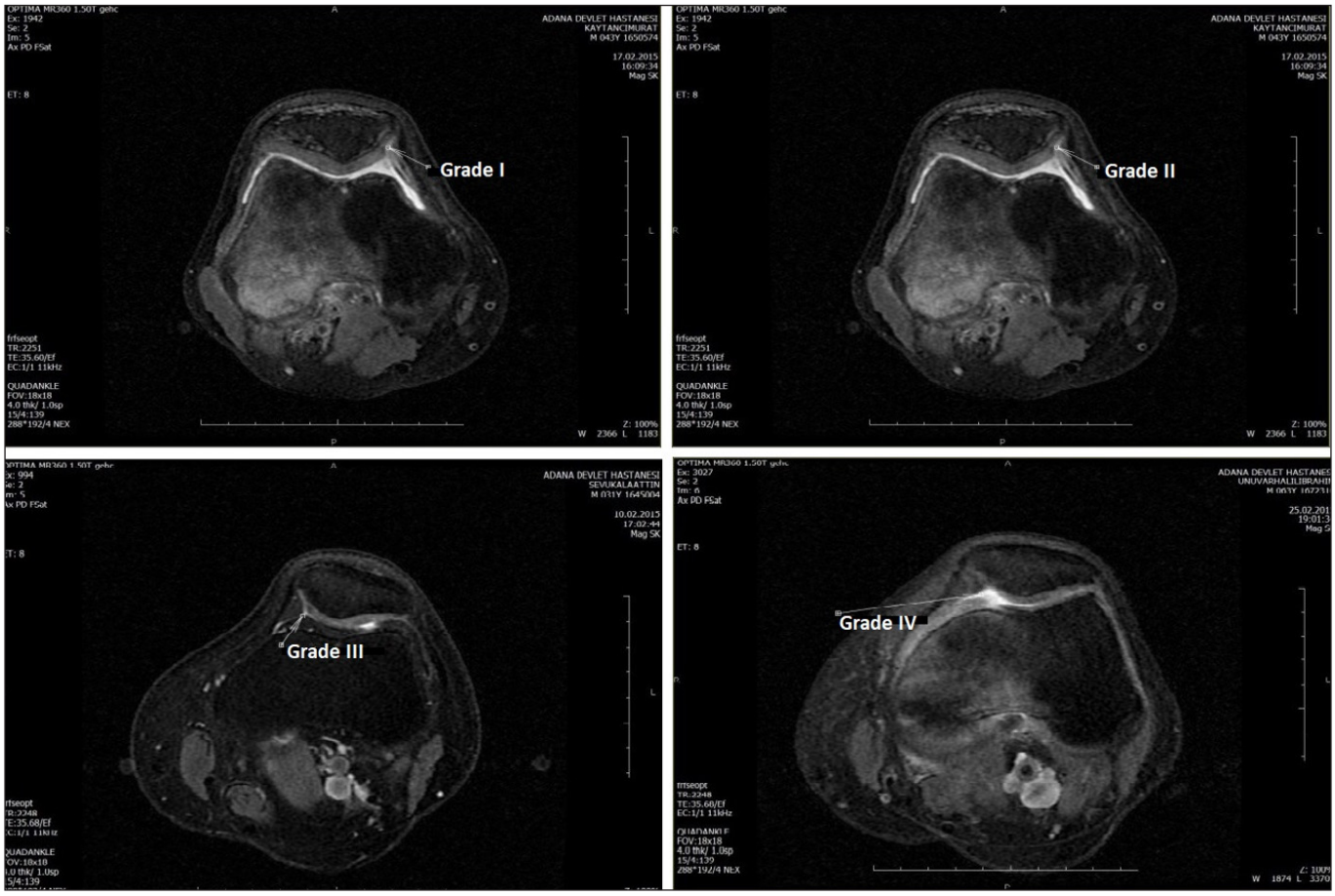

Figure 2. Grades of chondromalacia

Statistical Analysis

"Statistical Package for Social Sciences for Windows 21" (SPSS 21 Inc.) Program was used for the statistical analyses of the data that were obtained in the study. When the study data were evaluated, mean values, standard deviation, minimum (min.)-maximum (max.) values, and % from descriptive statistical methods were used. According to whether the data showed normal distribution, which test method should be used was decided according to the result of the Kolmogorov-Smirnov Normality Test. ANOVA One-Way Test was used in the analysis of quantitative data since the data were distributed normally. Analysis of the qualitative data was made by using the Chi-Square Test. Pearson Correlation Test was used to examine the magnitude, direction, and significance of the relations between the two variables. The results were evaluated at 95% Confidence Interval, and the significance was taken as $p<0.05$.

RESULTS

In the present study, the MRI results of 256 healthy people, including 122 female and 134 male who were aged between 18 and 81 were evaluated. While there was no significant difference (p=0.200) between the genders in the distribution of patella types, there was a significant difference (p=0.003) between the genders in the degree of chondromalacia (Table 1). In addition, while there was no significant difference (p=0.583) between patella types in people younger than 45 years old and over 45 years old, we found a significant difference (p<0.001) between the two groups in terms of chondromalacia grade (Table 2). Moreover, Grade 4 chondromalacia patella was not detected in individuals with Type I patella in both genders. Grade 4 chondromalacia patella was not detected in individuals with Type II patella in both male and female. Male with Type III patella did not have Grade 4 chondromalacia patella, but female with Type III patella had Grade 3 chondromalacia patella. Grade 2 chondromalacia patella was detected only in 2 males with Type IV patella. Type IV patella was not detected in female (Table 3). When the distribution of patella types was examined according to the age decades, Type I patella was detected mostly in Group V, Type II in Group IV, Type III in Group IV, and Type IV patella in Group II and Group III. Also, when the types of chondromalacia were evaluated, significant differences were detected between age groups (p<0.001) (Table 4).

Table 1. The distribution of patella types and chondromalacia patella classification morphometric measurements according to gender

Measurements	Females (n=122) n(%)	Males (n=134) n(%)	p
Patella Types	Type I=26 (21.3%) Type II=78 (63.9%) Type III=18 (14.8%) Type IV=0 (0.0%)	Type I=38 (28.4%) Type II=71 (53.0%) Type III=23 (17.2%) Type IV=2 (1.5%)	0.200
Chondromalacia patella classification	No chondromalacia patella =14 (11.5%) Grade 1=57 (46.7%) Grade 2=24 (19.7%) Grade 3=25 (20.5%) Grade 4=2 (1.6%)	No chondromalacia patella =31 (23.1%) Grade 1=50 (37.3%) Grade 2=40 (29.9%) Grade 3=13 (9.7%) Grade 4=0 (0.0%)	0.003

Table 2. The results of patella types and chondromalacia patella classification according to age groups

Measurements	45 years and younger (n=138) n (%)	45 Years and over (118) n (%)	p
Patella Types	Type I=35 (25.4%) Type II=78 (56.5%) Type III=23 (16.7%) Type IV=2 (1.4%)	Type I=29 (24.6%) Type II=71(60.2%) Type III=18 (15.3%) Type IV=0 (0.0%)	0.583
Chondromalacia patella classification	No chondromalacia patella=40 (29%) Grade 1=58 (42%) Grade 2=31 (22.5%) Grade 3=9 (6.5%) Grade 4=0	No chondromalacia patella=5 (4.2%) Grade 1=49 (41.5%) Grade 2=33 (28%) Grade 3=29 (24.6%) Grade 4=2 (1.7%)	<0.001

Table 3. The relation between patella types and the genders of chondromalacia distributions

Patella types	Gender n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Type 1						
	Male 10 (26.3%)	18 (47.4%)	7 (18.4%)	3 (7.9%)	0 (0.0%)	38 (100%)
	Female 3 (11.5%)	9 (34.6%)	7 (26.9%)	7 (26.9%)	0 (0.0%)	26 (100%)
	Total 13 (20.3%)	27 (42.2%)	14 (21.9%)	10 (15.6%)	0 (0.0%)	64 (100%)
Type 2						
	Male 17 (23.9%)	26 (36.6%)	22 (30.99%)	6 (8.45%)	0 (0.0%)	71 (100%)
	Female 7 (9.0%)	39 (50.0%)	14 (17.9%)	18 (23.1%)	0 (0%)	78 (100%)
	Total 24 (16.1%)	65 (43.6%)	36 (24.2%)	24 (16.1%)	0 (0.0%)	149 (100%)
Type 3						
	Male 4 (17.39%)	6 (26.09%)	9 (39.13%)	4 (17.39%)	0 (0.0%)	23 (100%)
	Female 4 (22.2%)	9 (%50.0%)	3 (16.7%)	0 (0.0%)	2 (11.1%)	18 (100%)
	Total 8 (19.5%)	15 (36.6%)	12 (29.3%)	4 (9.8%)	2 (4.9%)	41 (100%)
Type 4						
	Male 2 (100%)	0 (0.0%)	2 (100%)	0 (0.0%)	0 (0.0%)	2 (100%)
	Female 0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Total 0 (0.0%)	0 (0.0%)	2 (100%)	0 (0.0%)	0 (0.0%)	2 (100%)

Table 4. The distribution of patella types and chondromalacia patella classification according to different age groups

Groups	Group I n=25	Group II n=34	Group III n=53	Group IV n=79	Group V n=47	Group VI n=16	Group VII n=2
Patella Types							
Type 1	6	10	13	14	15	5	1
Type II	13	16	32	55	24	8	1
Type III	6	7	7	10	8	3	0
Type IV	0	1	1	0	0	0	0
p=0.743							
Chondromalacia Classification							
No chondromalacia patella	13	15	9	6	1	1	0
Grade 1	7	12	30	37	18	3	0
Grade 2	4	6	9	23	13	8	1
Grade 3	1	1	5	13	13	4	1
Grade 4	0	0	0	0	2	0	0
p<0.001							

DISCUSSION

One of the most common problems in orthopedics is patellofemoral joint diseases. Patellofemoral pain is defined as pain around the patella due to activities (squats, running, climbing, etc.) that load the patellofemoral joint without pathological changes. This is one of the most common forms of knee and lower extremity pain, with an annual prevalence of 23% in the general population and 29% in adolescents.[12] The negative effects of patellofemoral pain are high individuals with patellofemoral pain often report a lower quality of life. Patellofemoral malalignment creates an inappropriate biomechanical environment, causing instability due to ligament insufficiency, and chondropathy/arthrosis and/or anterior knee pain through strain and/or damage to soft tissues and cartilage. For this reason, it is one of the most emphasized problems. Alignment corrective interventions are among the surgical methods used to solve this biomechanical problem. When patellofemoral joint diseases were examined in the literature, many researchers focused on the patellar aspect of the joint and on the changes in patellar morphology. For this reason, having accurate anatomical knowledge on joint anatomy and functioning, and understanding different anomalies that may cause clinical manifestations accompanying joint damage are extremely important in diagnosis and treatment. Besides creating a shield to protect the distal femur, the patella also contributes to the cosmetic appearance of the knee. Moreover, there is a large variance in physical size and articular surface shape of the patella, and its morphology has an influence on patella kinematics.[13] Wiberg classified patella types into 3 by considering patella medial and lateral facet lengths.6 Then, the fourth type of patella was identified by Baumgartle.[7] According to this classification, when patella is classified, it was considered that the distinctions between Type II and Type III, and Type I and Type II were difficult; therefore, there might be differences according to the researchers who made the typing, which might then cause differences in the results of the first studies.[14,15] There are studies in the literature investigating the incidence of patella types both in Turkish society and in other societies. When studies conducted in Turkish society were evaluated, it was seen that patella Type II was most commonly detected in the study conducted by Atbasi et al.[15] 2013. In a study conducted by Kaplan et al.[16] which examined the patella type distribution in Sakarya, it was reported that Type II patella were detected by 70%. According to another study found Type I, II, and III were 24%, 70%, and 6%, respectively. They didn't found type IV.[17] In our study, the most Type II patella was found which supports the literature.

In a study conducted with 302 people (164 female, 138 male) by using MRI, they evaluated that there were 15 Type I patellas (9%), 114 Type II patellas (69.5%), and 35 Type III patellas (21.3%) and Type IV patellas was not detected in female; in male, it was reported that there were 26 Type I patellas (18.8%), 93 Type II patellas (67.3%), 18 Type III patellas (13%), 1 Type IV patella (0.7%).[9] When male and female were evaluated together, it was found that Type I patella was at a rate of 13%, Type II patella 68%, Type III patella 17.5%, and Type IV patella 0.3%. In their study, Arslan et al.[8] evaluated patella types and the frequency of chondromalacia in 1804 patients (806 females, 998 males), and reported that there were 159 Type I patellas (19.7%), 299 Type II patellas (37.1%), 342 Type III patellas (42.4%), and 6 Type IV patellas (0.7%) in female. They also reported that there were 199 Type I patellas (19.9%), 463 Type II patellas (46.4%), 321 Type III patellas (32.2%), 15 Type IV patellas (1.5%) in male. It was also found that Type II patella was most common in male, and Type III patella in female; and when calculated regardless of gender, Type II patella was most common. When other populations were examined, in the study conducted by the first studies that, Type II patella was detected in 57%, Type I patella in 24%, and Type III patella in 19%.[8,14] Gudas et al.[18] found that patients with a Type III patella shape (mean of 3.10±0.99) were less physically active compared to Type II (mean of 4.48±0.88; p=0.004) and Type I (mean of 4.55±0.72; p=0.002). The patients with Type I and II patella shapes had a similar level of physical activity (p=0.51) in their study. In another study, Rahman et al.[19] were measured 82 (52.6%) right knees, while were 54 (47.4%) left knees. Based on patella types, 94 (60.3%) patellae were Type I patella, 53 (34.0%) were Type II, and 9 (5.7%) were Type III patella in 156 Asian female patients.

In the present study, Type I patella was detected in 26 female (21.3%) (122 female 134 male), Type II patella in 78 female (63.9%), Type III patella in 18 female (14.8%), and Type IV patella was not seen in female. Type I patella was detected in 38 male (28.4%), Type II patella in 71 male (53.0%), Type III patella in 23 male (17.2%), and Type IV patella in 2 male (1.5%). In the present study, male and female (63.9%) and male (53.0%) had mostly Type II patella. Wiberg and Outerbridge believed in an association between Type II patella and chondromalacia patella, while many researchers rejected the hypothesis of an association between patella types in the etiology of chondromalacia patella.[6,11] However, in our study, the most Type II patella was found in both genders, which supports the Wiberg and Outerbridge hypothesis.

Moreover, it was reported in the study that was conducted by Hayırlıoğlu et al.[9] that 8 chondromalacia were detected in Type I patella, 31 chondromalacia in

Type II patella, 8 chondromalacia in Type III patella, and no chondromalacia was detected in Type IV. It was also observed that chondromalacia was most commonly detected in Type II patella in male and female. Patella problems arise in the knee when it is under heavy load. The cartilage under the patella begins to be damaged. This damage is called chondromalacia patella. Therefore, we can say that Type II patella is more inclined to condromalacia. In Hayırlıoğlu et al.[9] study, a total of 129 knees that were diagnosed with chondromalacia patella were evaluated in terms of chondromalacia degrees, and it was found that Grade 1 chondromalacia was in 22 knees, Grade 2 chondromalacia in 30 knees, Grade 3 chondromalacia in 28 knees, and Grade 4 chondromalacia in 49 knees. It was emphasized that the frequency of high-grade (Grade 3 and 4) chondromalacia was higher at 59%. Also, in their study, Arslan et al.[8] reported incidence of chondromalacia patella that there was Type I patella in female at a rate of 45.9% (73 people), Type II patella in 42.1% (126 people), Type III patella in 50.6% (173 people), and Type IV patella in 50.0% (3 persons); and in male, there was Type I patella in 23.1% (46 people), Type II patella in 22.4% (104 people), Type III patella in 27.4% (88 people), 13.3% (2 persons) in Type IV patella, respectively. In the present study, only 2 male in Type IV patella had Grade 2 chondromalacia patella, 51 chondromalacia in Type I patella, 125 chondromalacia in Type II patella, 36 chondromalacia in Type III patella. Type IV patella was not detected in female. When 214 knees that had chondromalacia patella were evaluated in terms of chondromalacia degree, Grade 1 chondromalacia was detected in 107 knees, Grade 2 was detected chondromalacia in 64 knees, Grade 3 chondromalacia was detected in 38 knees, and Grade 4 was detected chondromalacia in 2 knees. A total of 10 people with Type I patella did not have chondromalacia patella in male, but 28 had chondromalacia patella. Three people did not have chondromalacia patella in female with Type I patella, but 23 had chondromalacia patella. Grade 4 chondromalacia patella wasn't found in individuals with Type I patella in both genders. There was no chondromalacia patella in 17 people in male in Type II patella, but chondromalacia patella was detected in 54 people. A total of 7 people did not have chondromalacia patella in female with Type II patella, but 71 had chondromalacia patella. Grade 4 chondromalacia patella wasn't detected in individuals with Type II patella in both genders. Although there was no chondromalacia patella in 4 males with Type III patella, 19 had chondromalacia patella. In female with Type III patella, 4 females did not have chondromalacia patella, but chondromalacia patella was detected in 14 people. Male with Type III patella did not have Grade 4 chondromalacia patella, but female with Type III patella did not have Grade 3 chondromalacia patella. Grade 2 chondromalacia patella was detected only in 2 males with Type IV patella. Type IV patella was not detected in female. In the study conducted by Demir et al.[20] on one hundred and twenty-five patients with 3-4 degree chondromalacia patellae and an average age of 48.8±8.7, they stated that 62.4% of the patients were women and 55.2% were on the right side. Additionally, they did not find any significance between genders between those with and without chondramalacia.

There are studies in the literature trying to explain the associations of patella types with anterior knee pain, meniscopathy, and chondromalacia patella. In the study conducted on patella types, it was considered that patella types were not associated with chondromalacia patella, but could cause anterior knee pain. Wiberg and Outerbridge also considered that there might be an association between chondromalacia patella and Type III patella, but they could not prove it. In our study, no associations were detected between patella types and chondromalacia.[6,9,15,16] Another study conducted also showed a correlation between the retinaculum lateral width of the ligamentum patella and Type III patella.[21] Also, the correlations between articular cartilage defects and the shape of the patella would be extremely important for understanding the mechanisms of articular cartilage defects in the patellofemoral region. Gudas et al.[18] study suggests that a significantly higher number of articular cartilage defects cases in the patellofemoral region were documented in patients having a patella with a Type III shape. In their study, they observed that patients with Type III shape of the patella have lower levels of physical activity compared to patients with Type I and II shapes. Furthermore, Wiberg showed that the shape of the patella was correlated with anterior knee pain and that the Type III anatomical configuration of the patella leads to defects, while the type I could be emphasized as ideal.[6] In a study, patella subluxations and similar pathologies were excluded from Sirik&Uludag study. Medio-lateral ratio was used in their study to make the classification of patella types more objectively, and measurements were made by one single researcher like our study. Although high grade (Grade 3 and Grade 4) chondromalacia patella was found to be 18% in their study.[22] Like recurrent dislocation, recurrent subluxation is the second-decade disease in the age group. Patellar dislocation, either as a direct traumatic event in a patient with normal patellar alignment, or with a previous underlying patellofemoral malalignment; may occur, especially in patients with advanced subluxation. Moreover, Fithian et al.[23] investigated prospectively patients who presented with acute patellar dislocation between 2-5 years in their study. They divided the patients into two groups as acute and recurrent patellar dislocation. As a result, they found

that female between the ages of 10-17 had the highest risk for acute and recurrent dislocations. Besides, Dai et al.[24] showed that type III patella were associated with patellofemoral osteoarthritis in 150 knees. In our study, type III patella was more common in male and was seen in the 41-50 age group. It can be said that males with Type III patella and chondromalacia are more inclined to defects in the patellofemoral region.

In addition, the skin incision to be chosen for osteotomy in knee arthroscopy may vary. The patella is an important landmark in determining the type of incision. Patella type is also important for determining this incision type. Thus, the correct skin incision to be selected for osteotomy provides an advantage in terms of both wound problems and the fact that the heads of the screws to be placed are not directly under the skin. We also think that with this study, we will contribute to the selection of the right incision type by determining the patella types according to age.

Study Limitations

We recognize several limitations in this study. Firstly, our study only analyzed the imaging findings, which need to be studied in combination with the patient's symptoms in the future. Secondly, the physical activity status of the individuals should also be evaluated in terms of patella type and chondromalacia distribution. Thirdly, we think that if more knees are evaluated, determination of the standard of patella types may be more effective. Also, since our study was retrospective, intraobserver and interobserver comparisons have not been made. In addition, we could not obtain demographic data other than age and gender, which was a limitation of our study. The study can be conducted multicenterly with more patients and analyzed with demographic data other than age and gender. Moreover, another limitation of our study, are that the patients included in the study were diagnosed with chondromalacia by MRI without arthroscopy.

CONCLUSION

Our study involved healthy individuals who were between the ages of 18 and 81. When chondromalacia patella types were evaluated, significant differences were detected between age groups ($p<0.001$). Patella types did not differ at significant levels between the genders, and chondromalacia patella showed significant differences between the genders. Also, Type II patella was most commonly detected in male and female. In the comparisons made regardless of gender, Type II patella was detected to be the most common. When the distribution of chondromalacia types was evaluated regardless of gender according to patella types, it was found to be $p=0.091$, and $p=0.274$ for female, and $p=0.10$ for male. In our study, when the distribution of chondromalacia patella was evaluated regardless of gender, chondromalacia patella was most commonly detected in individuals with Type II patella. A few studies were detected in the literature examining patella types in different age decades. For this reason, in the light of the available data, we believe that the findings of our study will contribute to the literature in understanding patella morphometry in the field of anatomy, radiology, and orthopedics in terms of determining knee pathologies more clearly in the aging process.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Çukurova University Non-interventional Clinical Researches Ethics Committee (Date: 02.06.2017, Decision No: 38).

