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Letter to the Editor

# Artificial Intelligence in Dermatology and Future Treatment Plans

## Dermatolojide Yapay Zeka Kullanımı ve Gelecekteki Tedavi Planları

Mustafa Tümtürk

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**Dear Editor,**

Artificial intelligence in dermatology has the potential to revolutionize diagnostic and treatment processes. Artificial intelligence has emerged as a powerful tool to enhance the accuracy of skin disease diagnosis, personalize treatment plans, and improve patient outcomes.

Artificial intelligence plays a significant role in dermatological image analysis. Deep learning algorithms have achieved accuracy levels comparable to those of dermatologists in identifying skin lesions and other dermatological conditions (1). In particular, the use of Artificial intelligence in the early diagnosis of skin cancers such as melanoma can improve patient survival and treatment success (2). Artificial intelligence systems process large datasets, enabling faster and a more accurate diagnosis of skin diseases. This approach reduces the workload of dermatologists and increases their capacity to serve more patients.

In the future, one of the greatest contributions of artificial intelligence to dermatology will be the development of personalized treatment plans. Artificial intelligence can integrate various data sources, such as genetic information, lifestyle factors, and environmental influences, to recommend the most suitable treatment strategies for each patient (3). This treatment strategy can enhance treatment effectiveness while minimizing side effects.

The use of artificial intelligence in dermatology also raises ethical and safety concerns. Issues such as data privacy, algorithm transparency, and system reliability are important considerations for the successful integration of artificial intelligence applications (4). Moreover, maintaining human oversight of decision-making processes involving artificial intelligence is crucial for ensuring patient safety and ethical standards. During the development and implementation of artificial intelligence systems, it is essential to eliminate biases in algorithms and ensure that they are trained fairly.

Ethical considerations are significant aspects that must be addressed during the development and implementation of artificial intelligence systems. Note that attention should be paid to the diversity and representativeness of the datasets used to train artificial intelligence algorithms. This ensures that the algorithms provide accurate results across different skin types and ethnic groups. Additionally, maintaining human oversight of decision-making processes involving artificial intelligence is crucial for ensuring patient safety and ethical standards.

The role of artificial intelligence in dermatology is expected to expand in the coming years. Artificial intelligence can help researchers better understand skin biology and disease processes (5). This will enable the development of more targeted and effective treatment strategies. Furthermore, the broader use of artificial intelligence in dermatological research and clinical applications will improve the overall efficiency of the field and patient care. Artificial intelligence can automate routine diagnostic and monitoring tasks while allowing dermatologists to focus on more complex cases.

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## CONCLUSION

In conclusion, artificial intelligence offers a significant area of innovation and development in dermatology. However, to fully realize the potential of this technology, ethical and safety standards must be meticulously applied. This will enhance patient satisfaction and ensure the long-term success of dermatology. This guidance can contribute to future studies by providing direction.

## FOOTNOTES

**Conflict of Interest:** No conflict of interest was declared by the authors.

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Research

# Dyspnea and Quality of Life in Patients with Lung Cancer

## Akciğer Kanserli Hastalarda Dispne ve Yaşam Kalitesi

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## ABSTRACT

**Objective:** This study was planned to evaluate dyspnea symptoms and quality of life of patients with lung cancer and to determine the affecting factors.

**Methods:** The study sample consisted of 146 patients with primary diagnosis of lung cancer who were treated in the medical oncology clinic between January and April 2018. Data were collected using the patient personal, disease and treatment characteristics information form, cancer dyspnea scale and the European Cancer Quality of Life Research and Treatment Self-Assessment Questionnaire (EORTC QLQ-C30).

**Results:** A statistically significant difference was found in the role functioning sub-dimension of males, insomnia symptom sub-dimension of females; global health status and physical functioning sub-dimensions of the employees; fatigue and appetite loss symptom sub-dimensions of unemployed patients; diarrhea symptom sub-dimension of those with high income and economic difficulties sub-dimension of low-income patients ($p<0.05$). A statistically significant negative correlation was found between the dyspnea scores and quality of life scores of lung cancer patients ($p<0.05$).