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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Original Article

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Comparison of procalcitonin, C-reactive protein, white blood cell counts and hemogram subparameters in community acquired pneumonia patients

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ABSTRACT

Aims: Pneumonia is a clinically and radiologically detected inflammation of the lungs. Most of the pneumonia patients are community-acquired pneumonia cases. Hemogram and C-reactive protein (CRP) are commonly used to support diagnosis and follow-up of treatment. Procalcitonin is less accessible and expensive. And the use of hemogram subparameters is not very common. The aim of this study was to research the relationship between procalcitonin, CRP, White Blood Cell count (WBC) and hemogram subparameters in patients with CAP and the efficacy of new hematologic rates in differential diagnosis.

Methods: Patients who were diagnosed with community acquired pneumonia by applying to the chest diseases outpatient clinic of our hospital were retrospectively analyzed. 67 patients who were clinically and radiologically diagnosed without noticing male or female were included in our study. Anamnesis data and co-morbidities of the cases were questioned. Procalcitonin, CRP and hemogram (platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-lymphocyte ratio (MLR) were calculated and WBC value was examined) were recorded. The obtained data were evaluated statistically and compared in terms of variables.

Results: The mean age of our patients was 57 (18-71) years; there were 41 (61.19%) female and 26 (38.81%) male patients. 36 (53.73%) of our patients had chronic diseases; 21 (31.34%) had heart disease, 23 (34.32%) had diabetes, and 6 (8.95%) had kidney failure. Patients; 48 (71.64%) procalcitonin, 56 (83.58%) CRP, 38 (56.71%) WBC, 52 (77.61%) NLR, 34 (50.74%) PLR and 38 (56.71%) MLR values were high. Procalcitonin, CRP and NLR values were significantly higher than other subparameters. The CRP and NLR values of patients with an additional chronic disease were higher than patients without co-morbidities. In the correlation analyses, there was a strong correlation between procalcitonin, CRP and NRL, but the correlation between the others was not significant. ($p<0.001$).

Conclusion: Our study shows NLR from hemogram subparameters can be used safely in CAP patients. Procalcitonin is expensive test for. Considering that Procalcitonin is not available in primary care family health centers and CRP is found in some family health centers, the calculated use of NLR will support the diagnosis. Using fewer examinations in secondary and tertiary health facilities is also valuable in terms of reducing health costs.

Keywords: Pneumonia, NLR, procalsitonin, CRP

INTRODUCTION

Pneumonia is an inflammatory disease of the lung parenchyma caused by infectious agents (bacteria, viruses, parasites, fungi, etc.). It is a group of diseases with high mortality and morbidity in children and adults all over the world. Pneumonia that occurs during a person's daily life is called community-acquired pneumonia (CAP). It is stated that 5.6 million people are diagnosed with CAP annually in the United States of America (USA) and 1.1 million people require hospitalization due to CAP. CAP ranks sixth among all causes of death in the USA and first among deaths due to infections.[1,2] With age, the incidence increases. In a large-scale study in Germany, the overall incidence of CAP in adults over 18 years of age was 1,054 cases per 100,000 person-year observations. ≥18 adults, high mortality of hospitalized CAPs was observed in the hospital (18.5%) and after one year (44.5%). The mortality rate in older adults was more than doubled.[3] A large-scale research has been carried out in recent years by the Ministry of Health of the Republic of Turkey, the Directorate of Hygiene School of the Refik Saydam Sanitation Center and Başkent University. According to the final report announcing the results of the National Burden of Disease and Cost Effectiveness Project and published in December 2004; in the household survey,

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among the top 20 chronic and acute diseases diagnosed by a clinician in the last two months, pneumonias ranked 15th with a frequency of 1.15%.[4]

Pneumonia that occurs in individuals during their normal daily lives and in the community is defined as community-acquired pneumonia (CAP).[1,4] CAP is responsible for a significant proportion of doctor's consultation appointments, work-school day losses, treatment costs and disease-related deaths worldwide.[5,6] When the publications in our country covering pneumonia cases in the community are examined, it is seen that the rate of detecting the infectious agent varies between 21-62.8%.[7] Even if it is possible to determine the causative agent, empirical antibiotic treatment is required at least initially since culture and agent determination studies will require a certain amount of time.[8,9] Efforts are being made to prevent work-school power losses, reduce disease-related morbidities and reduce diagnosis and treatment costs are increasing. The reasons listed here have increased the need for the use of laboratory parameters in early diagnosis and prognosis by combining them with clinical findings. In recent studies, the role of many infectious markers in the diagnosis and prognosis of pneumonia has been investigated. The most commonly investigated include C-reactive protein (CRP), procalcitonin (PCT), platelet count, white blood cell (WBC) count, mean platelet volume (MPV) and interleukin-1.[10,11] C-RP is an elevated positive acute phase reactant in many infections and autoimmune diseases. Procalcitonin is a calcitonin precursor peptide that is absent or very low (<0.1 ng/ml) in healthy individuals and is increased in inflammatory and infectious conditions. In severe infectious conditions, sepsis and multiorgan failure, its synthesis is increased.[12]

Pneumonia severity index (PSI) and confusion, respiratory rate, blood pressure, 65 years and older (CURB-65), serum urea/creatinine values are commonly used tools among many scoring systems to assess disease severity and predict mortality in patients with CAP.[13] However, no scoring systems are ideal, and some scores are cumbersome to be used in everyday clinical practice. Inflammatory biomarkers such as blood-like CRP and procalcitonin may improve the prognostic accuracy of these scores.[14,15] However, these two biomarkers are not always reliable,[16] so the need to identify a reliable, inexpensive and easy-to-use biomarker arises. One of the markers studied involves the neutrophil-to-lymphocyte ratio (NLR), an easily measurable index. It is the ratio of the absolute number of neutrophils to the absolute number of lymphocytes. Under pathological stress, the number of neutrophils increases, while the number of lymphocytes decrease.

The aim of this study was to research the relationship between procalcitonin, CRP, white blood cell count (WBC), NLR and other hemogram subparameters in patients with CAP. The relationship was used to evaluate whether hemogram subparameters were as significant as CRP and procalcitonin in patients with community-acquired pneumonia.

METHODS

The study was carried out with the permission of Şişli Hamidiye Etfal Training and Research Hospital Clinical Researches Ethics Committee (Date: 02.05.2023, Decision No: 2316). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Due to the retrospective nature of the study, the need for written informed consent from patients was also waived.

Participants and Study Design

Between 10.10.2022 and 31.12.2022, patients diagnosed with CAP were admitted to the Chest Diseases Polyclinic of Health Sciences University Şişli Hamidiye Etfal Training and Research Hospital.

Patient records were examined retrospectively through the hospital computer data system. Patients with complete complaints, examinations and history file information, chest X-ray and/or computer tomography and laboratory tests were included in the study. Individuals over the age of 18, regardless of sex, were included in our study. Cases who had not been hospitalized for the last 15 days, who had not received antibiotic treatment in the last 15 days for any reason, who did not have known immune system disorders or malignancies, and who did not use steroids during the period of admission to our outpatient clinic were included in our study. Cases with missing files, immune system disorders and malignancies were not included in the study. The files and examinations of the patients were examined. Laboratory data of patients with confirmed diagnosis of pneumonia; procalcitonin, CRP and hemogram (neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and monocyte-to-lymphocyte ratio (MLR) were calculated and white blood cell (WBC) count value was examined) were uploaded to the excel program and the statistics were performed.

Statistical Analysis

For the Social Sciences (SPSS) for Windows 23.0 (IBM Corp., Armonk, NY) package program, patient data gathered within the scope of the study were assessed with the IBM Statistical Package .frequency and percentage values are given as frequency and percentage. Maximum, mean, and minimum descriptive values are given for continuous data. The normality test of the

data was performed by Kolmogorov-Smirnov Test. In the comparisons between the groups, "Independent Sample T-Test" was used for the two groups with normal distribution, "Mann Whitney-U Test" was used for those without normal distribution, and "Fisher's Exact Test or Chi-Square Test" was used for the comparison of categorical data items. Spearman's Correlation Examines was used to assess the relationship between laboratory measurements. The results were aforethought statistically remarkable when the p value was less than 0.05.

RESULTS

Between 10 September 2022 and 31 December 2022, patients diagnosed with CAP were admitted to the Chest Diseases Polyclinic of Şişli Hamidiye Etfal Training and Research Hospital, University of Health Sciences. Within four months of the study, 67 patients who were diagnosed with CAP clinically and radiologically who applied to the outpatient clinic were included without regard for sex. The median age of patients was 57.08±12.42 (18-71). A majority of the patients, 41 (61.19%) were female and 26 (38.81%) were male. The patient's body mass index (BMI) was 28.25±5.66 kg/m2. Additionally, 36 (53.73%) of our patients had chronic diseases; 21 (31.34%) had heart disease, 23 (34.32%) had diabetes and 6 (8.95%) had kidney failure. 23 (34.34%) of the patients were active smokers, 27 (40.29%) of them quit, and 17 (25.37%) of them had never smoked. Demographic data of the patients are demonstrated in Table 1.

Table 1. Baseline demographics of the study population

	Mean ± S.D.	Median (Min-Max)
Age	57.08±12.42	57 (18-71)
	n (67)	(%)
Gender		
Female	41	61,19
Male	26	38,81
Smoking		
Smoking	23	34,34
Quit	27	40,29
Never smoked	17	25,37
Chronic diseases		
Cardiac disease	21	31,34
Diabetes mellitus	23	34,32
Kidney failure	6	8,95
BMI	28.25±5.66	27.15 (17.28-49.7)

Cough was the most common complaint among the participants with 60 (89.55%) patients suffering from it. Chest pain was present in 46 (68.65%) patients, and sputum was in 52 (77.61%) patients. In addition, 41 (61.19%) patients had fever, 38 (56.71%) patients had shortness of breath, and 7 (10.44%) patients had hemoptysis.

The distribution of pneumonia was as follows: 29 (43.28%) had lobar pneumonia, 10 (14.92%) had multilobar pneumonia, and 28 (41.79%) had multisegmental nodular infiltration and interstitial changes.

The laboratory parameters were: glucose 144.97±51.32, alanine aminotransferase (ALT) 34.12±14.17, aspartate aminotransferase (AST) 43.01±26.27, urea 34.13±14.17, creatinine 0.37±0.21, lactic dehydrogenase 315±170, ferritin 393.57±351.84, hemoglobin 12.7±3.73, hematocrit 41.02±6.73. CRP was elevated in 56 (83.58%) patients, PCT in 48 (71.64%), WBC in 38 (56.71%), NLR in 52 (77.61%) patients, MLR in 38 (56.71%) patients, and PLR in 34 (50.74%) patients. The laboratory test results we used are demostrated in Table 2.

Table 2. Laboratory parameters of the study population

	Mean ± S.D.	Median (Min-Max)
WBC	9.79±4.73	8.32(3.38-19.88)
C-RP	84.67±48.70	77(1-303)
PCT	0.37±0.21	0.15(0.01-3.82)
NLR	7.90±4.27	5.38(1.11-55.67)
MLR	0.35±0.13	0.29 (0.20-0.51)
PLR	187±84	173 (92-573)

Laboratory data of CAP patients participating in our study were compared with correlation analysis. There was a low linear relationship between the NLR value and procalcitonin (r:0.454) value and a moderate linear relationship with the CRP (r:0.626) value of the patients. Similarly; There was also a moderate linear relationship between procalcitonin value and CRP values (r:0.595). There was no correlation between other hemogram subparameters and C-RP and procalcitonin. The results of the correlation analysis, in which the relationship between the laboratory measurements of the patients are evaluated, are given in Table 3.

Table 3. Evaluation of the relationship between NLR, procalcitonin and C-RP values

		NLR	PCT	C-RP
NLR	Correlation coefficient p-value	1.000 -	0.454 <0.001	0.626 <0.001
PCT	Correlation coefficient p-value	0.454 <0.001	1.000 -	0.595 <0.001
C-RP	Correlation coefficient p-value	0.626 <0.001	0.595 <0.001	1.000 -

DISCUSSION

Community acquired pneumonia (CAP) is responsible for the majority of admissions to hospitals, treatment expenses, lost work&school days and majority of deaths all around the world.[5,6] It's important to quickly diagnose the patient who has been admitted to the emergency department or to the polyclinic with complaints of

infection and to bring them into social life earlier. Studies on the usage of cheap and easily accessible blood biomarkers in the diagnostic phase of patients with CAP continue. In our study, we investigated the usability of hemogram sub parameters and especially NLR for this purpose. We found that NLR was as significant as other blood biomarkers such as PCT and CRP in diagnosis of CAP patients.

NLR is the ratio of the absolute neutrophil count to the absolute lymphocyte count. Under pathological stress, lymphocyte count decreases while neutrophil count increases. Early diagnosis and, accordingly, prompt treatment of patients with bacteremia, especially sepsis, are important as these improve prognosis. Initial stages of severe infection may be characterized by an increased number of neutrophils and fewer lymphocytes in the peripheric blood. Lowsby et al compared the neutrophil-lymphocyte ratio to conventional tests such as CRP and white cell count. According to the researchers NLR is not sufficient on its own to direct the clinical management of patients with suspected bacteremia even though it performs better than conventional infection markers. They reported that this has no advantage compared to WBC. Along with this, they stated that NLR was able to present some diagnostic benefits as a part of the general evaluation.[17] Jager et al.[18] described NLR as an indicator of bacteremia in medical emergencies. In their studies, they investigated the value of NLR in patients with CAP. They concluded that the NLR measured during an examination for pneumonia in the emergency department predicted the severity and outcome of CAP with a higher prognostic accuracy compared to conventional infection markers. In research conducted in Türkiye, Üçsular et al.[19] wrote that PLR and NLR were higher in all patients with hypersensitivity pneumonia compared to the control group and PLR and NLR, along with clinical, radiological and pathological findings, were cheap and simple parameters that may guide the diagnosis of hypersensitivity pneumonia and acute-chronic distinction of the illness. Şahin et al.[20] investigated the efficiency of WBC, CRP, PCT, NLR and PLR on diagnosis in patients, severity of the disease and response to treatment. They reported that PSI score of NLR showed significant correlation with leukocyte, neutrophil, lymphocyte, CRP, PCT and uric acid. Following the response to treatment they saw that leukocyte, NLR, CRP and PCT were rather beneficial, they reported that CRP and NLR which is especially cheaper and repeatable could be used more widely regarding PCR being more expensive compared to other measurements. We found that WBC, CRP, PCT, NLR and other hemogram sub parameters were high in our study. We detected WBC, CRP, PCT and NLR to be higher than other parameters.

More research is being conducted on NLR's ability to assist the diagnosis and prognosis of pulmonary infections observed in childhood age group and while being treated for nasocomial pneumonia. Omran et al.[21] reported that combined usage of lung ultrasound and NLR was beneficial for the differential diagnosis of viral/bacterial pneumonia in children. They proved that lung ultrasound was a noninvasive and reliable method for early diagnosis and differentiation of viral and bacterial pneumonia in little Egyptian children. The researchers evaluated this as "Combining NLR with lung ultrasound increased the diagnostic accuracy in evaluation of children suspected with pneumonia". Cheng et al.[22] retrospectively examined the patients hospitalized for acute stroke. They reported that NLR and serum fibrinogen may have greater negative diagnostic value in estimating stroke-related pneumonia in stroke patients, but combining NLR and serum fibrinogen can show an increasing value in predicting stroke-related pneumonia in patients with acute stroke. In a study NLR, CRP and PCT were compared to detect sepsis in 216 patients in intensive care and it was reported that NLR wasn't superior to other parameters.[23] In his study Zahorec defined NLR as a simple and quick parameter of systemic inflammation and stress in critically ill cases.[24] In two studies on COVID-19 correlation was observed between NLR and severity of the illness.[25,26]

In a study they conducted on 209 patients hospitalized for CAP, Curbelo et al.[27] reported that neutrophil levels and NLR are simple, cheap parameters with prognostic benefit, especially when measured in 3-5 days after CAP diagnosis. High NLR and/or neutrophil levels are associated with a higher risk of death in 90 days. In other studies, NLR is a simple, cheap and quick measurement in routine blood test and associated with adverse clinical outcomes in adult CAP patients.[28-30] In a review conducted on 3340 patients, NLR was featured as a simple, easily measured yet promising marker to estimate the outcomes in patients with CAP.[31] Meng et al.[32] couldn't find any connection between heparin-bound protein and CAP etiology but they showed that heparin-bound protein and NLR also increased with increasing severity as independent markers of 30-day death in CAP patients. Şahin et al.[20] saw that PCT widely used for the severity of diagnosis and treatment follow-up of patients with pneumonia was correlated with NLR and CRP. While they couldn't find any significant correlation between CURB-65 and PSI score with CRP, they saw a significant correlation between NLR and these scores. They concluded that WBC, NLR, CRP and PCT were rather beneficial for the follow-up of treatment response. In our study we found that NLR level was highly correlated with CRP ($p<0.01$). We found moderate correlation between NLR and PCT with WBC ($p<0.05$). There was no correlation between MLR and PLR with other values ($p>0.05$).

CONCLUSION

This study shows that NLR from hemogram subparameters can be used safely in patients diagnosed with community-acquired pneumonia. It should be borne in mind that procalcitonin is an expensive test. Considering that Procalcitonin is not available in primary care clinics and CRP is found in some of them, it has been shown that the use of NLR from hematological subparameters will support the diagnosis. Using fewer tests in secondary and tertiary health services also carries great value in terms of reducing health costs.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Şişli Hamidiye Etfal Training and Research Hospital Clinical Researches Ethics Committee (Date: 02.05.2023, Decision No: 2316).

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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Original Article

MEDICINE PALLIATIVE CARE

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Clinical and radiological outcomes of gunshot-induced femur fractures: a comparative study of monolateral external fixators and hybrid advanced ilizarov method

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ABSTRACT

Aims: Clinical and radiological outcomes, complication rates, and 10-year follow-up results of comminuted femoral open fractures resulting from firearm injuries were evaluated by comparing the Hybrid Advanced Ilizarov method (HAIM) and monolateral external fixator (MEF) of the limb reconstruction system (LRS) for treatment.

Methods: Nineteen patients (18 males, 1 female) treated with HAIM and 14 male patients treated with MEF-LRS for femoral comminuted open fractures due to firearm injuries were retrospectively analyzed. Complication rates, pin tract and deep infection rates, time to union, and the need for secondary surgeries were assessed. The Tegner activity score and Short Form-36 (SF-36) were used for comparative evaluation of functional and radiological outcomes and comfort levels with the fixator.

Results: There were no significant differences between the groups in terms of age, gender, follow-up duration, time to union, union rate, delayed union, or deep infection. No infections were detected in either group that required a change in the fixation method. There were no significant differences in radiological and functional outcomes between the groups. Significant differences were observed in terms of pin tract infections between the groups. The comfort level of MEF-LRS patients was significantly higher than that of HAIM patients.

Conclusion: In the treatment of femoral fractures due to firearm injuries in early and long-term follow-ups, similar complication rates and functional outcomes were achieved for both MEF-LRS and HAIM methods. When considering external fixator preference, MEF-LRS is a better alternative, with a lower rate of pin tract infections and higher patient comfort level.

Keywords: Femur fracture, hybrid advanced Ilizarov method, monolateral external fixator, pin tract infection

INTRODUCTION

Fractures caused by gunshot injuries often result in significant soft tissue damage and extensive fragmentation at the fracture site. Treating femoral diaphyseal fractures resulting from gunshot wounds poses a considerable challenge for orthopedic surgeons due to complications like soft tissue issues, neurovascular damage, and a heightened risk of infection.[1] The femur is particularly susceptible to damage, accounting for forty percent of lower extremity gunshot injuries. Contrary to popular belief, the heat generated by the firearm during discharge does not guarantee a sterile fracture environment.[2,3] In fact, the bullet, along with skin and clothing fragments, can contaminate the fracture site and introduce infection sources.

While minor gunshot wounds with acceptable infection rates and reasonable healing times have been successfully treated using simple debridement and early intramedullary nailing (IMN)[1,4,5] there is no established treatment protocol for contaminated injuries. Given that many of these injuries result in complex fractures, external fixators (EFs) provide a suitable treatment option. Depending on the fracture type and extent of soft tissue damage, hybrid advanced Ilizarov method (HAIM) or monolateral external fixation (MEF) may be favored. Recent advancements in MEF designs have improved application ease and patient adherence compared to traditional circular fixators.[6]

This retrospective study aims to assess the outcomes of HAIM and MEF in patients with open femoral fractures resulting from gunshot injuries.

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METHODS

The study was carried out with the permission of Gazi Yaşargil Training and Research Hospital Clinical Researches Ethics Committee (Date: 12.06.2022, Decision No: 2022/492). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Between March 1998 and October 2019, our institution treated forty-five patients with monolateral external fixation (MEF) using the Orthofix Limb Reconstruction System (Orthofix, Verona, Italy) in (**Figure 1**) or the hybrid advanced Ilizarov method (HAIM) in (**Figure 2**).[5] In 2019, we followed up with 33 of these patients (14 with MEF, 19 with HAIM) because 12 patients could not be reached for long-term follow-ups. These individuals underwent physical examinations and X-ray evaluations to assess knee and hip joint mobility, identify potential recurrent fractures, and detect chronic osteomyelitis or pin site issues in the fracture area.

Medical records were reviewed to classify fractures according to the Gustilo-Anderson and The Association for the Study of Internal Fixation (AO/ASIF) classification. The type of fixator employed, and the injury type were recorded. All patients received a tetanus toxoid vaccine, while prophylactic treatment consisted of intravenous first-generation cephalosporin (cephazolin 50 mg/kg/day), metronidazole (20 mg/kg/day), and aminoglycoside (2.5 mg/kg/day) for five days. Angiography was conducted for patients with impaired peripheral pulses or undetectable pulses by Doppler ultrasonography, with vascular repair performed as necessary.[7]

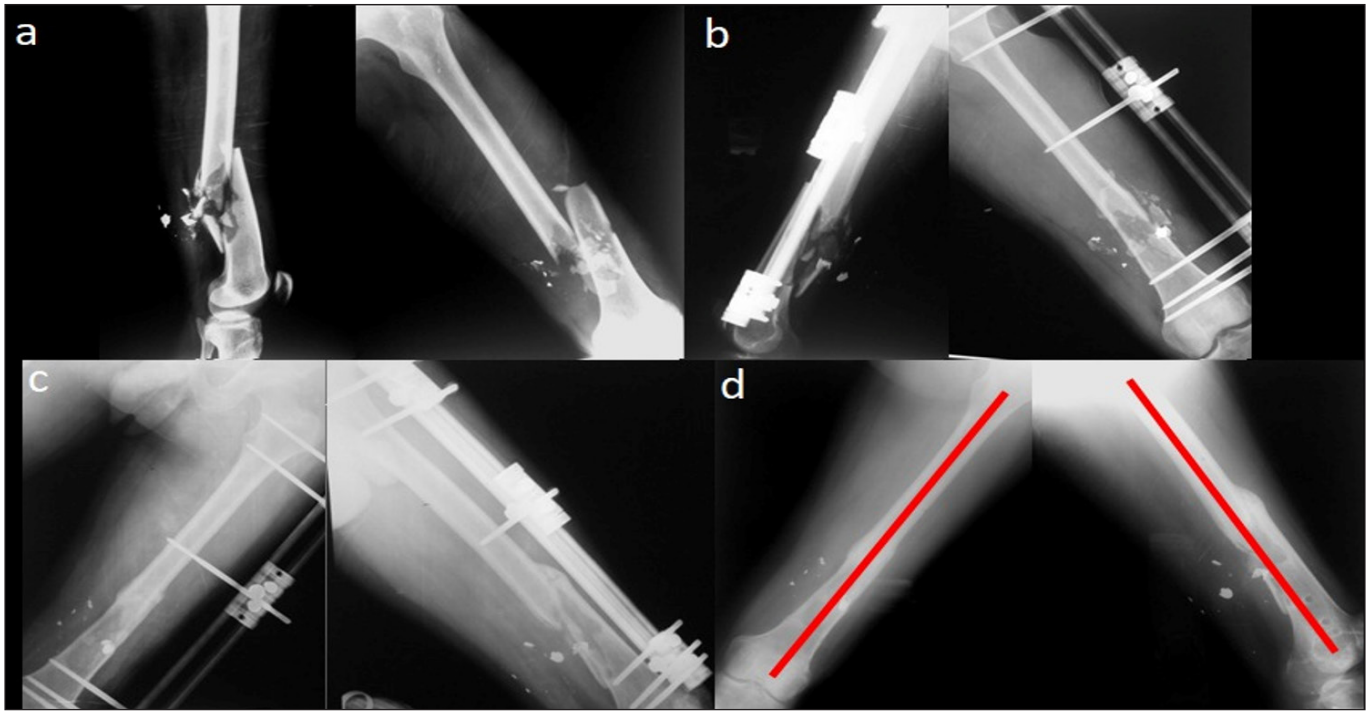

Figure 1. a) Two-way X-Ray Graph of The Femur Fracture, **b)** Two-way X-Ray Graph After Monolateral External Fixators Application, **c)** Two-way X-Ray Graph of After bone-healing, **d)** X-Ray Graph of the Removed the Fixator

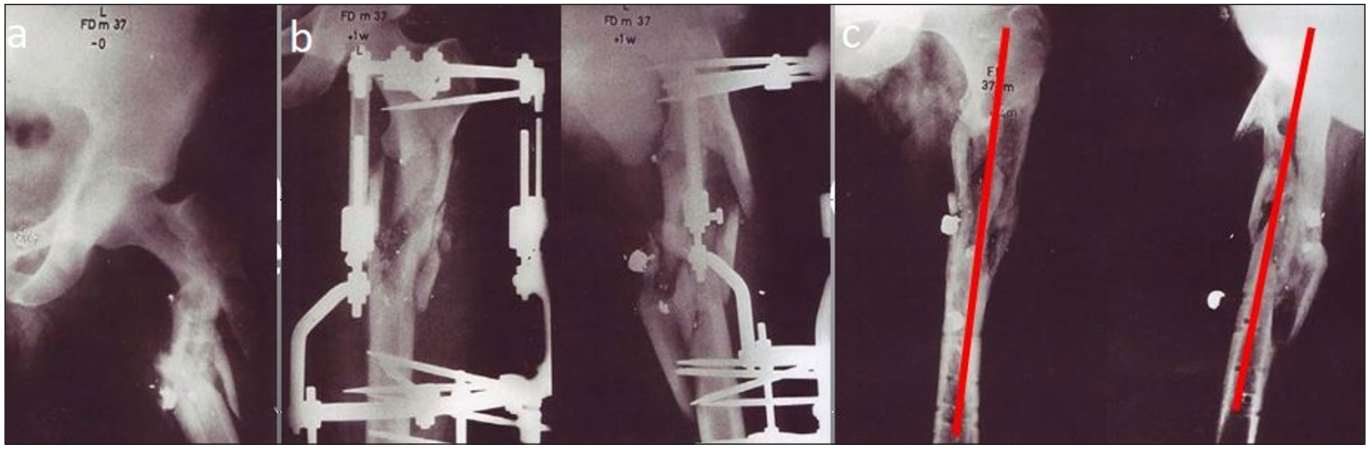

Figure 2. a) X-Ray Graph of The Femur Fracture, **b)** Two-way X-Ray Graph After Hybrid Advanced Ilizarov Application, **c)** Two-way X-Ray Graph of After the removed fixator and bone-healing

Surgical and treatment complications were documented, and radiographic measurements were taken before surgery and at the final follow-up. Radiographs were assessed for lower limb alignment and union. The duration of external fixator usage was calculated. Outcome evaluations included the Tegner activity score, Short Form-36 (SF-36), and criteria proposed by Thoresen.[8,9]

Postoperatively, wound care involved twice-daily cleaning using hydrogen peroxide or povidone-iodine solutions for wire tract hygiene during the first week. Daily care was administered to patients without wire tract infections. Infection severity guided treatment for cases with observed infections, ranging from local care for mild infections to wire or nail removal, curettage, and antibiotic therapy for more severe cases.

To prevent quadriceps atrophy and knee motion limitations, isometric and passive stretching exercises commenced on the first day post-surgery. Mobilization started on the second day for both groups, with weight-bearing allowed based on pain tolerance. Patients utilized two crutches for six weeks post-surgery and transitioned to a single crutch after the sixth week. By the end of the second month, all patients could walk unaided.

Fracture union progress was monitored using X-rays taken every 30 days, with bridging callus presence across at least three cortices indicating union. Pathological motion was assessed fluoroscopically after EF removal. Fixator removal occurred in outpatient clinics or operating rooms under general anesthesia, considering patient well-being. After EF removal, a brace protected the operated leg for six to eight weeks.

Statistical Analysis

Analysis employed the NCSS 2007 software, using descriptive statistics (mean, median, standard deviation, ratio, frequency, minimum, maximum), Student's t-test for normally distributed quantitative data comparisons, Mann-Whitney U test for non-normally distributed variables, and Fisher-Freeman-Halton exact test for qualitative data comparisons. Significance was established at $p<0.01$ and $p<0.05$ levels.

RESULTS

The study involved a cohort of 33 patients, comprising 32 males and 1 female, with an average age of 31.97 years (range: 18 to 49). The follow-up period averaged 10.2 years (range: 10 to 12) and 9.86 years (range: 10 to 11) for the MEF and HAIM groups, respectively. Among the fractures, 18% were located in the distal third of the femur, 76% were diaphyseal, and 6% were in the proximal third. Gunshot-induced fractures were predominantly caused by low-velocity (88%) and close-shot (12%) incidents. Vascular and neurological injuries were encountered in only one patient (3%) (Table 1).

Long-term follow-up revealed satisfactory knee range of motion for all patients, although patients treated with MEF experienced easier knee motion. The average fixator duration was 166.81±23.55 days. All fractures healed without requiring a second surgery, and no instances of recurrent fractures, neurovascular deficits, or compartment syndrome were observed.

Table 1. Descriptive characteristics of the groups

	MEF (n=14)	Ilizarov (n=19)	[a]p
	Mean±SD (Median)	Mean±SD (Median)	
Age (yrs.)	30.36±7.95	33.58±7.26	[b]0.235
External fixator time (days)	156.43±18.44	174.47±27.33	[b]0.041*
Follow-up time (months)	49.86±10.20 (53.5)	50.21±4.84 (50)	0.553
Time to union (days)	147.14±20.16	158.16±21.81	[b]0.149
Preoperative wait time (months)	4.07±0.83 (4)	4.11±1.45 (4)	0.760
Surgical time (minutes)	70.36±11.68 (65)	161.53±18.49 (160)	<0.001†
Fluoroscopy time (minutes)	0.77±0.23	3.63±0.79	[b]<0.001†
	n (%)	n (%)	[c]p
AO fracture type			0.791
B3	6 (42.9)	7 (36.8)	
C1	1 (7.1)	3 (15.8)	
C3	7 (50.0)	9 (47.4)	
Gustilo-Anderson fracture type			0.999
Type 3A	12 (85.7)	16 (84.2)	
Type 3B	2 (14.3)	2 (10.5)	
Type 3C	0 (0.0)	1 (5.3)	

aMann-Whitney U test, bStudent's t-test, cFisher-Freeman-Halton exact test, *p<0.05, †p<0.01

Over a 10-year follow-up, no patients experienced re-fractures, and physical examinations and X-rays detected no indications of chronic osteomyelitis or pin site infection in the femoral fracture area. Significantly higher VAS, SF-36, and Tegner activity scores were noted in the MEF group. The two groups exhibited no statistically significant differences in varus/valgus, ante/recurvation angle, mechanical axis deviation, knee extension/flexion deficit, and age.

In terms of pin side infections, noteworthy distinctions were found between the groups. The MEF group required removal of only one infected Schanz pin from the trochanteric region, while the HAIM group necessitated removal of four Schanz pins from the trochanteric region and one from the condylar region, followed by antibiotic treatment. No infections prompted a change in fixation method in either group (**Table 2**).

Discomfort with the fixator was reported by one MEF patient and three HAIM patients, with extreme discomfort rated at 5 points. Complications were generally manageable without lasting consequences. Limb shortening exceeding 2 cm occurred in two HAIM patients who sustained refractures from falls downstairs. In the MEF group, one patient experienced fracture recurrence with minor trauma following fixator removal.

DISCUSSION

Regrettably, gunshot-induced fractures have increased in prevalence in many regions due to escalating personal armament.[10] As with all open fractures, the goals of treating femoral open fractures due to gunshot injuries include preventing infection, promoting fracture healing, and restoring limb functionality.[11-13] External fixators (EFs) are an effective treatment choice for these fractures, considering their common fragmentation, contaminated nature, and challenges posed by early surgical intervention.[14] A notable outcome of this study is the congruence in treatment results and complications encountered between the two distinct fixation techniques.

Patient acceptance and wire tract infections represent major drawbacks of external fixation methods.[8,9,15-17] Wire tract infections, occurring in approximately 95% of cases, are the most frequent complications of external fixators.[7,8,17,18] Monolateral fixators may garner greater patient acceptance due to fewer pins and wires, whereas hybrid systems integrate advantages of both methods for enhanced patient comfort.[15-17] Hybrid systems involving arches and Schanz nails in the hip region and wire-nail combinations in the distal femur have shown promise in enhancing hip and knee mobility.[19]

Table 2. Clinical results of the groups

	MEF (n=14)	Ilizarov (n=19)	[a]p
	Mean±SD (Median)	Mean±SD (Median)	
Pin tract infection	1.50±0.52 (1.5)	2.95±0.23 (2)	0.010*
Varus/valgus	3.50±2.56 (4)	4.79±3.55 (4)	0.287
Ante/recurvatum	5.86±3.11 (5)	6.53±5.12 (5)	0.999
Rotation/internal	2.29±4.86 (0)	3.63±6.77 (4)	0.602
Rotation/external	-2.29±4.86 (0)	-3.63±6.77 (-4)	0.602
Shortness (cm)	0.53±0.64 (0.35)	1.05±0.81 (0.8)	0.035*
Knee flexion (degrees)	125.00±11.09 (127.5)	118.68±14.89 (125)	0.077
Loss of extension in the knee (degrees)	3.29±3.83 (2.5)	4.00±3.86 (5)	0.602
Knee ROM at the 3rd month	96.07±6.84 (95)	89.47±7.43 (90)	0.017*
Knee ROM at the 6th month	125.00±11.09 (127.5)	118.68±14.89 (125)	0.077
VAS post-op	6.00±1.11 (6)	6.63±1.16 (7)	0.174
VAS follow-up	0.71±1.14 (0)	1.95±1.78 (1)	0.021*
SF-36	92.50±6.56 (94.5)	82.05±12.06 (89)	0.001†
Tegner activity score	5.14±1.46 (6)	4.11±1.52 (5)	0.035*
Level of patient comfort	2.29±0.91 (2)	4.47±0.51 (4)	<0.001†
	n (%)	n (%)	[b]p
Pain			0.726
None	11 (78.6)	11 (57.9)	
Mild	2 (14.3)	5 (26.3)	
Moderate	1 (7.1)	2 (10.5)	
Severe	0 (0.0)	1 (5.3)	
Thoresen scoring			0.726
Poor	0 (0.0)	1 (5.3)	
Fair	1 (7.1)	2 (10.5)	
Good	2 (14.3)	5 (26.3)	
Excellent	11 (78.6)	11 (57.9)	

aMann-Whitney U test, bFisher-Freeman-Halton exact test, *p<0.05, †p<0.01

Pain significantly impacts patient quality of life and hampers compliance with physical rehabilitation. Pain sources include wires and nails attaching muscles and wire tract infections.[7,8,16] The MEF technique, avoiding trans osseous wires and employing fewer nails, notably reduces pain and improves joint mobility.

Pin tract infection frequency varies based on fixator design, pin location, tension, and surgical technique. The risk of infection is notably lower in gunshot-induced fractures treated with external fixators compared to other methods. External fixators provide mechanical stability against various forces and minimize postoperative complications such as reduction loss, angular deformities, and shortening.[20]

Ilizarov's external fixation offers the advantage of addressing technical errors without requiring re-surgery. Although limb shortening rates range from 8% to 16% with external fixation, our study achieved adequate femoral length in 94% of cases. Proper initial reduction contributes to avoiding femoral shortening.[1,10,21]

While knee flexion loss is often attributed to external fixators, it's primarily associated with fracture location, soft tissue damage, and lower extremity injuries. Physiotherapy initiated promptly after stabilization mitigates motion restrictions. In our study, no significant intergroup differences were observed in knee motion[8,16]

CONCLUSION

Our data suggest comparable healing time, joint range of motion, and angular deformity outcomes between MEF and HAIM treatment groups. MEF may offer an alternative to HAIM, characterized by reduced patient complaints, lower wire tract infection rates, and enhanced patient comfort 22 MEF's design for deformity surgery provides adequate stabilization and mitigates many complications seen in external fixators. As a low-infection-rate option with similar functional and radiological outcomes to intramedullary fixation methods, MEF holds promise. Further studies comparing MEF with intramedullary fixation methods are warranted for a more comprehensive understanding.[21-23]

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Gazi Yaşargil Training and Research Hospital Clinical Researches Ethics Committee (Date: 06.12.2022, Decision No: 2022/492).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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Original Article

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Evaluation of 8-10 age group children's attitudes and perceptions about smile aesthetics

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ABSTRACT

Aims: The aim of this study is to determine the attitudes and perceptions of 8-10-year-old children regarding smile aesthetics.

Methods: The cross-sectional study included 159 children aged 8-10 and their parents who were undergoing treatment in the Department of Pedodontics at İstanbul University. Participants were asked to fill out a questionnaire consisting of 26 questions. The first 8 questions aimed to assess the socio-demographic characteristics of the families, while the remaining 18 questions measured the attitudes and perceptions of children regarding smile aesthetics in 7 categories. The categories included satisfaction/dissatisfaction, honesty, sacrifice/deceit, selfishness, extroversion/introversion, personal happiness, intelligence, health status, and leadership. Photographs of children with different dental conditions (normally aligned teeth, crowded incisors, and diastema) were shown to the participants. Statistical analyses were performed using SPSS 25.0 software.

Results: Data regarding the seven areas of interest showed that children aged 8-10 years viewed their peers with normally-aligned teeth more favourably as far as extroversion and health status were concerned (p=0.042 and p=0.022 respectively). However, there was no statistically significant difference with regard to satisfaction/dissatisfaction, honesty, sacrifice/deceit, selfishness, personal happiness, intelligence and leadership in children with harmonious, as opposed to crowded or diastema.

Conclusion: Our study suggests that smile aesthetics have a significant impact on social perception during childhood. Orthodontic treatments not only affect smile aesthetics but also influence individuals' social aspects.

Keywords: Child, smile aesthetics, social perception

*This study was presented as an oral presentation at 29th International Congress of Turkish Pedodontics (12-15 October 2023, Ankara, Turkey)

INTRODUCTION

Physical beauty is a significant social issue today, and facial aesthetics are one of its key components.[1-3] Many individuals often find the oro-facial region a matter of considerable concern as it tends to attract the most attention during interpersonal interactions and serves as the primary channel for vocal, physical, and emotional communication.[4] Smile aesthetics, a crucial component of dentofacial aesthetics, has gained great importance.[3,5] Psychosocial significance may be attributed to characteristics such as the color, shape, size, position, and exposure of teeth, irrespective of the presence of any relevant functional or aesthetic impairment.[6] Dental aesthetics is a dynamic concept with parameters that change over time.[7] Recently, increased interest in aesthetic dentistry has resulted from the growing demand for orthodontic and dental treatments among individuals of different age groups. In addition to buccal corridors, gingival display, arch width, tooth shapes and asymmetries, age is another factor that influence the perception of smile aesthetics.[8] Studies in the literature have found a correlation between different age groups and the perception of a smile.[9] Previous investigations have explored aesthetic perceptions related to smiles that exhibit features such as diastema and midline deviation, smile arc, absent teeth, buccal corridor, and gummy smile across a variety of age groups.[10] The results from many of these studies suggest varied perceptions within specific age brackets, which can be attributed to changing attitudes, lifestyles, and opinions. These factors may undergo modifications as individuals age, potentially influencing perceptions of smile aesthetics.[10] Researches also underscores the importance of considering the aesthetic expectations of patients from a young age.[11-14]

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Studies have shown that dental and smile aesthetics play a crucial role not only in interpersonal relationships but also in self-confidence, psychological well-being, and social behaviors. Individuals with an attractive smile are known to be more successful in school and job interviews and even in partner selection.[15-18] Studies have reported that children with normally aligned teeth are perceived by their peers as more intelligent, friendly, and sociable.[11] Similarly, children with crowded, diastema, decayed, and misshapen teeth are reported to be socially disadvantaged compared to those with normally aligned teeth.[11,19] While there are numerous studies evaluating aesthetic perceptions of different smile types in adults, there are limited studies assessing the attitudes and behaviors of children and adolescents regarding smile aesthetics.[20-22] In the studies conducted by Zhaoc et al.[20] and Musskopf et al.[21] the perception of smile aesthetics was evaluated in different age groups with different scales. In the study conducted by Lombardo et al.[22] children in the 8-10 age group with normally aligned teeth were found to be more honest and happy by their peers. Therefore our aim was to evaluate the attitudes and perceptions of Turkish children aged 8-10 regarding smile aesthetics.

METHODS

The study was carried out with the permission of Kocaeli University Non-invasive Clinical Researches Ethics Committee (Date: 08.12.2022, Decision No: GOKAEK-2022/20.17). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study, conducted between March 2022 and March 2023, employed a descriptive cross-sectional design to determine the attitudes and perceptions of 8-10-year-old children towards smile aesthetics. Sample size calculation was performed using the G-Power program (ver. 3.1.9.7; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) for ANOVA: Fixed effects, omnibus, one-way test, considering an effect size of 0.25 (medium), alpha (α) error of 0.05, power of 80%, and assuming three groups. The minimum sample size was calculated as 159.

Patients with systemic diseases, previous orthodontic treatment and difficulty in understanding were excluded from the study. Before the study, written informed consent was obtained from parents of all patients.