**Conclusion:** As a result, as the perception of dyspnea worsened, so did the quality of life. Healthcare professionals should evaluate dyspnea in patients with lung cancer and implement treatment care by considering the quality of life and the factors that affect it.

**Keywords:** Dyspnea, lung cancer, quality of life

## ÖZ

**Amaç:** Bu çalışma, akciğer kanserli hastaların dispne semptomu ve yaşam kalitesini değerlendirmek ve etkileyen faktörleri belirlemek amacıyla planlandı.

**Gereç ve Yöntem:** Araştırmanın örneklemini Ocak-Nisan 2018 tarihleri arasında medikal onkoloji kliniğinde tedavi gören, primer tanısı akciğer kanseri olan 146 hasta oluşturmuştur. Veriler hasta kişisel, hastalık ve tedavi ilişkin özellikler bilgi formu, kanser dispne ölçeği ve Avrupa Kanser Yaşam Kalitesi Araştırma ve tedavi öz değerlendirme anketi (EORTC QLQ-C30) kullanılarak toplanmıştır.

**Bulgular:** Erkeklerin yaşam kalitesi rol fonksiyon alt boyutunda, kadınların uykusuzluk semptomu alt boyutunda; çalışabildiğini ifade edenlerin yaşam kalitesi genel sağlık durumu ve fiziksel fonksiyon alt boyutunda; çalışamadığını ifade edenlerin ise yorgunluk ve iştah kaybı semptomları alt boyutunda; gelir durumunun iyi olduğunu ifade edenlerin yaşam kalitesi diyare semptomu alt boyutunda, gelir durumunun kötü olduğunu ifade edenlerin ekonomik güçlükler alt boyutunda istatistiksel olarak anlamlı bir fark bulundu ($p<0,05$). Akciğer kanserli hastaların dispne puanları ile yaşam kalitesi puanları arasında istatistiksel olarak negatif yönde anlamlı bir ilişki bulundu ($p<0,05$).

**Sonuç:** Sonuç olarak, nefes darlığı algısı kötüleştikçe yaşam kalitesi de kötüleşti. Sağlık profesyonelleri; akciğer kanserli hastalarda nefes darlığını değerlendirmeli, yaşam kalitesini ve etkileyen faktörleri göz önünde bulundurarak tedavi bakım uygulamalıdırlar.

**Anahtar Kelimeler:** Dispne, akciğer kanseri, yaşam kalitesi

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## INTRODUCTION

Although lung cancer is a common disease, it is associated with a high mortality rate (1). In 2018, 18.1 million individuals were newly diagnosed with cancer and 9.6 million died worldwide. Lung cancer accounts for 2.9 millions of these cancers and accounts for 1.76 million deaths (2). According to current statistics (2018), the total cancer incidence was 210.2 per 100,000 people in Türkiye; and a total of 163.417 people were newly diagnosed with cancer. In Türkiye, lung cancer ranks first in males at a rate of 21.0 per 100,000 individuals in all age groups; while it ranks fifth in females at a rate of 5.1 per 100,000 individuals in all age groups (3).

Most patients experience physical and psychosocial symptoms that negatively affect their quality of life during the disease process (4-6). Dyspnea is among the most common symptoms experienced by patients with lung cancer. Dyspnea symptom causes difficulty performing daily activities, negatively affecting quality of life (4-8). Most patients describe dyspnea as "a very distressing condition". Dyspnea is defined as a disturbing condition of an individual's inability to breathe or uncomfortable awareness of breathing (9,10). Dyspnea, which can be observed in all stages of cancer, is particularly evident in lung cancer and mostly (50-70%) toward the end of life (11). Dyspnea symptoms vary among individuals. Personal, disease, and treatment-related characteristics affected this symptom (12).