Data Collection and Analysis

The research was conducted by the Department of Pedodontics at İstanbul University Faculty of Dentistry. To determine the attitudes and perceptions of 8-10-year-old children towards smile aesthetics, participants in the sample groups were instructed to examine one of several photographs and subsequently fill out a questionnaire. The questionnaire was created by two pedodontic specialists (EBTİ and EA) based on 'Smile perception questionnaire for children between the ages of 8 and 10' (SPQ 8-10) developed previously,[23] professional knowledge, and literature review. For reliability, the test-retest technique was used, where 40 children who participated in the study were systematically and randomly selected for retesting, and the survey form was reapplied to these children. The survey was conducted face-to-face. Furthermore, to achieve valid and reliable results, the prepared survey form was presented to two pedodontic experts and a language expert assisted the experts in the evaluation of questions for comprehensibility before implementation and revised based on their feedback.

The first eight questions of the questionnaire aimed to assess the socio-demographic characteristics of the families. The remaining 18 questions measured the attitudes and perceptions of children regarding smile aesthetics in seven categories: satisfaction/dissatisfaction, honesty, sacrifice/deceit, selfishness, extroversion/introversion, personal happiness, intelligence, health status, and leadership.

After the parents answered the first eight questions on behalf of the child, the remaining questions were answered by the child after showing them selected photos. The selection of which photo to show to each child was randomized using the envelope method. A total of six envelopes were prepared. The first child drew one of the six envelopes, the second child drew one of the five remaining envelopes, and this cycle repeated until all envelopes were used.

Children were asked to answer the questions using a five-point Likert scale ranging from "Strongly Agree" to "Strongly Disagree". The options were scored from 0 to 4: 0 points for "Strongly Disagree," 1 point for "Disagree," 2 points for "Neither Agree nor Disagree," 3 points for "Agree," and 4 points for "Strongly Agree."

The survey questions were carefully formulated considering the age of the participants, and attention was paid to the internal coherence questions to determine whether the responses were given automatically or thoughtfully. These internal coherence questions used in the questionnaire were presented in both negative and positive formats. Consequently, questions 10, 13, 15, 18, 21 and 26 featured inverted response values; for instance, "Strongly Agree" corresponded to a value of 0, while "Strongly Disagree" equated to a value of 4.

Regarding the photos used in the survey, 10 colored photos of ten Turkish children (5 girls, 5 boys) aged 9 were used. Two female and two male residents in the

department of Pedodontics scored each child from 1 to 5 based on their suitability for the general physical structure of Turkish children, without distinct physical features such as red hair or blue eyes. The highest-rated children were chosen for the survey. Photos were manipulated using Adobe Photoshop CS6 (Adobe Systems Inc., San Jose,CA) to obtain versions with normally aligned teeth (ok type), crowded incisors (c type), and diastema (d type). This resulted in six photos (Figure).

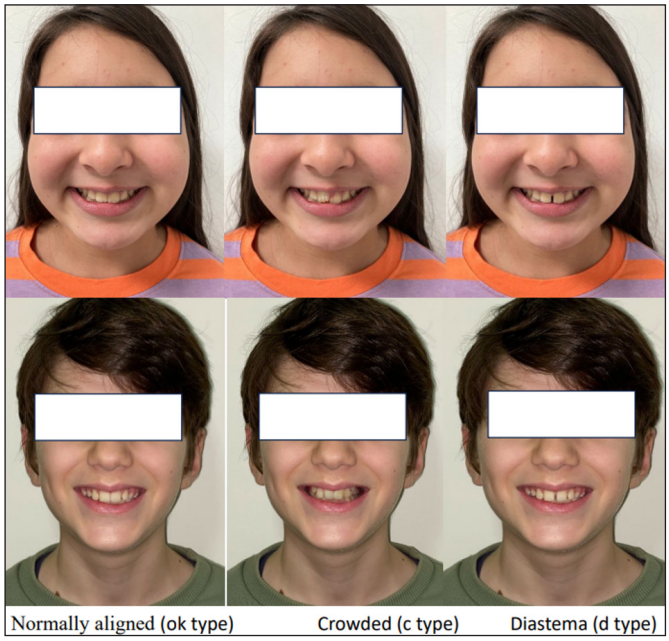

Figure. Photographs of children with normally aligned, crowded, and diastema

Fifty three children analysed either a male or female child's photograph, with normally aligned teeth, 53 children analysed either a male or female child's photograph, with crowded teeth, and 53 children analysed either a male or female child's photograph, with diastema.

Statistical Analysis

Data analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows version 25.0 (IBM Corp., NY, USA). The normal distribution of variables was examined using visual (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov Test). Descriptive analyses were presented as percentages and mean±standard deviation (SD) for continuous variables and median (minimum-maximum) values where applicable. Categorical variable comparisons in independent groups were made using the Pearson chi-square test. For non-normally distributed data, Kruskal-Wallis test was used for comparisons among three or more groups, and ANOVA was used for normally distributed data that met the assumptions. For variables that showed statistical significance, pairwise comparisons were conducted using Mann-Whitney U test for non-normally distributed data, Tukey test for homogeneous variances, and Tamhane's T2 test for non-homogeneous variances. Significance level was set at $p<0.05$.

Test-retest Reliability

40 randomly selected children from the original sample were retested in the same way 15 days later after the verification of the validity of the test. Each child received the same photograph as in the initial test. Correlations of rank between the 18 responses obtained in the first test and the 18 responses obtained in the second test were calculated (Table 1).

Table 1. Test-retest reliability: the number in the first column corresponds to question in the questionnaire. Correlation between test and retest indicate the validity of the results, as a positive correlation was found in all cases

Question number	Test – Retest	P value
9	0.840	0.000
10	0.942	0.000
11	0.560	0.000
12	0.343	0.030
13	0.340	0.032
14	0.716	0.000
15	0.363	0.022
16	0.709	0.000
17	0.405	0.009
18	0.557	0.000
19	0.489	0.001
20	0.623	0.000
21	0.334	0.035
22	0.952	0.000
23	0.719	0.000
24	0.932	0.000
25	0.618	0.000
26	0.458	0.003

RESULTS

A total of 168 children and their families agreed to participate in the study. Nine patients were excluded due to five families refusing to sign the informed consent form and four being incompletely filled out. According to the research findings, the average age of the 159 participating children was 8.9±0.84 years, with 47.2% being boys and 52.8% girls. 69.8% of the children had come to hospital with their mothers and whereas 30.2 % of the participants were the fathers in the study. The mean age of the parents were 38.67±5.76 years (minimum 25, maximum 53). The majority of the children's families had an educational level of high school or below (84.9%). Again, the majority of family members had marked the question about "your profession" as 'homemaker/not employed' (64.2%). Our results suggested that, 57% of

the participants' monthly income was below the poverty line. (The socio-economic status of the families was determined according to Turkish Statistical Institute (TURKSTAT) data.[24]) The majority of families had 2 or more children (35.2% had 2, 38.4% had 3 and 20.8% had ≥4 children), and the child they brought for treatment was mostly their second child (74%).

When analyzing the survey results, a significant difference was found between the "ok type" and other two groups in terms of "health status" (p=0.022) (Table 2). Children aged 8-10 statistically found their peers with "ok type" teeth more extroverted compared to those with crowded teeth and diastema since, a statistically significant difference was found in terms of friendship relationships between the "ok type" and other two groups (p=0.042) (Table 3). In contrast, no significant results were found for personal happiness, intelligence, leadership, satisfaction, and honesty indicating that these criteria were not perceived to be affected by smile type.

Table 2. Comparison of the smile type shown as a photograph and the answers given by children regarding "health status" category in the questionnaire using the Pearson chi-square test

Groups	Strongly disagree	Disagree	Neither disagree nor agree	Agree	Strongly agree	Total
C type	7	19	5	17	5	53
D type	5	23	4	16	5	53
Ok type*	5	6	5	32	5	53
Total	17	48	14	65	15	159

*p=0.022, Ok type: normally aligned teeth, C type: crowded incisors, and D type: diastema

Table 3. Comparison of the smile type shown as a photograph and the answers given by children regarding "extroversion/introversion" category in the questionnaire using the Pearson chi-square test

Groups	Strongly disagree	Disagree	Neither disagree nor agree	Agree	Strongly agree	Total
C type	3	11	7	28	4	53
D type	3	4	5	34	7	53
Ok type*	2	1	4	34	12	53
Total	8	16	16	96	23	159

*p=0.042, Ok type: normally aligned teeth, C type: crowded incisors, and D type: diastema

DISCUSSION

In daily life, the focus of interpersonal communication is predominantly on the orofacial region.[25] Consequently, facial aesthetics, due to the psychological impact it creates, holds great importance in individuals' overall quality of life. Smile aesthetics also plays a key role in general aesthetics.[26] The aesthetic norms of today's society encourage individuals to seek orthodontic and dental treatment to achieve a beautiful and harmonious smile.[9]

The perception of smile aesthetics is subjective and shaped by an individual's experiences and social surroundings.[27] There are studies in the literature that deal with aesthetic perceptions of smile types in different age groups in a range between 13 and 60 years old.[28-30] Since orthodontists mostly manages and treats malocclusions in younger patients, there occurred a need to consider the aesthetic expectations of patients at a young age.[23] Additionally, analyzing children's perceptions of dental aesthetics has become an important topic to understand societal values.[2]

The purpose of selecting children in the 8-10 age group for evaluating the perception of smile aesthetics in this study is due to the completion of eruption of the front four incisors in this age group, the possibility of preventive orthodontic treatment before fixed treatments during this period, and the comprehensive exploration of the inner motivation of children in this age group for orthodontic treatment not being extensively studied.

Children participating in our study statistically found their peers with normally aligned teeth to be more extroverted compared to those with crowded teeth and diastema teeth (p=0.042). This aligns with the results of Lombardo et al.'s[22] study on the same age group, where children with normally aligned teeth were perceived as more talkative by their peers (p<0.05).

Shaw,[11] conducted a study in 1981 on 840 children aged 11-13, evaluating their aesthetic perceptions of smiles using the Visual Analog Scale (VAS). The study found that children with normally aligned teeth were considered more attractive by their peers (43.1 mm, p<0.01). However, our study did not find a statistically significant difference in this aspect among the three groups (p>0.05).

In Verdecchia et al.'s[23] study, children with normally aligned teeth were perceived as statistically more advantageous in terms of honesty, personal happiness, and intelligence compared to their peers with proclined and crowded teeth (p<0.05). In our study, no significant difference was observed among the three groups regarding honesty, personal happiness, and intelligence (p>0.05). We suggest that these different results of our study may be attributed to ethnic and cultural disparities, individual characteristics, socio-economic status, elements of social media, parental influence and the surrounding environment.

Our study has a few limitations. Firstly, only the first impression was analyzed in our survey study. Secondly, the study population were small children between 8 to 10 years-old and these small children often needed assistance during the study. Additionally, we believe that the overall facial appearance in the

presented photographs could introduce bias. In future studies, investigating the same smile in different facial combinations could mitigate this bias.

CONCLUSION

Our study suggests that smile aesthetics have a significant impact on social perception in this sample of 8-10 years-old children. Our results showed a correlation between normally aligned smile and the level of desirability perceived by peers, with highly significant findings in relation to qualities such as extroversion and health status. Conversely, regarding the attributes of personal happiness, intelligence, leadership, satisfaction, and honesty, the results did not reach statistical significance to suggest a preference for aesthetic smiles over those with crowded teeth or diestema teeth. Orthodontic treatments not only affect smile aesthetics but also influence individuals' social aspects. When making clinical decisions during orthodontic treatment, psychological and aesthetic factors should be evaluated together.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kocaeli University Non-invasive Clinical Researches Ethics Committee (Date: 08.12.2022, Decision No: GOKAEK-2022/20.17).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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Original Article

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Prognostic evaluation of newborns with neonatal hyperbilirubinemia

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ABSTRACT

Aims: We aimed to investigate the effect of phototherapy treatment by showing that it increases systemic inflammation and changes in NLR (neutrophil count/lymphocyte count), PLO (platelet count/lymphocyte count), systemic Inflammation Index (platelet count × neutrophil count/lymphocyte count ratio) in peripheral blood.

Methods: It was conducted at Balıkesir University Health Practice and Research Hospital between April 2023 and August 2023. 60 babies with a gestational age of ≥36 weeks and a birth weight of ≥2500 g were included in the study.

Results: A statistically significant difference was detected between WBC, lymphocyte count, monocyte count, neutrophil count, lymphocyte/monocyte, systemic inflammatory index before and after phototherapy ($p<0.05$).

Conclusion: We concluded that phototherapy is associated with the inflammatory process and may increase cytokine release. To investigate these effects of phototherapy, studies on larger populations are needed.

Keywords: Neonatal jaundice, systemic inflammatory index, phototherapy

INTRODUCTION

Neonatal hyperbilirubinemia effects at least 2/3 of newborn. Most of them are benign and resolve spontaneously. However, some need phototherapy.[1] Blue light of 430-480 nm size is used in the treatment of hyperbilirubinemia.[2] Phototherapy treatment has been shown to stimulate the release of cytokines and growth factors by acting on cell surface receptors. Recent studies suggest that phototherapy increases the release of cytokines and causes an inflammatory process.[3] The effectiveness of phototherapy increases as the body cell surface increases.[4] Exposure of cells to this light may cause DNA chain breaks and chromatid fractures.[5]

In terms of phototherapy, serum crystalline level is evaluated and determined according to the Bhutani curves determined by the American Academy of Pediatrics (APA).[6,7] Nowadays, LED devices for phototherapy have begun to be widely used and fewer side effects have begun to be observed. In a study, the difference between conventional phototherapy and LED phototherapy devices was examined, and it was found that LED phototherapy devices had less effect on eosinophils, albumin and uric acid.[8]

Phototherapy application provides protection against acute bilirubin encephalopathy and kernicterus and saves blood exchange.[9-11]

In our study, we aimed to determine the place of phototherapy in the inflammation process by calculating the change in NLR (neutrophil count/lymphocyte count), PLO (platelet count/lymphocyte count), systemic inflammation index (platelet count x neutrophil count/lymphocyte count ratio) in peripheral blood before/after phototherapy.

METHODS

The study was carried out with the permission of the Balıkesir University Non-invasive Clinical Researches Ethics Committee (Date: 23/08/2023 Decision no: 2023/116). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study was conducted at Balıkesir University Health Practice and Research Hospital between April 2023 and August 2023. Newborns with a gestational age of ≥36 weeks and a birth weight of ≥2500 g were included in the study. 60 newborns younger than the 15th postnatal day were included in the study. Phototherapy treatment was given to 30 newborns, and 30 newborns were healthy controls who had blood tests done for any reason and did not receive phototherapy treatment. The charts of the newborns who received phototherapy with the diagnosis

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of indirect hyperbilirubinemia were retrospectively analyzed. Newborns who had complete blood counts one hour before phototherapy starts and twenty-four hours after phototherapy ends were included in the study. Newborns whose gestational age was less than 36 weeks, who were diagnosed with sepsis, and who had congenital anomalies were excluded from the study. NLR (neutrophil count/lymphocyte count), PLO (platelet count/lymphocyte count), systemic inflammation index (platelet count × neutrophil count/lymphocyte count ratio) were calculated from the blood taken before phototherapy, and from the peripheral blood taken for control 24 hours after phototherapy was given. The neonates' birth week, delivery method, birth weight, maternal age, maternal education level, and bilirubin level were recorded.

Statistical Analysis

SPSS 23.0 package program was used for statistical analysis of the study. Descriptive statistics of continuous variables are shown with mean, standard deviation, median, minimum and maximum values, and categorical variables are shown with frequency and percentage. Suitability of continuous variables to normal distribution Shapiro It was examined with the Wilk test. One-way analysis of variance (ANOVA) was used for comparisons of normally distributed continuous variables between 3 or more groups. Mann Whitney U test was used for comparisons of variables that did not show normal distribution between 2 groups, and Kruskal Wallis test was used for comparisons of 3 or more groups. Pearson chi-square, Yates corrected chi-square and Fisher exact chi-square tests were used for group comparisons of categorical variables. In all statistical comparisons in the study, comparisons with a p value below 0.05 are considered statistically significant.

RESULTS

60 newborns were included in the study. The control group consisted of 30 newborns and was the group in which venous blood was taken for any reason without phototherapy. Phototherapy treatment was applied to the patient group of 30 newborns. Criteria for inclusion in the study were postnatal age of less than 15 days, gestational age between 36 and 42 weeks, and birth weight of 2500 g and above. The median birth weight of all babies included in the study was 3120±408 g. Median bilirubin levels were determined as 16±1.9 g/dl. Maternal ages ranged from 18 to 42 years. The weight loss of the newborns at application was between 5-8%.

Of the newborn receiving phototherapy, 12 had newborns ABO group incompatibility, 2 newborns had Rh incompatibility. There was no subgroup incompatibility. No cause was found in the others. 33 of them were born by cesarean section. 20% of the newborns' mothers were uneducated and 15% were university/college graduates. 30% of the newborns included in the study were admitted on the 3rd postnatal day. There was no statistically significant difference in terms of maternal age, education level and phototherapy treatment (p>0.05). Additionally, when the groups that received phototherapy and those that did not receive phototherapy were compared, no statistically significant difference was found between week of birth, method of delivery and day of admission (p>0.05).

WBC, hemoglobin, lymphocyte, monocyte, neutrophil, and platelet values in the peripheral blood of the newborns taken before/after phototherapy were recorded. Lymphocyte/monocyte count ratio, neutrophil/platelet count ratio, systemic inflammatory index (neutrophil × platelet count/lymphocyte count) values were calculated. A statistically significant difference was detected between WBC, lymphocyte count, monocyte count, neutrophil count, lymphocyte/monocyte, and systemic inflammatory index before and after phototherapy (p<0.05) (Table).

Table. Change and statistical analysis of peripheral blood values before/after phototherapy (p<0.05*)

Values	Before phototherapy	After phototherapy	p
WBC (×10⁹/L)	15106±2744	16625±2198	0.01*
Hemoglobin (g/dl)	16.7±1.3	16.9±1.1	0.1
Lymphocyte (×10⁹/L)	4514±1977	10580±5640	0.01*
Monocyte (×10⁹/L)	1159±490	1653±795	0.02*
Neutrophil (×10⁹/L)	8846±2472	9943±2044	0.0**
Platelet (×10⁹/L)	361033±58597	368500±56475	0.34
Lymphocyte/monocyte	4.27±2.15	3.10±1.60	0.01*
Neutrophil/lymphocyte	2.25±0.9	2.27±0.7	0.07
Neutrophil*platelet/ lymphocyte	848550±413427	917219±323494	0.02*

There was no significant difference in WBC, hemoglobin, lymphocyte, monocyte, neutrophil and platelet values after phototherapy compared to the control group. (p>0.05) (Table).

DISCUSSION

In our study, when the values before/after phototherapy were compared, a difference was detected especially between WBC, lymphocyte and monocyte levels, and these results are like the study by Kurt et al.[3] In the study conducted by Kurt et al.[3] an increase in WBC, lymphocyte, and monocyte was observed after phototherapy, but no statistically significant difference was detected with wbc. It has been said that the increase in WBC can be explained by the stress of newborns in

the first days. In a similar study, it was reported that phototherapy did not increase cytokine release but caused an increase in peripheral blood cells.[12]

In the study conducted by Yılmaz et al.[13] the effects of phototherapy on peripheral blood cells were examined, 30 term and 30 preterm babies who received phototherapy were taken, a significant decrease was detected in WBC, RBC, Hgb, MCV, RDW values in term babies after phototherapy, and a significant increase was detected in the MCHC and monocyte rate. It has been said that the change here can be attributed to ABO and Rh incompatibility. In our study, the monocyte percentage increased significantly after phototherapy. In a study conducted on babies with neonatal sepsis, the neutrophil/lymphocyte ratio was found to be significantly high, and it was suggested that it could be used as a marker of infection.[14]

In the study conducted by Khera et al.[15] it was found that platelet values decreased significantly after phototherapy. In this study, neonates with direct hyperbilirubinemia, whose mothers used anti-platelet medication, and who had sepsis were excluded from the study. Platelet values of these babies were measured 24 hours after phototherapy. Low platelet count was observed in 74% of the patients included in the study. The occurrence of thrombocytopenia did not vary depending on gender and gestational age. Thrombocytopenia has been attributed to the acceleration of platelet turnover due to ultraviolet light damage. A similar result was found in another study.[16]

A significant difference was observed between the neutrophil*platelet/lymphocyte ratio, calculated as the systemic inflammation index, before and after phototherapy.[17] We think that this marker, which is mostly used as a prognostic indicator in inflammatory diseases, is due to the relationship of phototherapy with the inflammatory process. In a study conducted on patients with Ulcerative Colitis, a significant relationship was found between the systemic inflammation index and disease progression.[18] In the study conducted by Ercan et al.[19] it was shown that the systemic inflammation index is effective in determining mortality in dialysis patients. The neutrophil/lymphocyte ratio was used to predict the prognosis of acute cholecystitis patients and was found to be compatible with the severity of cholecystitis. Additionally, it may differ depending on the shock index and serum lactate level measured in multitrauma patients.[20,21]

When the immunomodulatory and immunotoxic effects of phototherapy were examined, it was shown that especially the number of CD4 lymphocytes increased after phototherapy.

CONCLUSION

We concluded that phototherapy, which is an effective treatment method that is frequently used today and prevents kernicterus from bilirubin toxicity, may be associated with the inflammatory process. More studies are needed on a larger population to investigate these effects of phototherapy. Shock index in future trauma patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Balıkesir University Non-invasive Clinical Researches Ethics Committee (Date: 23/08/2023 Decision no: 2023/116).

Informed Consent: Because the study was designed retrospectively, no written informed consent forms were 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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Original Article

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Evaluation of single center clinical experience in patients undergoing modified Limberg flap technique in pilonidal sinus disease

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ABSTRACT

Aims: Pilonidal sinus disease (PSD) is a chronic inflammatory disease that is seen especially in young men, is often located in the sacrococcygeal region and negatively affects the quality of life and daily life of the person. In this study, we aimed to share our experience with the literature by examining our clinical approach and results in the patient group who underwent Modified Limberg flap technique electively in PSD.

Methods: Patients who underwent elective modified Limberg flap application due to PSD in the general surgery clinic were included in the study. Demographic and clinical parameters of the patients were investigated retrospectively.

Results: The mean age of 76 patients included in the study was 27.5±8.5 years (18-51 years). The median duration of hospitalisation was 2 days. The most commonly preferred prophylactic antibiotic at surgery was cefuroxime + metranidazole combination (60.5%) or cefuroxime alone (32.9%). Drain use was present in approximately 40% of the cases. Subcutaneous tissues were closed with a single layer of polyglactin suture in most cases (94.7%). During the median follow-up period of 12 months, postoperative recurrence was observed in only 6 cases (7.9%).

Conclusions: Modified Limberg flap technique is a well-defined, safe and feasible surgical method. Since it is an effective off-midline technique, its application by experienced surgeons in complicated and recurrent cases in elective PSD surgery and its transfer to junior and resident surgeons will be effective in terms of moving away from midline techniques.

Keywords: Pilonidal sinus disease, modified Limberg flap, pilonidal sinus excision

INTRODUCTION

Pilonidal sinus disease (PSD) is a chronic inflammatory disease seen especially in young men, frequently localised in the sacrococcygeal region and negatively affects the quality of life and daily life of the person. Surgery is generally recommended for treatment, however, conservative methods such as phenol therapy can also be applied. Despite it is considered a chronic disease, patients may also present with pilonidal abscess clinic and may require emergency intervention in the form of surgical drainage.[1,2]

Successful treatment of the disease is determined not only by wound dehiscence, recurrence and low complications, but also by findings such as rapid and comfortable return to daily life and acceptable aesthetic appearance. In addition to various excision techniques, primary closure, flap methods can be applied in surgical treatment, and unroofing curettage and marsupialisation methods can also be preferred in selected cases.[2,3]

Due to complications such as recurrence and wound dehiscence, which are observed more frequently than primary closure technique, the application rate has decreased in recent years, but it is known that the preference for this technique is still high. Methods using flaps are increasingly preferred due to their advantages such as shifting the midline, decreasing the depth distance and low recurrence rates.[3]

Among the flap methods are Z-plasty, W-plasty, V-Y advancement flap, Limberg flap, Karydakis flap, gluteus maximus myocutaneous flap and fasciocutaneous rotation flaps. In the selection of these techniques, the experience of the surgeon is important, as well as the size and condition of the disease at the time the operation is decided, aesthetic concerns and patient comfort are also important.[4,5]

In this study, we aimed to share our experience with the literature by analysing our clinical approach and results in a group of patients who underwent elective Modified Limberg flap technique in PSD.

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METHODS

The study protocol was approved by the University of Health Sciences Gülhane Training and Research Hospital Clinical Researches Ethics Committee (Date: 27.09.2023, Decision No: 2023/206). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Procedure and Population

Patients who underwent elective modified Limberg flap application due to PSD in the general surgery clinic were included in the study.

Patients over the age of 18 who underwent elective excision and modified Limberg flap application due to PSD in the general surgery clinic between January 2017 and June 2023 in a single tertiary hospital were included in this descriptive retrospective cohort study after receiving ethical approval from the local committee. Patients who underwent other procedures due to pilonidal sinus disease, patients who underwent emergency pilonidal abscess drainage, and patients with missing or missing hospital records were excluded from the study as well as patients under the age of 18.

Demographic and clinical data of the patients such as age, gender, comorbidities, body-mass index (BMI), American Society of Anesthesiologists (ASA) scores, smoking and alcohol consumption status, preoperative crystallised phenol treatment status, operative findings such as preoperative symptom duration, duration of surgery, drain usage, postoperative findings such as postoperative antibiotic usage choices, hospital stay, complications were analysed retrospectively. Preoperative laboratory values such as hemoglobin (g/dl), hematocrit (%), albumin (g/dl), creatinine (mg/dl), Platelet (10^3/µl), blood urea nitrogen (mg/dl), C-reactive protein (mg/dl), leukocyte (10^3/µl), neutrophil (10^3/µl) as well as lymphocyte (10^3/µl) were also evaluated.

Surgical Technique

Following appropriate field cleaning with 10% povidone iodine solution and sterile dressing, marking and drawing was performed with sterile surgical skin marker. The pilonidal sinus orifices were taken to the central region and the patient was descended to the presacral fascia with a rhomboid incision. In order to ensure that the lower end of the flap did not reach the midline to include the entire lesion, excision was completed in the PSD region in the shape of a rhombus, with the lower corner on the left and right lateral sides of the midline, and then, after ensuring haemostasis in the operation area, the area was washed with 0.9% saline and aspirated. A flap was prepared from the right gluteal region, including the skin, subcutaneous tissues, fatty planes and the fascia over the gluteus maximus muscle, and the flap was freed sufficiently without creating flap tension, and the flap was prepared and shifted to cover the loin and the corners to be mutually equal. Afterwards, depending on the preference of the surgeon, following the use of Jackson-Pratt drain, the layers from the presacral fascia were closed mutually with the help of absorbable polyglactin sutures in the anatomical plan. Skin was closed with non-absorbable polypropylene sutures using matress technique or surgical skin stapler depending on the surgeon's preference. The patient was terminated with appropriate wound dressing.

Statistical Analysis

Statistical evaluation was performed using SPSS program version 22.0. The conformity of the variables to the normal distribution was analysed using visual (histograms and probability plots) and analytical methods ("Shapiro-Wilk tests"). Continuous variables distributed normally were expressed as mean ± standard deviation, and continuous variables not distributed normally were expressed as median (minimum-maximum value). Categorical data were shown as numbers (percentages). P value <0.05 was considered statistically significant.

RESULTS

The mean age of 76 patients included in the study who operated with Modified Limberg flap technique was 27.5±8.5 years (18-51 years). Also, 86.8% of the patients were male and 13.2% were female. The male/female ratio was 6.6/1. Most patients (80.3%) had a preoperative ASA score of I. Comorbid diseases accompanied 15.8% of the cases. The median symptom duration was 4.5 months. Approximately one-fourthof the cases had been previously treated with phenol. Table 1 shows the descriptive characteristics of the patients.

Table 1. Descriptive characteristics of patients

Characteristic	n (%)
Age*	27.5 ± 8.5
Gender	
Female	10 (13.2)
Male	66 (86.8)
American Society of Anesthesiologists Score	
I	61 (80.3)
II	15 (19.7)
Body-Mass Index (kg/m2)	27.0 ± 3.7
Smoking	44 (57.9)
Alcohol Consumption	20 (26.3)
Comorbidity	12 (15.8)
Diabetes mellitus	7 (9.2)
Hypertension	5 (6.6)
Symptom duration (month)**	4.5 (1-24)
Preoperative crystallized phenol treatment	21 (27.6)

*Mean ± Standard Deviation, * * Median (minimum-maximum).

The preoperative hematological and biochemical laboratory parameters of the patients are shown in Table 2. Examining the mean laboratory values of the patients, it was observed that they were within normal limits.

Table 2. Laboratory results of the patients

	Mean ± Standard Deviation
Haemoglobin (g/dl)	13.0 ± 1.2
Hematocrit (%)	37.9 ± 3.1
Albumin (g/dl)	4.1 ± 0.4
Creatinine (mg/dl)	0.8 ± 0.1
Platelets (10^3/µl)	298 ± 62
Blood urea nitrogen (mg/dl)*	33 (9-42)
C-Reactive Protein (mg/dl)*	4.2 (0.1-32.4)
Leukocyte (10^3/µl)*	7.4 (4.1-15.6)
Neutrophil (10^3/µl)*	5.5 (2.9-12.7)
Lymphocyte (10^3/µl)*	1.2 (0.5-2.8)

*Median (minimum-maximum)

The most commonly preferred prophylactic antibiotic at surgery was cefuroxime+metranidazole combination (60.5%) or cefuroxime alone (32.9%). Drain use was present in approximately 40% of the cases. Subcutaneous tissues were closed with a single layer of polyglactin suture in most cases (94.7%). The most preferred polyglactin suture materials were 2-0 (81.6%) and 3-0 (11.8%) absorbable polyglactin sutures. The skin was closed by mattress technique with polypropylene sutures in a significant proportion of patients (90.8%). The most preferred polypropylene suture materials were 3-0 (73.7%) and 2-0 (11.8%) non-absorbable polypropylene sutures. The median operation time was 50 minutes. Complications were observed in 22.4% of the cases. Nevertheless, these complications were limited to wound infection (13.2%) and wound dehiscence (9.2%). The median duration of hospitalisation was two days. During the median follow-up period of 12 months, postoperative recurrence was observed in only 6 cases (7.9%) (Table 3).

Table 3. Characteristics of patients related to surgery

Characteristic	n (%)
Antibiotic treatment	
Cefuroxime + Metranidazole	46 (60.5)
Cefuroxime	25 (32.9)
Metranidazole	5 (6.6)
Drain usage	31 (40.8)
Closure of subcutaneous tissues	
Single layer polyglactin	72 (94.7)
Double layer polyglactin	4 (5.3)
Type of polyglactin	
0-0	3 (3.9)
1-0	2 (2.6)
2-0	62 (81.6)
3-0	9 (11.8)
Skin closure	
Mattress with polypropylene	69 (90.8)
Surgical skin stapler	7 (9.2)
Polypropylene type	
0-0	6 (7.9)
1-0	5 (6.6)
2-0	9 (11.8)
3-0	56 (73.7)
Duration of operation (minutes)*	50 (25-110)
Complication	14 (22.4)
Wound infection	10 (13.2)
Wound dehiscence	7 (9.2)
Duration of hospitalization (days)*	2 (1 - 11)
Follow-up period (months)*	12 (12-18)
Recurrence	6 (7.9)

*Median (minimum-maximum)

DISCUSSION

PSD has an important place in general surgery practice and may require both elective and emergency interventions. This disease, which is especially characterized by sacrococcygeal region involvement and is blamed at a higher rate, can adversely affect the quality of life and the incidence rate has been reported as 26/100,000. Although it is 2 times more prevalent in the male population than in the female population, it peaks between 15-30 years of age and creates a high cost-effectiveness on the health system.6 Untreated disease often leads to infection and very rarely to squamous cell carcinoma within the sinus tracts in chronic non-healing tissues, leading to a wide range of complications.[7]

There are discussions in the literature on the relationship between the ideal treatment in PSD and the condition of the disease at the time of detection, risk factors, surgeon's experience and patient selection; and recently, especially depilative and ablation laser treatment applications and crystallised phenol treatment sessions are increasing in popularity.[7,8]

Even though it is stated in the literature that crystallised phenol applications can be applied with high success and low complication rates, it is observed that its application in uncomplicated cases is more prominent, and in some studies, it is also observed that it is applied as a stepwise treatment with excisional surgery. Furthermore, there are studies reporting that tissue adhesives such as fibrin glue are treatment options as monotherapy or surgical adjunct.[9,10] In our study, crystallized phenol treatment was found to be applied in the preoperative period in 27.6% of the patients.

Depilatory or ablation laser applications have also been increasing recently. It is stated in the literature that it is safe and successful in reporting aesthetically pleasing results, however, its high costs and the fact that it is not widespread in clinical practice emerge as its negative features.[11,12] In this study, laser application is not included in the history of any patient and in the practice of our clinic.

The idea of "tailored surgery" being the ideal treatment in PSD is at the forefront, and the superiority of the off-midline technique over the midline technique has been clearly stated, especially in scientific studies, and it has been revealed that it reduces the risk of recurrence. Among these techniques, especially Modified Limberg and Karydakis flap techniques stand out with their low complication rates and satisfactory results. Moreover, in many comparison studies, no significant differences were observed between the two techniques in terms of both complication rates and recurrence.[13,14] In this study, the results of Modified Limberg flap technique applied extensively in our clinic were emphasized.

Although the use of drains in the modified Limberg flap technique, like other flap techniques, is observed to be routine in some studies and related to the surgeon's preference and the condition of the operation in some studies, the use of drains with negative vacuum suction system is recommended to limit complications such as seroma and haematoma formation.[14,15] In this study, Jackson-Pratt drain utilisation remained at 40.8%.

The subcutaneous tissues are closed with absorbable polyglactin and the thickness of the suture material used and the number of layers applied are important for the flap to adhere to the intact tissue in a healthy way, to prevent necrosis and to provide tension-free tissues. Despite there is a consensus in the literature regarding the use of the mentioned suture material under the skin, it is advocated that the tissue depth is appropriate for the number of layers.[16,17] Single layer (94.7%) and 2-0 polyglactin suture (81.6%) were utilized more frequently in this study. In addition, the matress primary closure technique with 3-0 polypropylene suture for the skin was determined as the primary preference.

In the systematic review of Boshnaq et al.[18] the postoperative complication rate was 11.5%, the recurrence rate was 7.5% and the mean follow-up period was 18 months. In the studies of Destek et al.19, the mean operational time was 54 (44-75) minutes, the recurrence rate was 7.5%, and the mean length of hospital stay was 2.3 days. In the single-blinded, parallel, randomized study of Alvandipour et al.[20] 11.1% fluid collection and 3.7% surgical site infection were observed as complications, yet no recurrence was detected during the follow-up period. In this study, apart from the high complication rates, other findings were observed to be consistent with the literature.

This study has some limitations such as its retrospective design, the fact that operations are not performed by a single surgeon, the small number of patients and the absence of a comparison group. Nonetheless, the fact that the population is only on an elective single surgical procedure and the design of the study in a center with a high patient volume are seen as an important reason for these limitations.

CONCLUSION

Modified Limberg flap technique is a well-defined, safe and feasible surgical method. Since it is an effective off-midline technique, its application by experienced surgeons in complicated and recurrent cases in elective PSD surgery and its transfer to junior and resident surgeons will be effective in terms of moving away from midline techniques.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Gülhane Training and Research Hospital Clinical Researches Ethics Committee (Date: 27.09.2023, Decision No: 2023/206).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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Original Article

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Turkish literature on hip arthroscopy: a bibliometric approach

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ABSTRACT

Aims: This study aimed to analyze research productivity and trends in Turkey using published articles on hip arthroscopy.

Methods: Studies indexed in the Science Citation Index Expanded (SCIE) and Emerging Sources Citation Index (ESCI) of the Web of Science (WoS) database from 1981 to 2023 have been examined. The analysis included the number of articles by year, country, institution, citation count, and journal of publication. Additionally, the Scopus database was analyzed for comparison.

Results: Research revealed 35 articles in the WoS database and 115 articles in the Scopus database as of November 2023. In the WoS database (journals published in the ESCI and SCIE indexes), Turkey ranked 16th out of 64 countries, while in the Scopus database, Turkey ranked 13th.

Conclusion: Compared to other countries, Turkey has a significantly low number of articles. However, the increase in publications aligns with the global trend.

Keywords: Bibliometric analysis, hip arthroscopy, publications

INTRODUCTION

The first recorded hip arthroscopy on cadavers took place in 1931, executed by Michael S. Burman.[1] In 1939, Takagi published the first clinical application.[2] This topic remained unpopular for an extended period. Subsequent studies were restricted until the commencement of the 1980s when numerous articles were published.[3] It has attracted interest, particularly in younger patients with hip pathology, as a non-arthroplasty and minimally invasive procedure.[4,5] This technique has proven effectiveness for various intra- and extra-articular hip problems. With the advancing comprehension of hip pathophysiology, hip arthroscopy is likely to have a greater impact on the diagnosis and management of hip disorders. Indications for hip arthroscopy will continue to evolve, leading to some indications gaining popularity while others become less effective and their use in these areas declines.[6-8] As the procedure becomes more popular, the industry will be incentivized to innovate, leading to quicker development of specialized hip instrumentation. Hip arthroscopy represents an exciting advancement in orthopaedic surgery with promising potential benefits for patients.[9,10]

Articles on hip arthroscopy began to be published globally in the 1980s, and the number of publications has since increased rapidly. The first article on this topic in Turkey was published in 2005. When analysing the number of articles, it is evident that there is an increasing trend both in Turkey and worldwide. However, this technically challenging method, which offers promising results for patients, is not currently available in Turkey. The evaluation of the current situation in Turkey is crucial for this technically challenging method that offers promising results for patients, as stated in the literature.

Bibliometric analyses are an effective method for tracking long-term research trends in a field.[11-14] This method enables objective evaluation of research contributions by different countries, institutions, journals, and authors in the scientific field. It further facilitates analysis of research trends and identification of current perspectives. Bibliometric studies are widely used in orthopaedics and remain popular today.[15-19] However, there are no bibliometric studies on hip arthroscopy in Turkey in the existing literature.

METHODS

Our study is a bibliometric analysis, and therefore does not require ethics committee approval. No ethical norms were violated during the development and publication of this research.

Numerous online databases are available for bibliometric analysis. This study chose Web of Science (WoS), Science Citation Index Expanded (SCI-E), and Emerging Sources

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Citation Index (ESCI) for their high scientific quality and reliability. For the document type, "article" was selected. The WoS database was accessed on 15 November 2023, retrieving articles related to hip arthroscopy from around the world and Turkey between 1981 and November 2023. As the WoS database combines references to both 'Turkey" and 'Türkiye" as one entity, the corresponding data and percentages were merged to produce the final results.

Search terms, selected from the MESH library, were: "hip arthroscopy" [All Fields] OR "arthroscopy of the hip" [All Fields]. The literature, filtered using exclusion criteria from the study plan, was downloaded in Word and Excel file formats. The data obtained were then analyzed. Bibliometric parameters such as publication year, language used, first author's name, country of publication, total citations, journal title, and affiliated institutions were considered in the evaluation.

Excel files were utilized to create graphs and tables, employing percentage and frequency values for table creation. In addition to Scopus and WoS database's own graphs, the VOSviewer tool (Leiden University, The Netherlands) was used to produce bibliometric networks and visualizations.[20,21]

We opted to compare the Scopus database with the WoS database, using identical search criteria, keywords, and timeframes.

RESULTS

A total of 2,726 articles were indexed as SCI-E and ESCI in the WoS database worldwide. The first year with 10 or more studies on hip arthroscopy per year was 2001, and the first year with 100 or more studies was 2012. Years with 100 or more studies per year are shown in Table 1. Fifty percent of the studies on hip arthroscopy were conducted after 2018. In Turkey, the WoS database contains 35 studies on hip arthroscopy. The first study on this topic was published in 2005, with no more than five studies conducted in any given year (Table 2).

Table 1. According to the WOS database, more than 100 articles on hip arthroscopy have been published worldwide over the years

Year	Number of articles	% of 2726
2023	152	5.576
2022	256	9.391
2021	309	11.335
2020	265	9.721
2019	230	8.437
2018	222	8.144
2017	166	6.090
2016	182	6.676
2015	126	4.622
2014	144	5.282
2013	105	3.852
2012	102	3.742

Table 2. Distribution of studies in Turkey by year according to the Wos database

Years	Number of articles	% of 35
2023	5	14.286
2022	5	14.286
2021	1	2.857
2020	1	2.857
2019	4	11.429
2018	2	5.714
2017	5	14.286
2016	2	5.714
2015	2	5.714
2014	2	5.714
2013	2	5.714
2011	1	2.857
2010	1	2.857
2007	1	2.857
2005	1	2.857

In 64 countries, a total of 2,726 articles were indexed. Table 3 reveals that 22 countries published more than twenty articles; the USA emerged as the leader with 1,663 publications, followed by the UK (159 articles) and Germany (153 articles). Worldwide, 96.22% of publications were in English, with German in second place at 3.11%. All publications from Turkey were in English. With a total of 35 articles, Turkey ranks 16th in the number of articles published on hip arthroscopy. The majority (77.143%) of these papers were published in SCI-E indexed journals, with the remaining 22.857% in ESCI indexed journals. A total of 138 different institutions in Turkey have contributed to the literature on hip arthroscopy. İstanbul University (with 8 articles) and Ankara University (with 5 articles) were the most prolific institutions. Further details on leading publishing institutions are shown in Figure 1.

Table 3. According to WOS database results, the countries that publish the most on hip arthroscopy worldwide

Rank	Country	Number of articles	% of 2726
1	USA	1663	61.005
2	England	159	5.833
3	Germany	153	5.613
4	Canada	140	5.136
5	Australia	131	4.806
6	Switzerland	123	4.512
7	China	89	3.265
8	Spain	71	2.605
9	Japan	70	2.568
10	Israel	65	2.384
11	South Korea	63	2.311
12	Italy	53	1.944
13	Denmark	50	1.834
14	France	42	1.541
15	Mexico	38	1.394
16	Turkey	35	1.284
17	Sweden	33	1.211
18	Chile	30	1.101
19	Brazil	26	0.954
20	Ireland	25	0.917
21	Belgium	24	0.880
22	Egypt	21	0.770

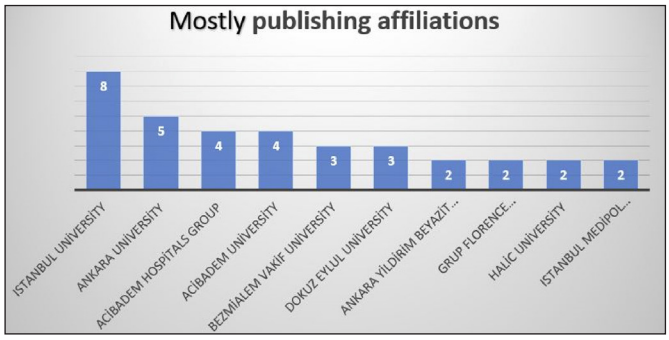

Figure 1. Mostly publishing affiliations

Research papers focusing on hip arthroscopy from Turkey received a total of 149 citations, averaging 4.26 citations per paper with an H-index of 7 (**Figure 2**). The article by Çetinkaya et al., published in 2016, was the most cited work on hip arthroscopy in Turkey according to the WoS database. Since its publication, it has been cited 23 times, averaging 2.88 citations per year. **Table 4** outlines the top 20 most cited papers on hip arthroscopy from Turkey, based on WoS database records.