Diagnosis and initiation of treatment in patients with lung cancer negatively affects the individual physically, emotionally, socially, and economically and decreases quality of life (13-15). The treatment applied to the patients aims to heal the symptoms, increase quality of life, and prolong life span. Quality of life is defined as "satisfaction and happiness of the individual regarding his/her own life" (16,17). Dyspnea negatively affects the patient's personal care, level of performing daily activities, functional capacity, and quality of life, making it difficult for patients to adhere to treatment (18,19). Therefore, determining the degree of dyspnea experienced by lung cancer patients and how it affects the patient's quality of life are very important in terms of compliance and effectiveness of treatment (7,16). In the literature; studies determining symptoms in patients with cancer and evaluating quality of life usually cover all types of cancer (19-21). All symptoms were evaluated globally in these studies, covering all cancer types. Therefore, these studies have provided an overview of the life quality of cancer patients (19,20). Studies examining dyspnea symptoms in patients with lung cancer and disease-specific quality of life are limited (15,22). More detailed and clear information can be obtained from studies focusing on a single type of cancer and symptom. In this context, more successful symptom management will be achieved by evaluating the symptoms of dyspnea and quality of life experienced by patients with lung cancer (4,15,22). Therefore, this study was planned to examine dyspnea symptoms and quality of life and to determine the factors affecting the quality of life in patients with lung cancer.

## METHODS

### Setting and Participants

This study is descriptive and cross-sectional. The sample comprised 146 patients admitted to the medical oncology clinic between January and April 2018 to receive treatment, with a primary diagnosis of lung cancer, who did not have any cognitive and mental disorders or a psychiatric disease. According to the sample calculation with a known universe, 187 lung cancer patients treated in the medical oncology department of the University Hospital constituted the study population, considering repetitive hospitalizations according to January-April 2017 data. According to the sampling formula with a known universe, at least 126 patients were selected to be sampled at a 95% confidence level and 5% tolerance. Considering the risk of missing data, 146 patients were included in the study.

The purpose of this study was to answer three specific questions:

1. Is there a difference in the severity of dyspnea symptoms experienced by patients with lung cancer and their personal and disease-related characteristics?

2. Is there a difference between the quality of life of patients with lung cancer and personal and disease-related characteristics?

3. Is there a relationship between the severity of dyspnea symptoms experienced by patients with lung cancer?

### Measures and Tools

Patients with lung cancer were invited to participate in the study. The inclusion criteria of patients who agreed to participate in the study were evaluated. Patients meeting the inclusion criteria were accepted to the study. The research data were collected by face-to-face interview using the patient's personal, disease, and treatment-related characteristics information form, the cancer dyspnea scale, and the European Cancer Quality of Life Research and treatment self-assessment questionnaire (EORTC QLQ-C30 version 3.0). The conversation took about 15 minutes.

### Patient Characteristics Information

The form was created by the researchers in accordance with the literature and is divided into two sections (17).

The first section involves questions regarding the personal characteristics of the patient (gender, age, marital status, income status, employment status, etc.), and the second section involves questions regarding the disease- and treatment-related characteristics (status of metastasis, ECOG performance, chemotherapy, radiotherapy, surgical treatment status, etc.).

### Cancer Dyspnea Scale

The scale was developed by Tanaka et al. (23) in Japan in 2000 to evaluate dyspnea frequently seen in patients with cancer. It consists of 12 items and 3 sub-dimensions that include feelings of anxiety, effort, and discomfort. Three subdimensions and total score values were used to evaluate the scale. The sense of effort has 5 items (4th, 6th, 8th, 10th, and 12th items), the sense of discomfort has 3 items (1st, 2nd, and 3rd items), and the sense of anxiety has 4 items (5th, 7th, 9th, and 11th items). The scale is a 5-point Likert scale. The total score obtained from the scale is 48 (the highest scores in the sub-dimensions are 20 for exertional dyspnea, 16 for anxiety-related dyspnea, and 12 for dyspnea due to feeling of discomfort). The higher the total score, the higher the dyspnea severity. The scale's validity and reliability study was conducted by Bitek and Tokem (11). Cronbach's alpha value of the scale was determined as ≥0.72. In this study, Cronbach's alpha value was found to be ≥0.70.