Table 4. The top 20 most cited articles on hip arthroscpoy published in Turkey according to WOS database results

Title	Authors	Source title	Publication year	DOI	Total citations	Average per year
Arthroscopic labral repair versus labral debridement in patients with femoroacetabular impingement: a minimum 2.5 year follow-up study	Çetinkaya, et al.	Hıp Internatıonal	2016	10.5301/hipint.5000290	23	2.88
Arthroscopic treatment of femoroacetabular impingement: early outcomes	Polat, et al.	Acta Orthopaedıca Et Traumatologıca Turcıca	2013	10.3944/AOTT.2013.3041	18	1.64
The Effect of Traction Force and Hip Abduction Angle on Pudendal Nerve Compression in Hip Arthroscopy: A Cadaveric Model	Kocaoglu, et al.	Arthroscopy-The Journal Of Arthroscopıc And Related Surgery	2015	10.1016/j.arthro.2015.03.040	16	1.78
Avascular necrosis of the femoral head after hip arthroscopy	Şener, et al.	Hıp Internatıonal	2011	10.5301/HIP.2011.8693	16	1.23
Arthroscopic Retrograde Osteochondral Autologous Transplantation to Chondral Lesion in Femoral Head	Çetinkaya, et al.	Orthopedıcs	2014	10.3928/01477447-20140528-64	12	1.2
Arthroscopic-assisted retrograde mosaicplasty for an osteochondral defect of the femoral head without performing surgical hip dislocation	Kocadal, et al.	Sıcot-J	2017	10.1051/sicotj/2017030	8	1.14
Arthroscopic excision of acetabular osteoid osteoma in a 7-year-old patient	Aşık, et al.	Knee Surgery Sports Traumatology Arthroscopy	2015	10.1007/s00167-014-2978-5	8	0.89
Are pelvic anatomical structures in danger during arthroscopic acetabular labral repair? Definition of safe bone depth	Gereli, et al.	Knee Surgery Sports Traumatology Arthroscopy	2017	10.1007/s00167-015-3797-z	7	1
Arthroscopic bullet extraction from the hip in the lateral decubitus position	Sözen, et al.	Hıp Internatıonal	2010	10.1177/112070001002000221	7	0.5
Evidence for reliability, validity and responsiveness of Turkish version of Hip Outcome Score	Polat, et al.	Acta Orthopaedıca Et Traumatologıca Turcıca	2017	10.1016/j.aott.2017.05.001	6	0.86
Arthroscopic Fixation of a Posterior Acetabular Wall Fracture: A Case Report	Gürpınar, et al.	Cureus Journal Of Medıcal Scıence	2019	10.7759/cureus.6264	4	0.8
Arthroscopic Microfracture of Hip Chondral Lesions	Atilla, et al.	Arthroscopy Techniques	2017	10.1016/j.eats.2017.08.040	4	0.57
Arthroscopic diagnosis and treatment of an acetabular labrum bucket handle tear:: a case report	Sözen, et al.	Archıves Of Orthopaedıc And Trauma Surgery	2005	10.1007/s00402-005-0013-5	4	0.21
Hip arthroscopy for Legg-Calve-Perthes disease in paediatric population	Kanatlı, et al.	Acta Orthopaedıca Et Traumatologıca Turcıca	2019	10.1016/j.aott.2019.03.005	3	0.6
Bullet in Hip Joint	Kaya, et al.	Eurasıan Journal Of Medıcıne	2013	10.5152/eajm.2013.29	3	0.27
The effectiveness of peripheral compartment first access and periportal capsulotomy technique for arthroscopic management of femoroacetabular impingement: A prospective case series	Özbek, et al.	Acta Orthopaedıca Et Traumatologıca Turcıca	2021	10.5152/j.aott.2021.21174	2	0.67
Arthroscopic removal of an intraarticular bullet from the hip joint: A case report	Gürpınar, et al.	Journal Of The Pakıstan Medıcal Associatıon	2018		2	0.33
Robotic hip arthroscopy: a cadaveric feasibility study	Işık, et al.	Acta Orthopaedıca Et Traumatologıca Turcıca	2014	10.3944/AOTT.2014.3273	2	0.2
Comparison of Acetabular Labral Reconstruction With 7-mm Tibialis Anterior Allograft and 5-mm Iliotibial Band Autograft at Minimum 2-Year Follow-up	Kocaoğlu, et al.	Amerıcan Journal Of Sports Medıcıne	2022	10.1177/03635465221077114	1	0.5
Diabetic hip arthropathy is associated with a higher prevalence of femoral head chondromalacia: a case-controlled study	Luo, et al.	Hıp Internatıonal	2019	10.1177/1120700018813829	1	0.2

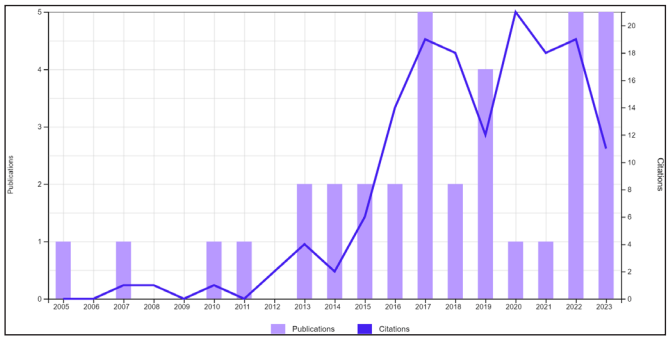

Figure 2. The publication years and number of citations of articles originating from Turkey

Articles on hip arthroscopy from Turkey indexed in the WOS database were mostly published in Acta Orthopaedica et Traumatologica Turcica (7 articles), Hip International (6 articles), Arthroscopy Techniques (2 articles), Arthroscopy: The Journal of Arthroscopic and Related Surgery (2 articles) and Cureus Journal of Medical Science (2 articles).

Results of Analyzing the WoS Database with the VOSviewer

Keyword analysis: Turkish studies from the WoS database were examined using the VOSviewer application to identify and analyze frequently occurring keywords. We identified 85 unique keywords that occurred at least once. The size of each node represents the frequency of each keyword, while the lines connecting the nodes indicate co-occurrence relationships (Figure 3). The most common keywords were hip arthroscopy (18 instances), arthroscopy (7 instances), femoroacetabular impingement (6 instances), and hip (4 instances) (Table 5).

Table 5. The mostly occured keywords on hip arthroscopy published in Turkey according to WOS database results

Keyword	Occurrences	Total link strength
Hip arthroscopy	18	57
Arthroscopy	7	25
Femoroacetabular impingement	6	19
Hip	4	16
Labrum	2	9

Scopus Database Results

According to the Scopus database, 6,475 articles were published globally from 1981 to 2023, with the number of articles consistently rising. Analysis of studies from Turkey revealed 115 articles published between 2005 and 2023. The number of articles in Turkey increased rapidly in the last two years (Figure 4).

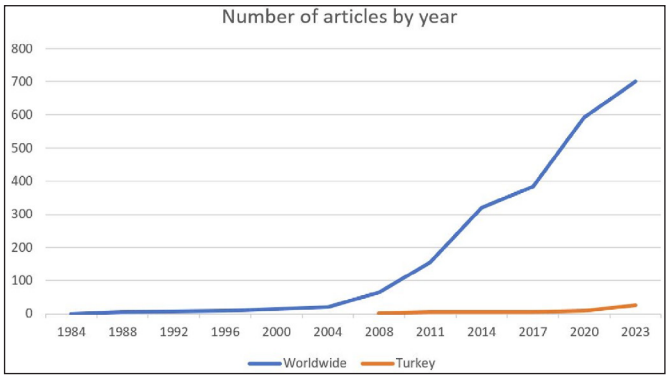

Figure 4. Publications per year according to Scopus database

The USA has the highest number of publications in the field of hip arthroscopy worldwide, with 3,299 papers. The United Kingdom is second with 440 publications, followed by China with 433. With 115 publications, Turkey ranks 13th globally (Figure 5).

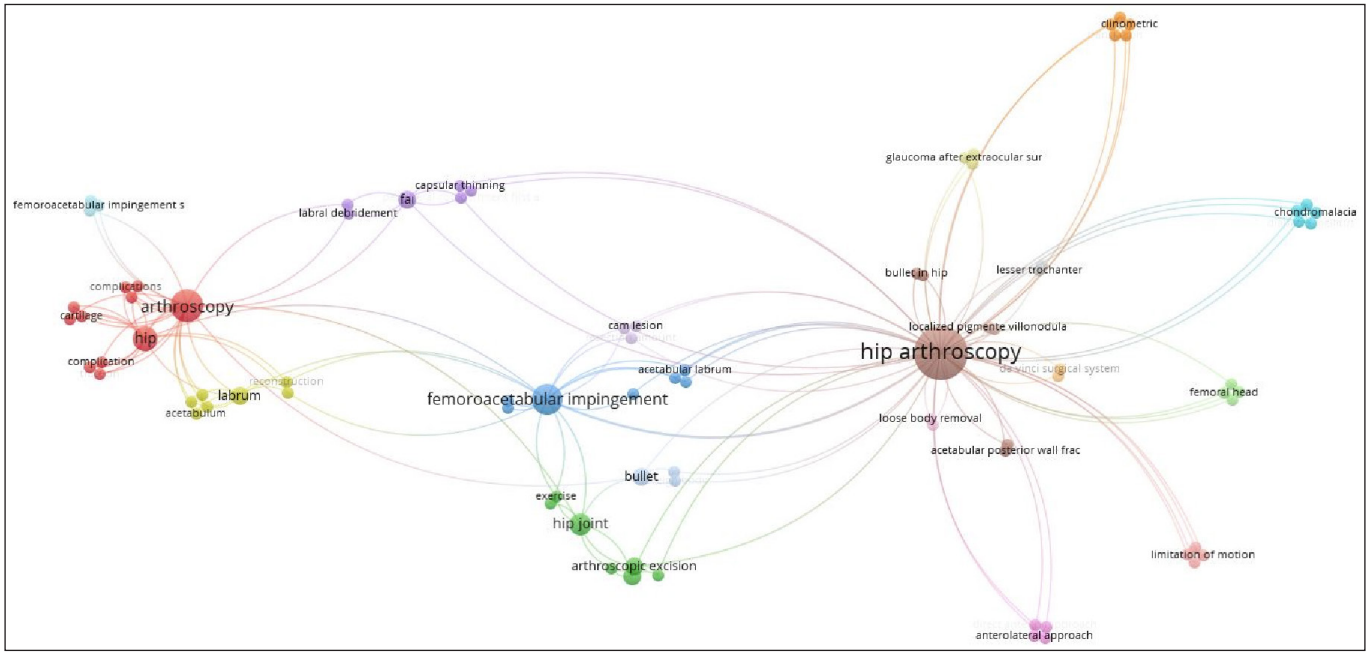

Figure 3. VOSviewer results of keyword analysis

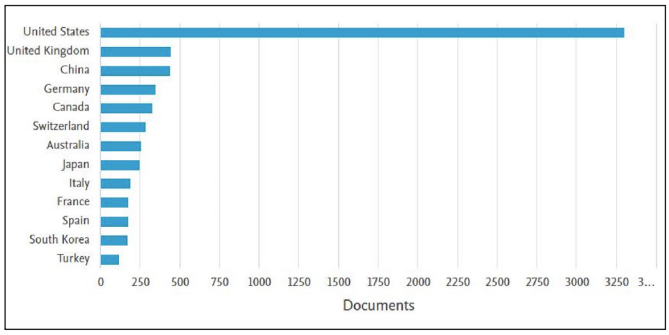

Figure 5. Number of publications from Scopus by country

İstanbul University (14 publications), İstanbul Medical Faculty (10 publications), Ankara University (9 publications), Dokuz Eylül University (8 publications), and Hacettepe University (8 publications) made the most significant contributions to the literature on hip arthroscopy in Turkey.

The highest number of articles on hip arthroscopy from Turkey, indexed in the Scopus database, were published in Acta Orthopaedica et Traumatologica Turcica (10 articles), followed by Hip International (9 articles). Figure 6 provides an overview of the most published journals on hip arthroscopy from Turkey.

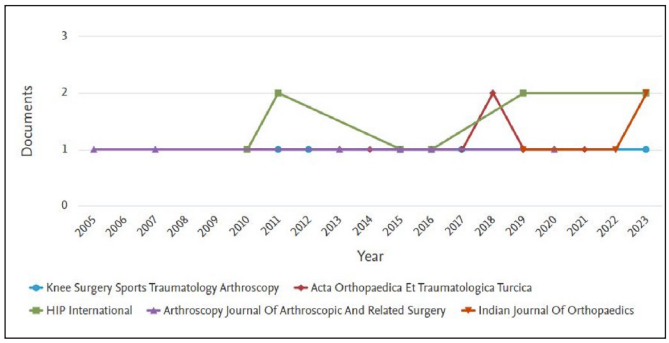

Figure 6. Distribution of publications originating from Turkey according to journals in the Scopus database

DISCUSSION

The first recorded article on hip arthroscopy in the WoS database dates back to 1981. The number of publications has grown annually, surpassing 10 articles annually in 2001 and 100 articles annually in 2012. In Turkey, the first publication was in 2005, showing an increasing trend over the years. Similar outcomes were observed in the Scopus database. The rise in the quantity of publications in recent years indicates the growing interest in hip arthroscopy, a trend expected to continue.

Bibliometric studies reveal the scientific effectiveness and contributions of countries. After examining databases such as WoS and Scopus, the results consistently highlight the extensive dominance of the USA. Turkey ranks 16th in the number of articles published on hip arthroscopy according to the WoS database and 13th according to the Scopus database. An evident correlation exists between the financial development of countries and their contributions to science.

English is the predominant language of publication, accounting for 96.22% in the WoS database and 95% in Scopus. All publications from Turkey were in English, highlighting English as the primary language for scholarly literature.

Based on WoS database findings, Turkey has produced 35 articles on hip arthroscopy. A total of 77.143% of these articles were published in SCI-Expanded journals, while 22.857% were published in ESCI indexed journals. Compared to this, Scopus reported 115 articles related to hip arthroscopy from Turkey. This difference could be attributed to the difference in the number of journals indexed by Scopus and ECSI/SCIE. The Scopus database covers a larger number of journals than the WoS database.

Bibliometric analysis also identifies leading institutions in a field. According to the WoS database, despite contributions from 138 different institutions, İstanbul University (8 articles) and Ankara University (5 articles) were significant contributors. Scopus results showed İstanbul University with 14 articles, followed by İstanbul Faculty of Medicine (10 articles) and Ankara University (9 articles). Most literature emanated from established institutions in Turkey's major cities, likely due to better resources and support for publishing.

We summarized the top 20 most cited articles from Turkey, based on WoS database data. These articles received a total of 149 citations, averaging 4.26 citations each, with an H-index of 7. However, these figures are relatively low compared to the global literature.

In both the WoS database and Scopus, Orthopaedica et Traumatologica Turcica and Hip International published the greatest number of articles on hip arthroscopy in Turkey. Identifying journals with a high percentage of articles on a specific topic can guide authors in selecting journals for future studies. In this context, bibliometric analysis can be useful.

Keywords are crucial in understanding reader interests and the information needed to meet those interests. In studies from Turkey, prominent keywords were hip arthroscopy, arthroscopy, femoroacetabular impingement, and hip. These terms are generally used, but with more articles, keyword frequencies are expected to cluster around more specific terms.

CONCLUSION

This study's results will aid in reviewing and evaluating the literature on hip arthroscopy from Turkey. Turkey was not among the top ten countries in terms of the number of publications. The analysis of publication years indicates that hip arthroscopy has become more popular in recent years, but the rate of increase in Turkey has not matched that of the world. Hip arthroscopy has gained significant attention in the orthopaedic literature over the past two decades, and this trend is anticipated to continue.

ETHICAL DECLARATIONS

Ethics Committee Approval: Since the study is a bibliometric analysis, there is no need for an ethics committee approval.

Informed Consent: Since the study is a bibliometric analysis, there is no need for an informed consent.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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Review

MEDICINE PALLIATIVE CARE

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Hemorheology in thyroid abnormalities: old team player, new insights

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ABSTRACT

Thyroid dysfunctions significantly impact various physiological processes, extending their influence on hemorheological properties and microcirculation. This comprehensive review explores the intricate relationship between thyroid disorders and hemorheology, emphasizing the substantial effects on blood flow dynamics and tissue perfusion. Examining the alterations in blood viscosity, erythrocyte behavior, and microvascular circulation in both hypothyroidism and hyperthyroidism reveals crucial insights into the pathophysiology of these conditions. Furthermore, elucidating the hemorheological changes associated with thyroid dysfunctions offers potential avenues for improved clinical management strategies. This review synthesizes current research findings, highlighting the importance of considering hemorheological aspects in understanding the complexities of thyroid-related complications and advancing patient care paradigms.

Keywords: Hemorheology, thyroid dysfunction, hypothyroidism, hyperthyroidism, erythrocyte deformability, erythrocyte aggregation, blood viscosity, plasma viscosity

INTRODUCTION

The thyroid gland plays a crucial role in regulating various bodily functions by producing hormones that act as chemical messengers. The primary hormones produced by the thyroid gland are thyroxine (T4) and triiodothyronine (T3). These hormones are essential for maintaining metabolic rate, energy production, and body temperature. They also influence the growth and development of tissues and organs throughout the body, including the brain, heart, muscles, and bones. Moreover, thyroid hormones help regulate heart rate, digestion, and the body's response to other hormones, impacting overall health and well-being.

Hyperthyroidism refers to the excessive synthesis and secretion of thyroid hormones from the thyroid tissue due to its over-activity. Moreover, factors such as exogenous intake of thyroid hormones, release from an alternate source within the body, or the circulation of previously produced hormones owing to thyroid gland destruction may contribute to thyrotoxicosis, a condition where an excessive presence of thyroid hormones in circulation occurs without the presence of hyperthyroidism.[1-3]

Hypothyroidism is characterized by an underactive thyroid gland, which fails to produce an adequate amount of thyroid hormones essential for regulating various bodily functions. This deficiency in thyroid hormone production can lead to a slowdown in metabolism and affect numerous physiological processes in the body. Some common causes of hypothyroidism include autoimmune disorders (such as Hashimoto's thyroiditis), thyroid gland inflammation, surgical removal of the thyroid gland, or radiation therapy affecting the thyroid.[4]

Hemorheology is a scientific field that delves into the fluidic attributes of blood. It explores the fluidity features of blood plasma and the constituents within blood, including red blood cells, white blood cells, and platelets. Its focus encompasses the assessment of blood's fluidic properties within both microcirculation and macrocirculation. For optimal tissue perfusion, it is imperative for blood to possess suitable rheological characteristics. Failure to meet these criteria may lead to disruptions, particularly in microcirculatory function.[5,6]

Thyroid dysfunctions significantly influence blood-related parameters and contents of plasma, affecting the blood's flow characteristics. The involvement of thyroid hormones in the regulation of erythropoiesis, especially their interaction with specific receptors present on hematopoietic stem cells, plays a pivotal role.[7] This review underscores the pivotal interplay between thyroid dysfunctions and hemorheological alterations, highlighting

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the critical role of blood flow properties in understanding and managing thyroid-related complications.

FACTORS DETERMINING HEMORHEOLOGY

The factors influencing the fluidity characteristics of blood can be broadly categorized into two primary groups: those stemming from the endothelial lining of blood vessels and those originating from the inherent physical properties of blood itself. Parameters linked to the physical traits of blood encompass the hematocrit percentage, effects associated with the elasticity/deformability and aggregation tendencies of erythrocytes, as well as plasma and whole blood viscosity. These factors are subject to variation due to various pathogenic conditions and are also susceptible to alterations based on physiological circumstances, including ambient temperature, nutritional status, hydration levels, physical exertion, and other related physiological states.

Hematocrit signifies the proportion of erythrocytes within the total blood volume. With an elevation in hematocrit values, blood viscosity proportionally rises.[8] This augmentation becomes notably more significant when hematocrit surpasses 60%, manifesting as a logarithmic, rather than a linear, escalation. Studies reveal that at moderate and high shear rates, a single unit rise in hematocrit corresponds to a 4% upsurge in blood viscosity.[7] Consequently, an elevation in hematocrit directly influences the fluidic attributes of blood.

Red blood cells (erythrocytes)

Erythrocytes constitute the most abundant cellular elements in the blood plasma and are known for their flexible cellular structure. Typically measuring around 8 µm in diameter, 2 µm in thickness, and displaying a biconcave disc shape, these circulating erythrocytes demonstrate the capacity to flex and bend when traversing small-diameter capillaries. This flexibility (deformability of the erythrocytes) ensures the smooth continuity of blood flow within the capillary circulation.[9]

Erythrocyte deformability (ED)

The principal factors governing deformability include the cytoplasmic viscosity of the erythrocyte, membrane properties, and the geometric structural attributes of the erythrocyte.

Cytoplasmic viscosity of erythrocytes

Also referred to as internal viscosity, it is chiefly determined by the concentration of hemoglobin within erythrocytes, denoted as MCHC (mean corpuscular hemoglobin concentration). Increased MCHC levels, indicative of heightened internal viscosity of erythrocytes, are associated with decreased deformability characteristics of erythrocytes.[10]

Erythrocyte membrane characteristics

Erythrocytes must exhibit high flexibility combined with stable membrane properties for efficient microcirculation. The membrane's stability is equally vital as its flexibility. In instances where erythrocytes lack the necessary stability (as observed in erythrocyte membrane disorders like hereditary spherocytosis), they become susceptible to premature breakdown during circulation. The structural balance of proteins within the erythrocyte membrane, including spectrin, actin, ankyrin, tropomyosin, protein 4.1, and 4.9, and their interplay, is responsible for maintaining the optimal balance between stability and flexibility in the erythrocyte membrane. When defects exist in membrane proteins, both the flexibility and stability of erythrocytes are significantly reduced, leading to conditions marked by increased vulnerability to cell breakdown, often accompanied by hemolytic anemia.[10,11]

Erythrocyte geometry and structural features

Under static conditions, erythrocytes in healthy individuals maintain a biconcave shape. The typical erythrocyte diameter measures around ~8 µm, with a thickness of ~2 µm, a surface area of approximately ~135 µm², and a volume of ~90 fL. These geometric attributes have the capacity to alter within physiological thresholds in response to flow dynamics or osmotic pressure, contributing to erythrocyte flexibility. The biconcave shape dictates a specific surface area-to-volume ratio for erythrocytes, typically denoted as 1.5 for healthy cells. Pathological conditions like hereditary spherocytosis, hemolytic anemias, malaria, and certain disorders exhibit a diminished surface area-to-volume ratio, causing a decline in erythrocyte flexibility and deformability characteristics.[12]

The deformability characteristic of erythrocytes plays a crucial role not just in determining the oxygen delivery to tissues but also serves as an indicator of their lifespan. The loss of deformability implies that the erythrocytes might be older. As these older erythrocytes lose their ability to deform, they become unable to traverse narrow splenic sinuses, ultimately leading to their breakdown.

Furthermore, the deformability of erythrocytes holds considerable importance in sustaining microcirculation within peripheral tissues. Pathologies such as erythrocyte membrane disorders, infections, sepsis, metabolic syndromes, diabetes mellitus, and similar conditions known to impair deformability, also disrupt the transportation of oxygen to the tissues.[13]

Erythrocyte aggregation (EA)

Aggregation is a behavior displayed by erythrocytes when subjected to low shear stress conditions, typically occurring during stasis when blood flow moves slowly. Under low shear stress, they tend to form

clusters known as rouleaux formation. These clusters can be two-dimensional, formed by the gathering of multiple erythrocytes, or they can manifest in a three-dimensional structure when the rouleaux adhere to each other. Aggregation is a reversible behavior; when shear stress intensifies, erythrocytes revert to their individual states.[14]

Factors affecting aggregation include not only the cellular properties of erythrocytes but also plasma-derived elements.[15] Components such as fibrinogen and von Willebrand factor in the plasma content, along with the ratio of acute-phase reactants during inflammatory processes, influence erythrocyte aggregation. Additionally, changes in the behavior of erythrocyte aggregation are observed in various pathological conditions.[12,16]

Two distinct models have been proposed to describe erythrocyte aggregation behavior: 1) the bridging model and 2) the depletion model.

The Bridging model postulates that macromolecules such as albumin and fibrinogen, adhering to the surface of adjacent erythrocytes, establish bridges, thereby hindering the forces responsible for disaggregation and facilitating erythrocyte clustering.[14,17]

Conversely, the Depletion model suggests that macromolecules present on the erythrocyte surface exhibit a lower concentration compared to the surrounding environment, indicating a relative depletion at the cellular surface. The sparsity of these macromolecules on the erythrocyte surface leads to the creation of an osmotic gradient, inducing fluid movement within the intercellular space. Consequently, this fluid movement exerts forces that draw nearby erythrocytes towards each other.[14,17]

The two models proposed to elucidate the erythrocyte aggregation mechanism present contrasting views regarding the density of macromolecules on the erythrocyte surface. The Bridging model is based on the assumption of higher macromolecular concentration, while the Depletion model contends the opposite by suggesting a lower concentration on the erythrocyte surface.[18]

VISCOSITY

Plasma viscosity (PV)

Blood plasma serves as the matrix supporting the various cellular components within the bloodstream, encompassing dissolved minerals, plasma proteins, vitamins, and other solutes. The viscosity of plasma primarily relies on its protein content. Pathological conditions like multiple myeloma and macroglobulinemia, marked by increased plasma proteins, exhibit heightened plasma viscosity during inflammatory processes. Conversely, conditions characterized by reduced fibrinogen or immunoglobulins show a decrease in plasma viscosity.[9] Elevated plasma viscosity impedes the smooth flow of blood within the vascular system and can lead to microcirculatory blockages. With Newtonian fluid characteristics, normal plasma viscosity at 37°C is typically within the range of 1.10 - 1.35 cP.[8]

Whole blood viscosity (WBV)

Blood fluidity exhibits non-Newtonian characteristics, demonstrating an increase in viscosity at low shear rate levels. In other words, it displays a "shear-thinning" property. Changes in whole blood viscosity are directly related to alterations in plasma viscosity, either increasing or decreasing. Factors impacting plasma viscosity also influence whole blood viscosity yet changes in the latter can occur despite constant plasma viscosity, owing to the non-Newtonian traits of whole blood. Alterations in whole blood viscosity can be observed due to erythrocytes' deformability and aggregation properties, while the hematocrit value remains a contributing factor. Blood flow in the vascular system encounters diverse vessel sizes, resulting in varied shear rates—higher in capillary vessels than in larger diameter vessels. As shear rates rise, whole blood viscosity declines. Temperature serves as another influential factor, as an increase in temperature correlates with decreased whole blood and plasma viscosity.[19]

HYPERTHYROIDISM AND HEMORHEOLOGY

Thyroid hormones impact numerous systems, including the cardiovascular system. Apart from accelerating metabolic rate, they induce relaxation of arterial smooth muscles and lead to vasodilation in the peripheral vascular system.[20,21] These effects culminate in a lowered resistance within peripheral vasculature. As this resistance diminishes, renal perfusion also decreases, triggering activation of the Renin-Angiotensin-Aldosterone system. Consequently, sodium and fluid retention occur, resulting in hypervolemia.[20] These shifts in blood volume directly impact the rheological properties of blood through alterations in viscosity.

Apart from the hemodynamic effects, it is recognized that lipid profiles, plasma proteins, and electrolyte concentrations change in the hyperthyroid patient group.[22] These alterations also elevate plasma viscosity, consequently contributing to hemorheological irregularities. The direct influence of thyroid hormones on erythrocytes leads to structural changes, negatively impacting erythrocyte aggregation and deformability.

In hyperthyroid conditions, an upsurge in red blood cell count and hematocrit levels is observed due to the heightened activity of these hormones. Consequently, this escalation often translates into an elevation in whole blood viscosity, impacting the blood's flow properties. Moreover, these thyroid-induced alterations contribute to modifications in erythrocyte aggregation behavior, potentially influencing blood clotting tendencies and circulation dynamics within the body.

In hyperthyroidism, there is a notable rise in various coagulation factors, including fibrinogen and other clotting components, which collectively contribute to a hypercoagulable state. The heightened presence of these factors promotes increased blood clotting tendencies and raises the risk of thrombosis.[23,24] Additionally, the surplus of fibrinogen and coagulation factors influences plasma viscosity, amplifying the resistance to blood flow within the vessels. This escalation in plasma viscosity is further compounded by the rise in whole blood viscosity, primarily due to the augmented erythrocyte count and hematocrit levels typical in hyperthyroid conditions. Moreover, the heightened erythrocyte count and altered behavior of erythrocytes in hyperthyroidism foster an increased tendency for these blood cells to form aggregates. These combined effects on plasma and whole blood viscosity, as well as the tendency for erythrocyte aggregation, contribute to altered hemorheological properties, potentially impacting blood flow and predisposing individuals to thrombotic events.

In hyperthyroidism, dysregulation in hemodynamic mechanisms arises from the hypermetabolic state induced by excessive thyroid hormone production. This condition often leads to cardiac complications, notably cardiac arrhythmias such as atrial fibrillation. Atrial fibrillation, a common occurrence in hyperthyroid individuals, disrupts the regular rhythm of the heart's upper chambers, affecting blood flow patterns and potentially contributing to disturbances in microcirculation.[25,26] Furthermore, the hypermetabolic state characteristic of hyperthyroidism results in an escalated demand for oxygen by the body tissues. This increased demand prompts a rise in the production of erythrocytes, consequently elevating both erythrocyte mass and count in the bloodstream. These alterations significantly impact the hemorheological status by influencing blood viscosity and circulation dynamics, potentially affecting overall blood flow and hemodynamic stability.

In light of this information, it's conceivable to anticipate potential hemorheological disturbances in hyperthyroid patients, potentially affecting tissue perfusion adversely. Considering the coexistence of other conditions like diabetes and hypertension, which influence peripheral circulation, close monitoring of hemorheology in hyperthyroid patients becomes increasingly critical.

HYPOTHYROIDISM AND HEMORHEOLOGY

In hypothyroidism, hemorheological parameters are affected in various ways. Plasma viscosity may undergo changes attributed to alterations in blood composition and fluid dynamics. The condition, characterized by decreased metabolic function, can lead to elevated levels of certain proteins such as lipoproteins and globulins. These heightened protein concentrations in the bloodstream may contribute to increased plasma viscosity.[27] Additionally, reduced metabolic activity in hypothyroidism might lead to fluid retention or alterations in fluid balance in the body. Changes in hydration levels can influence plasma viscosity, with decreased fluid levels potentially contributing to an increase in viscosity. Furthermore, disturbances in lipid metabolism associated with hypothyroidism, leading to elevated lipid levels like cholesterol, may further influence plasma viscosity. The condition's effects on blood circulation and flow dynamics within vessels might also indirectly impact plasma viscosity due to variations in blood flow patterns, emphasizing the multifaceted nature of hypothyroidism's impact on plasma viscosity. The condition often leads to a decreased red blood cell count or erythrocytes, resulting in lowered hematocrit levels, which can contribute to reduced whole blood viscosity. Moreover, hypothyroidism may cause variations in plasma protein levels, including factors involved in blood clotting, potentially influencing the viscosity of the plasma component of blood and subsequently affecting whole blood viscosity. Additionally, the condition's effects on blood flow patterns within vessels can indirectly impact whole blood viscosity by altering shear stress and circulation dynamics. Changes in lipid metabolism associated with hypothyroidism, such as increased cholesterol levels, may further contribute to variations in whole blood viscosity. However, the precise impact of hypothyroidism on whole blood viscosity may vary among individuals based on the interplay of these factors within their physiological makeup.[28,29]

In hypothyroidism, modifications in erythrocyte deformability and aggregation behaviors often manifest due to changes in blood composition and rheological characteristics. The condition can result in reduced erythrocyte deformability, possibly attributed to alterations in lipid metabolism, particularly elevated cholesterol levels. These changes impact the flexibility and pliability of erythrocyte membranes, potentially hindering their capacity to alter shape and traverse through smaller blood vessels efficiently. Additionally, hypothyroidism might augment erythrocyte aggregation tendencies. Elevated plasma protein levels, variations in fibrinogen concentrations, and disrupted blood flow dynamics may collectively contribute to an increased inclination for erythrocytes to aggregate or adhere

together. These adjustments in plasma composition, along with modifications in erythrocyte deformability and aggregation, could influence overall blood rheology, potentially impeding blood flow and microcirculation, thereby playing a role in the condition's pathophysiology.[30]

CONCLUSION

Hemorheological status carries a great importance in thyroid dysfunctions, due to its influence on blood flow dynamics and tissue perfusion. Understanding these hemorheological changes and their impact on microcirculation is crucial. These alterations can affect tissue oxygenation, nutrient delivery, and waste removal, contributing to various complications associated with thyroid dysfunctions. Management strategies that address these hemorheological aspects could potentially help mitigate the adverse effects on microcirculation, thereby improving clinical outcomes in individuals with thyroid disorders.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

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Review

MEDICINE PALLIATIVE CARE

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Approach and intervention in blood pressure abnormalities

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ABSTRACT

Hypertension is when blood pressure (BP) is measured above the limits of what is considered normal. Almost all guidelines define hypertension as a systolic blood pressure (SBP) above 140 mmHg and a diastolic blood pressure (DBP) above 90 mmHg. Blood pressure should not be seen only as a numerical value that should be monitored and lowered when it rises. Blood pressure is an important vital sign that can provide important clues to the clinician about the patient's current condition. Long-term control of hypertension in individuals significantly reduces cardiovascular risk. In the case of hypertensive emergencies or urgent situations, antihypertensive treatment should be initiated after consideration of the approach to the recommendations. Recent observational studies suggest that pharmacologic treatment of acute and asymptomatic in-hospital BP elevations may not be beneficial and may even increase the risk of in-hospital and post-discharge complications. The patient's current clinical status and additional comorbidities should be evaluated, and attention should be paid to contraindications and drug dosage adjustments.

Keywords: Hypertension, systolic blood pressure, diastolic blood pressure

INTRODUCTION

Hypertension is when blood pressure (BP) is measured above the limits of what is considered normal. There continues to be controversy about the blood pressure values that should be considered abnormal. Guidelines define hypertension as a systolic blood pressure (SBP) above 140 mmHg and a diastolic blood pressure (DBP) above 90 mmHg.[1] These abnormal values are expected to be seen in more than one measurement for the diagnosis of hypertension. While long-term control of hypertension in individuals significantly reduces cardiovascular risk, the benefit of controlling acute BP elevations in hospitalized patients is controversial.[2]

In the case of hypertensive emergencies or urgent situations, antihypertensive treatment should be initiated after consideration of the approach to the recommendations. However, current hypertension guidelines do not address in-hospital asymptomatic -BP elevations or recommendations for their diagnosis, management, and follow-up. Recent observational studies suggest that pharmacologic treatment of acute and asymptomatic in-hospital BP elevations may not be beneficial and may even increase the risk of in-hospital and post-discharge complications.[3]

MANAGEMENT OF THE PATIENT WITH HYPERTENSION

Medical Management of Hypertension

On admission to the ward for patients already diagnosed with hypertension and under pharmacologic treatment, it is necessary to assess the patient's current clinical condition and continuation of drug therapy before deciding to continue routine use of the patient's medications. Attention should be paid to drug contraindications and dosage adjustments for the individual's comorbidities and concomitant acute organ dysfunctions. Drugs that are contraindicated due to comorbid conditions and drugs that are considered to be harmful due to comorbid conditions are compiled in Table 1 and Table 2.[4,5]

Table 1. Drug groups contraindicated in the treatment of hypertension due to concomitant conditions

Clinic	Medicines
Grade 2-3 AV block	Beta-blockers, calcium –channel blockers (non-dihydropyridine), reserpine
Depression	Reserpine
Liver disease	Methyldopa
Bronchospastic airway disease	Beta blockers
Pregnancy	ACE inhibitors, angiotensin II receptor antagonists
Hyperkalemia	
Bilateral renal artery stenosis	
Gut	Diuretics

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Table 2. Drugs considered harmful in the treatment of hypertension with concomitant conditions

Comorbidity	Medicines
Kidney failure	Potassium-sparing diuretics
Peripheral vascular disease	Beta blockers
Diabetes mellitus	Beta blockers, high dose diuretics
Gut	Diuretics
Dyslipidemia	Beta blockers, high dose diuretics
Liver disease	Labetalol
Renovascular disease	ACE inhibitors, angiotensin II receptor blockers
Dyslipidemia	Diuretics, beta blockers
Heart failure	Beta blockers (except carvedilol, metoprolol, bisoprolol), calcium antagonists (except amlodipine and felodipine)
Orthostatic hypotension	Alpha blockers

Blood Pressure Monitoring

Blood pressure monitoring can provide many clues about the clinical status of patients on inpatient wards. There is no recommendation in the guidelines regarding the frequency of -BP monitoring in patients followed in the inpatient ward.[5,6] The frequency of this monitoring depends on the clinician's judgment according to the stability of the patient. Studies do not recommend strict BP monitoring in stable patients. Routine BP monitoring, especially at night, is not recommended for stable patients because it may affect sleep quality and increase stress levels.[7]

Increased BP is seen in 50% to 70% of patients followed in inpatient wards, and the majority of these patients are asymptomatic.[8] Patients with BP >140/90 mmHg, with or without a previous diagnosis of hypertension, are considered to have asymptomatic hypertension unless there are findings suggestive of end-organ damage. Aggressive antihypertensive therapy in an asymptomatic patient may result in ischemic events such as acute kidney injury and myocardial damage.[9]

A critical issue related to in-hospital BP elevation is how to measure BP in the hospital. Although automated devices are frequently used in the BP monitoring of clinic inpatients because they are fast and practical in terms of continuous monitoring, when we look at the studies between manual measurement and device measurement, the automatic findings obtained by device measurement cannot be completely trusted, and the manual method should be considered as the reference standard, especially in critical situations.[10] Especially in the case of arrhythmia, the automated device is likely to produce inaccurate results, and manual measurement is absolutely necessary. BP should be measured in both arms at the first measurement and in necessary critical situations.

In addition to the measurement method and errors during measurement, factors contributing to the high prevalence of in-hospital blood pressure elevations include uncontrolled pain, noise, anxiety, and disturbed sleep patterns. Patients already on antihypertensive medication may also have experienced an interruption in their regular doses.[2]

Intervention for Elevated Blood Pressure

Finding elevated BP during inpatient follow-up prompts many clinicians to initiate antihypertensive treatment quickly. Increased BP can inform the physician about many aspects of the patient's clinical course and should not be seen only as a value to be lowered. The treatment and follow-up course should be established by evaluating some parameters.

If increased BP in the inpatient is considered as a spectrum, this spectrum ranges from asymptomatic hypertension to severe hypertension. Classification of BP is important for rapid identification and clinical differentiation of hypertensive crises, triage to an intensive care unit, and determination of the need for oral/intravenous (IV) therapy. The classification of BP in adults is compiled in **Table 3**.[6]

Table 3. Classification of blood pressure

	Systolic (mmHg)	Diastolic (mmHg)
Optimal	<120	<80
Normal	<130	<85
High-Normal	130-139	85-89
Stage 1 Hypertension	140-159	90-99
Stage 2 Hypertension	160-179	100-109
Stage 3 Hypertension	>180	>110

Apart from essential and secondary hypertension, some secondary factors may cause acute elevation of BP in hospitalized patients. These secondary factors include pain, anxiety, hypervolemia, medications, urinary retention, and alcohol withdrawal.6 At this point, it should be kept in mind that the presence of a hypertensive emergency should be evaluated during the approach to patients with hypertensive BP monitoring during routine visits or acute elevations in blood pressure, and if there are no emergency or urgent conditions, the underlying causes should be evaluated by history and physical examination, and treatment should be organized.[11]

Emergencies in the Hypertensive Patient

Approximately 1-2% of patients with hypertension have a hypertensive crisis.[12] In a hypertensive crisis, it is the rate of rise in blood pressure rather than the level of blood pressure that is important.[13] Various triggering events can lead to hypertensive emergencies. Hypertensive crisis is divided into two categories, and this distinction is important for establishing the treatment course.[14]

Hypertensive emergencies: situations where rapid parenteral lowering of blood pressure is essential to prevent target organ damage. Hypertensive emergencies are compiled in Table 4.[14]

Table 4. Hypertensive emergencies

Acute coronary syndromes	Eclampsia
Pulmonary edema	Adrenergic crisis
Acute renal failure	Acute aortic dissection
Serious epistaxis	Serious burns
Acute intracranial event	Severe postoperative hypertension

Hypertensive urgencies: severe elevation of BP in the absence of target organ damage. It is usually recommended to lower blood pressure with oral antihypertensives over a few hours or a few days. Hypertensive urgent conditions are compiled in Table 5.[14]

Table 5. Hypertensive urgencies

Sudden and rapid rise in blood pressure not accompanied by target organ damage
Postoperative blood pressure elevation
Patients with uncontrolled hypertension undergoing emergency surgery
Patients with ischemic heart disease accompanying hypertension

The levels of hypertension that constitute a hypertensive emergency are not universally established, although there are some memorable values. Long-term hypertensive patients can tolerate blood pressure >200/120 mmHg without target organ damage. In some cases, a hypertensive emergency may develop in the presence of lower BP and a sudden rise in BP. As a result, the diagnosis of hypertensive emergency or urgency is based on the clinical presentation of the patient, not on limit values. There is also no threshold value for differentiating between hypertensive emergency and hypertensive urgency. The distinguishing feature here is the identification of end-organ damage.15

Once it has been established that a true hypertensive emergency is present or likely, laboratory tests such as metabolic panels, urinalysis, and cardiac enzymes may be useful. An electrocardiography (ECG) should be performed in every patient with suspected cardiac ischemia. Brain computed tomography (CT) is recommended in patients with acute neurologic complaints or findings on examination. Chest radiography should be performed on patients with shortness of breath. A chest radiograph may also show widening of the mediastinum or aortic dissection, but this is a relatively insensitive marker, and CT angiography of the chest and abdomen should be performed to rule out or confirm dissection.[16,17]

Rapid lowering of BP is the mainstay of treatment for hypertensive emergencies. The aim would be to lower mean arterial pressure by 20% to 25% within the first 1 to 2 hours. Since this rapid reduction is the goal, oral medications have no role in the treatment of a hypertensive emergency. Intravenous vasoactive drops such as labetalol, esmolol, nicardipine, and nitroglycerin are typically effective options. Intravenous drugs that can be used in hypertensive emergencies in Turkey compiled in Table 6.[4,16]

In hypertensive emergencies, the patient should be treated with intensive care. The first drug of choice should be sodium nitroprusside. If the patient has renal insufficiency, continuous infusion of sodium nitroprusside for more than 48-72 hours may cause thiocyanate toxicity. Oral antihypertensive therapy should be adjusted after blood pressure reaches desired levels.[18]

For adults without organ damage, a gradual normalization of blood pressure is recommended. The key feature of management is that the reduction in blood pressure should be gradual over several days if there is no evidence of organ damage. Table 6 shows some of the drugs that can be used in hypertensive emergencies in Turkey, their side effects, and their dosing. Table 7 summarizes some oral medications that can be used in hypertensive urgent situations, their side effects, and dosing.[4,16]

Table 6. Intravenous drugs available in hypertensive emergency in Turkey

Medicine	Dose	Side Effects
Sodium nitroprusside	0.25-10 µg/kg/min infusion	Hypotension, vomiting
Nitroglycerin	5-100 µg/min infusion	Headache, vomiting
Labetalol	20-80 mg bolus, 0.5-2 mg/min infusion	Nausea and vomiting, heart block
Furosemide	40-60 mg bolus	Hypotension
Nicardipine	2-10 mg/hour infusion	Reflex tachycardia
Hydralazine	10-20 mg bolus	

Table 7. Oral drugs available in hypertensive urgency in Turkey

Medicine	Way of delivery	Dose	Cautions to be Considered
Captopril	Sublingual	25-50 mg	Should not be given if renal artery stenosis is present
Amlodipine	Oral	5-10 mg	May cause headaches and reflex tachycardia
Doxazosin	Oral	4-8 mg	May cause dizziness and orthostatic hypotension

Treatments for Specific Hypertensive Emergencies

In the presence of hypertensive encephalopathy, it is recommended to reduce BP by 25% within the first 1 hour and to 160/100 mmHg within 2 to 6 hours; hydralazine should be avoided.[16]

In cases of acute coronary syndrome, it is recommended to reduce SBP to <140 mmHg within 1 hour and

maintain DBP >60 mmHg. Esmolol, nitroglycerin, metoprolol, and labetalol may be preferred; hydralazine should be avoided.[16]

If acute heart failure develops, it is recommended to lower the SBP below 140 mmHg within the first 1 hour. Loop diuretics are necessary in the majority of cases; beta-blockers should be avoided.[16]

If aortic dissection is present, it is recommended to reduce the SBP to <120 mmHg within the first 20 minutes, while at the same time reducing the heart rate to <60 beats/min. The use of both beta-blockers and concomitant vasodilator agents is recommended.[16]

If increased blood pressure is accompanied by a hemorrhagic cerebrovascular event, guidelines recommend regulating SBP to <180 mmHg. Some recent studies and meta-analyses have defined a reduction in SBP to the 130-140 range as safe. Acute lowering of SBP to <130 mmHg is potentially harmful and should be avoided. The patient should be neurologically assessed every 15 minutes while blood pressure is being lowered. Labetalol or nicardipine may be preferred; hydralazine should be avoided.[19]

If an ischemic cerebrovascular event is present, IV thrombolytic therapy should be evaluated. If available, BP should be reduced to below 185/110 mmHg before starting IV thrombolytics, and blood pressure should be maintained below 180/110 mmHg for the first 24 hours after IV thrombolytics. If thrombolytic therapy is not indicated, antihypertensive therapy is recommended if blood pressure is above 220/120 mmHg. BP should not be lowered by more than 15% in the first 24 hours. Antihypertensive treatment is not recommended at blood pressure values below 220/120 mmHg. In ischemic SVO, nicardipine or labetalol may be preferred as antihypertensives. Hydralazine should be avoided.[19]

On the other hand, severe hypertension in pregnancy requires emergency treatment. Pregnant women should be prescribed nifedipine, methyldopa, or labetalol during pregnancy; ACE inhibitors or ARBs should not be given. IV hydralazine or oral nifedipine may be used to lower blood pressure during the acute event.[20]

THINGS TO KEEP IN MIND

Blood pressure should not be seen only as a numerical value that should be monitored and lowered when it rises. Blood pressure is an important vital sign that can provide important clues to the clinician about the patient's current condition.

When encountering increased blood pressure in patients followed in the ward, the priority should be to differentiate hypertensive emergencies by physical examination and history and to prevent target organ damage. If there is a hypertensive emergency, aggressive antihypertensive treatment should be organized in the first hours; otherwise, the treatment route should be created in this direction by focusing on the underlying causes.

While antihypertensive treatment is being organized, the patient's current clinical status and additional comorbidities should be evaluated, and attention should be paid to contraindications and drug dosage adjustments.

CONCLUSION

There is overwhelming evidence of the benefit of identifying and treating hypertension in the community. However, while diagnostic and treatment algorithms exist for hypertensive emergencies in hospitalized patients, little is known about the clinical significance of asymptomatic and short-term blood pressure elevations.

Acutely high BP in hospitalized patients does not always need antihypertensive treatment as long as there are no symptoms or immediate damage to an organ. This is until reliable measurement protocols are created for these patients. There is even the possibility that antihypertensive treatment in these situations may lead to ischemic conditions.

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Case Report

MEDICINE PALLIATIVE CARE

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Zona zoster; an atypical presentation with severe pre-lesion pain: a case report

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ABSTRACT

The Varicella Zoster virus can initially cause chickenpox in humans and then become latent. It can later reactivate for various reasons and manifest as shingles in dermatome areas, characterized by redness, rash, and neuropathic pain. In this case, we want to highlight a Zoster case with atypical symptoms resembling acute coronary syndrome, but without the presence of a rash. The patient is a 78-year-old female who presented to the emergency department with complaints of chest pain resembling acute coronary syndrome.

Keywords: Differential diagnosis, atypical zona, acute coronary syndrome

INTRODUCTION

Varicella zoster virus (VZV) is an alpha herpesvirus with a double-stranded DNA genome. VZV infects humans, and its primary targets are T lymphocytes, epithelial cells, and ganglia. The primary infection results in chickenpox, during which VZV becomes latent in ganglionic neurons. After the primary infection, VZV, which is a neurotropic virus, becomes latent in neurons in the peripheral autonomic ganglia. Latent VZV can reactivate and cause herpes zoster (shingles) spontaneously or by following one or more triggering factors. Zoster typically manifests as a painful or itchy cutaneous vesicular rash that appears in a characteristic dermatomal distribution.[1,2]

Zoster can lead to chronic pain (postherpetic neuralgia) as well as other serious neurological complications such as meningoencephalitis, myelitis, cranial nerve palsy, and vasculopathy. It can also result in ophthalmic complications (keratitis, retinopathy) and gastrointestinal complications (ulcers, hepatitis, pancreatitis), among others.[3,4]

In this case, we wanted to highlight a case of zoster presenting with atypical symptoms resembling acute coronary syndrome but without any rash.

CASE

A 78-year-old female patient presented to the emergency department with complaints of pain in the left retrosternal area radiating to the back, which started 1-2 hours prior to arrival. The pain did not alleviate with movement or change in position and was constant. Her medical history included a lobectomy of the right lower lobe and radiotherapy for lung carcinoma 5-6 years ago. Recent follow-up consultations at the Medical Oncology Clinic did not reveal any recurrence or residual findings. Laboratory tests and imaging were normal. She had recently undergone eradication treatment for *H. pylori* infection following an endoscopy for dyspeptic symptoms, and it was the 9th day of treatment. Physical examination revealed normal lung sounds and equal expansion of both hemithorax's with no pathological sounds. Cardiac examination was unremarkable, peripheral circulation was normal, and blood pressure measured from both arms was within the normal range. Oxygen saturation was not low. The ECG was in sinus rhythm without any pathology, and the chest X-ray showed no abnormalities. Blood tests for troponin were normal, and there were no abnormalities in other blood parameters. The patient was admitted to the internal medicine clinic for further evaluation and management. She received treatment with NSAIDs, tramadol, and paracetamol for ongoing pain. A cardiology consultation was requested, but cardiac pathology was not suspected. Consultations were also requested from the physical medicine and rehabilitation and psychiatry departments, and a preliminary diagnosis of fibromyalgia syndrome was made. The patient was started on Duloxetine and Tramadol for pain

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management. On the 3rd day of follow-up, a physical examination revealed erythematous, pruritic, and painful vesicular eruptions consistent with dermatomes extending from the left anterior axillary line to the left posterior vertebral line. A dermatology consultation confirmed the diagnosis of herpes zoster, and the patient was immediately started on acyclovir treatment at a dose of 10 mg/kg three times a day. Topical steroid and vitamin B12 were added to the treatment. The patient completed a 10-day course of treatment. Due to severe and refractory pain, Gabapentin was initiated, and pain control was achieved before discharge.

DISCUSSION

The clinical presentation of varicella and zoster, which typically includes a distinctive generalized or unilateral dermatomal vesicular rash, serves as the main basis for diagnosis. However, sometimes the diagnosis can be made in the presence of additional symptoms, such as facial paralysis,[5] meningitis,[3] paralysis,[6] gastrointestinal involvement,[7] or as in our case, in the absence of rash and only with pain symptoms (zoster sine herpete).[8] There are two common ways to find out if VZV has been activated and to confirm the diagnosis: polymerase chain reaction (PCR) for finding VZV DNA and enzyme-linked immunosorbent assay (ELISA) for measuring anti-VZV antibodies, specifically anti-VZV immunoglobulin (IgG and IgM) levels.[8]

Antiviral treatment is recommended for immunocompromised patients, those over the age of 50, and those with severe rash or rash on the face or eyes, as well as patients with any complications of herpes zoster. Oral acyclovir, valacyclovir, or famciclovir are commonly used for treatment.[9,10] Treatment is typically given for 7-10 days and reduces the time to cessation of new lesion formation, crusting of the lesions, and relief of acute pain.[11] Hospitalized patients or those with neurological complications are treated with intravenous acyclovir for 7-10 days, as intravenous treatment has been shown to reduce the risk of internal organ involvement and cutaneous dissemination. Initiation of antiviral treatment within 3 days of rash onset is recommended, but if new lesion formation continues in later days, treatment should still be initiated. While antiviral treatment reduces the acute pain associated with herpes zoster, it has not been reliably shown to reduce the risk of postherpetic neuralgia (PHN).[12] Prednisone reduces acute pain and improves clinical outcomes in patients with herpes zoster,[13] but it does not decrease the risk of PHN,[14] and caution should be exercised when using steroids due to the elderly age and the presence of additional diseases like diabetes and hypertension in this patient population. Antiviral treatment should always be given to all patients receiving steroids.[12]

Zoster pain symptoms can be treated with non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen in primary care. Local lidocaine can reduce pain, but it should only be used on intact skin due to the risk of irritation. For more severe pain, opioids and opioid agonists (such as oxycodone or tramadol), anticonvulsants (such as gabapentin or pregabalin), or tricyclic antidepressants (such as nortriptyline) can be used.[12]

Postherpetic neuralgia (PHN) is the most serious complication of herpes zoster and is seen in approximately 15% of cases. Age is the most important risk factor for PHN and rapidly increases after the age of 50.4 In addition to age, the risk is also increased in immunocompromised patients, organ transplant recipients, patients receiving chemotherapy for cancer or with autoimmune diseases, individuals with HIV infection, and patients with various chronic diseases.[15] Treatment of PHN is generally challenging, and significant improvement in pain is not seen in most patients. The treatments used are symptomatic rather than targeting the underlying cause of pain. Topical lidocaine, topical capsaicin, gabapentin, pregabalin, and tricyclic antidepressants are commonly used in treatment.[16] The tolerability of topical treatments is often difficult due to pain and rash. Additionally, all systemic medications have potential side effects that may be challenging for elderly patients, and dosages need to be closely monitored for each patient. Referral to a pain specialist may be necessary for patients.

It has been shown that the zoster vaccine is safe and effective in healthy individuals, but it is not yet included in routine vaccination programs.[12]

Due to the acute onset of chest and back pain in our case, acute cardiac emergencies such as acute coronary syndrome, acute valve diseases, and aortic dissection, as well as acute respiratory emergencies such as pneumonia, pneumothorax, and pleural effusion, were ruled out through physical examination, laboratory tests, and imaging investigations. In the literature, there are cases of herpes zoster presenting with chest pain and without the presence of rash.[17] As a result, cases presenting without a rash, like the one in our case, can be missed or misdiagnosed, and patients may not receive timely antiviral treatment. Sometimes, this can keep the varicella-zoster virus (VZV) active, which can cause persistent herpetic neuralgia and then damage the nerves in a way that leads to postherpetic neuralgia (PHN).[18] More seriously, continuous reactivation of VZV can result in fatal complications such as encephalitis, cerebrovascular disease, and paralysis.[19,20] Compared to the pain experienced by classical herpes zoster patients, it has been shown that the pain in patients with zoster sine herpete is more severe both initially and one to three months after the onset of symptoms.[18]

CONCLUSION

In summary, the symptoms and signs of zoster can be subtle, and when other causes are ruled out, zoster sine herpete should always be included in the differential diagnosis for patients with unexplained and more severe radicular-neuropathic pain. A detailed medical history should be obtained from these patients, and the possibility of zoster without a rash should be kept in mind.

ETHICAL DECLARATIONS

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

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Case Report

MEDICINE PALLIATIVE CARE

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A rare complication of central fascial paralysis associated with quinolone

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ABSTRACT

Quinolones, which are broad-spectrum antibiotics, are frequently preferred in the treatment of infections. In infections developing in immunosuppressed patients, side effects of quinolones, which are started empirically without determining the agent and etiology, are also quite common. In this article, central facial paralysis due to ciprofloxacin initiated for anal abscess in an immunosuppressed patient receiving chemotherapy for multiple myeloma is described, and we aim to draw attention to this rare side effect. To the best of our knowledge, this is the first case reported in the literature.

Keywords: Central fascial paralysis, quinolone, ciprofloxacin

INTRODUCTION

For nearly 30 years, ciprofloxacin, one of the fluoroquinolone groups of antibiotics, has been used prophylactically and therapeutically in respiratory, gastrointestinal, genitourinary, skin, bone, ophthalmic, and soft tissue infections. Ciprofloxacin stops DNA replication by blocking the A subunit of DNA gyrase. This is how all fluoroquinolones work.[1,2] This group of antibiotics, which has a wide range of side effects, can affect many systems, such as the gastrointestinal tract, central nervous system, and skin. Dizziness, mild QT prolongation, tendinopathy, aortopathy, and phototoxic effects are common side effects.[3,4] Neuropathy findings are rare side effects.[5]

Among its neurotoxic effects, psychosis, seizures, encephalopathy, myoclonus, ataxia, dysarthria, dysarthria, chorea and oral facial dyskinesia have been reported.[6-9] However, central facial paralysis due to ciprofloxacin has not been reported before. Peripheral neuropathy is a rare side effect of ciprofloxacin, and its occurrence in many diseases complicates and delays the diagnosis. Neuropathy is a finding that increases in prevalence with increasing age, occurring in 6% of the population over 60 years of age. It is frequently seen as a symptom of some diseases or a common side effect of certain medications. While it is seen as a finding in diabetes, inflammatory, and hereditary diseases, it is a common side effect of chemotherapy drugs, some antibiotics (metronidazole), amiodarone, and phenytoin.[10] The mechanism by which ciprofloxacin causes neuropathy is not known. However, studies have found that quinolone use increases the risk of neuropathy.[11] According to the FDA, neuropathy can start at any time during ciprofloxacin treatment. It may persist for months or years after the drug is discontinued or may not resolve at all.

CASE

A 67-year-old man with diabetes mellitus, stage 2 chronic kidney disease, benign prostatic hyperplasia, and multiple myeloma He presented to the emergency department with complaints of pain in the perianal region, lower abdominal quadrants, and suprapubic region, nausea, and decreased oral intake, which had been gradually increasing for 1 week. The immunocompromised person who was being treated for multiple myeloma with bortezomib dexamethasone thalidomide was admitted to the general surgery ward with a perianal abscess already known. The investigations revealed elevated CRP and leukocytosis. The broad-spectrum antibiotic ciprofloxacin (2*400 mg IV) was started. The abscess was drained. Him complaints decreased after the drainage. Facial asymmetry, which was more pronounced when speaking, and lisping in speech started 24 hours after ciprofloxacin was started. He was evaluated by a neurology physician with a detailed examination. No other etiologic cause was found in the patient who developed left central facial paralysis. In the etiology of central facial paralysis, there

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was no evidence of lymphopenia/lymphocytosis, rash, stomatitis, oral ulcers, otitis, sinusitis, conjunctivitis, tonsillitis, or hepatosplenomegaly specific to viral infections. The patient did not clinically suggest a viral infection, and viral markers were not tested. Apart from a perianal abscess, no other infectious foci were identified, and no systemic signs were observed. In the absence of autoimmune disease diagnosis, symptoms, or history, the elevated acute phase reactant was considered secondary to an infection. Brain CT and diffusion MRI imaging for vascular etiology showed no evidence of ischemic cerebrovascular disease or vascular malformations. No neoplastic findings were observed in the imaging. The patient does not have a history of trauma or congenital diseases. Blood tests revealed no electrolyte imbalance or acute renal failure. However, it was thought that acute central facial paralysis might be one of the rare neurotoxic side effects of ciprofloxacin, which had been recently started, and ciprofloxacin antibiotherapy was discontinued. Ampicillin-sulbactam antibiotherapy was started. The patient was not using steroids. Approximately 48 hours after ciprofloxacin was discontinued, the facial asymmetry resolved spontaneously. It was evaluated as short-term central facial paralysis due to ciprofloxacin.

DISCUSSION

Neuropathy occurs as a side effect of many drugs. Many drugs, such as chemotherapeutics, antiretroviral agents, statins, and cardiovascular drugs, have neurotoxic side effects, especially affecting peripheral nerves, which play a role in the etiology of neuropathy. In previously reported cases, the peripheral neuropathy effect of ciprofloxacin has been mentioned, and in the pathogenesis, it has been found that the dorsal root ganglia and epineural blood vessels in the peripheral nervous system are vulnerable to toxins.[12] The incidence of drug-induced neuropathy has not been clearly demonstrated. This is because the severity and symptoms of the underlying disease may have suppressed the symptoms of neuropathy. In a cancer patient receiving chemotherapy, drug-induced neuropathies such as paresthesia may be detected early or late, depending on the relationship between the physician and the patient. Early detection of neurotoxic side effects suggests that symptoms may improve earlier and the permanent or prolonged effects of neuropathy may be prevented.[12,13] Morales et al.[14] showed that the incidence of quinolone-associated neuropathy increased by 1.7% compared to non-quinolone users. The relative incidence increased by 3% for each additional day of quinolone use. Etminan et al.[11] showed that the risk of peripheral neuropathy increased with fluoroquinolone use.

Our patient had a diagnosis of multiple myeloma and a history of bortezomib use. Neurotoxic side effects such as paresthesia are common with bortezomib use, but in our case, the last dose of the drug was administered 2 weeks before the development of an anal abscess, and there were no neurologic symptoms before ciprofloxacin. The patient also had a diagnosis of diabetes mellitus. He had no previous symptoms of diabetic peripheral neuropathy, and his blood sugars were regulated. In a patient with chronic kidney disease, there may be an increase in the neurotoxic effect of the drug due to its accumulation. Bortezomib use, diabetes, and chronic kidney disease may have facilitated the neuropathy effect of ciprofloxacin. Symptoms resolved spontaneously after drug discontinuation. No additional treatment including steroids was given.

The FDA has recommended immediate discontinuation of fluoroquinolone-induced neuropathy. Symptomatic treatment may be given in cases where neuropathy symptoms are severe and prolonged. Since the pathogenesis has not been elucidated, there is no consensus on a specific treatment. In a patient who developed palatal tremor due to ciprofloxacin, sodium valproate was administered after discontinuation of the drug, and symptoms resolved after 2 days.[15] In a patient who developed psychosis due to ciprofloxacin, symptoms resolved spontaneously 24 hours after discontinuation.[16] In a patient who developed ciprofloxacin-induced peripheral neuropathy, intravenous immunoglobulin, steroids, and physical therapy rehabilitation were administered, and significant improvements were observed in control electromyograms. 5 Many drugs, such as lidocaine, methadone, ketamine, acetaminophen, gabapentin, and fentanyl, have been tried for treatment, but their efficacy has not been demonstrated.[17,18]

The limitations in the diagnosis of this patient include the lack of viral marker testing and the absence of electromyography (EMG). Viral marker testing was not performed because there was no clinical suspicion of a viral infection. EMG could not be conducted because it was not performed at the center where the patient was admitted.

CONCLUSION

Ciprofloxacin is a neurotoxic antibiotic with the side effect of neuropathy. The symptom scale is ambiguous, and early detection of neuropathy and discontinuation of ciprofloxacin treatment may lead to an earlier resolution of symptoms. More studies are needed to elucidate the pathogenesis and solve the mechanism of neuropathy.

ETHICAL DECLARATIONS

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

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ZENGİN Musa

PUBLICATION RULES, PUBLICATION POLICY, GENERAL PRINCIPLES AND SUBMISSION RULES

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

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