### EORTC QLQ-C30 version 3.0

Quality of life was measured using the EORTC Quality of Life Questionnaire-Cancer 30 (EORTC QLQ-C30) Version 3.0 (24). The 30-item EORTC QLQ-C30 assesses global health status, five functional status (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), and nine symptoms/items (fatigue, nausea-vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulty). Five functional status and symptoms were rated on a scale from 1 (not at all) to 4 (very much). Global health status is rated on a scale from 1 (very bad) to 7 (excellent). All scales and items were transformed into scores ranging from 0 to 100. Higher scores on the five functional subscales and global health status indicate better quality of life. Lower scores on the eight symptom items and financial difficulty represent better quality of life. In this study, we used the Turkish version of the EORTC QLQ-C30 (25).

### Statistical Analysis

SPSS 22 statistical software was used to analyze the research data. Percentage and mean were used for the personal, disease-, and treatment-related characteristics of patients with cancer, dyspnea symptoms, quality of life, and affecting factors; spearman correlation analysis was used for the relationships between continuous variables. The difference between the means of the two independent groups was tested using Mann-Whitney U test, and the difference between the means of the three groups was tested using Kruskal-Wallis analysis of variance. The statistical significance level was set as $p<0.05$.

### Ethical Considerations

Approval from the Scientific Research Ethics Committee of the Tarakya University Faculty of Medicine and research permission were obtained from the institution where the study was conducted (08.01.2018/TUTF-BAEK 2018/05). The purpose and scope of the study were communicated to the patients in the sample group before the study and their verbal consent was obtained.

## RESULTS

The mean age of patients with lung cancer who participated in the study is 60.85±9.81 years. The diagnosis time of the patients was 1.83±2.53 years, and approximately half of the patients (49.3%) had an Eastern Cooperative Oncology Group (ECOG) performance score of "1". Most patients (82.9%) were male, most (94.5%) were married, and 71.1% were primary school graduates. More than half of the patients (69.2%) quit smoking. In addition, 38.4% of the patients had metastasis, approximately 25% (22.6%) did not undergo any surgical operation related to the diagnosis of lung cancer, and more than half (58.4%) did not receive radiotherapy. The majority of patients (85.6%) had middle incomes, (85.6%) were unemployed, and almost all (97.3%) had health insurance (Table 1).

The mean score of the EORTC QOL-C30 global health status subdimension of the patients was found to be moderate (50.11±22.29). It was determined that the patients obtained the highest score from the cognitive functioning (82.87±20.43) and the lowest score from the physical functioning (61.41±24.89) in the functional subdimension. In the symptom sub-dimension; it was determined that the highest mean score was obtained from fatigue (48.47±27.05) and the lowest mean score was obtained from diarrhea (16.89±26.04). The three most common symptoms were fatigue, appetite loss, and pain (Table 2).

The mean score of the effort subdimension of the dyspnea scale was 4.67±4.03, the mean score for the anxiety sub-dimension was 2.28±3.08, the mean score for the discomfort sub-dimension was 4.62±3.10, and the total mean score was 26.33±6.15 being at a moderate level (Table 2).

A statistically significant difference was found between the sex of the patients participating in this study and the EORTC QLQ-C30 role functioning sub-dimension (p<0.05). Male patients played higher role functioning scores than female patients (p=0.045). A statistically significant difference was found between the gender and insomnia sub-dimension (p<0.05). Female patients experienced more insomnia than male patients (p=0.011) (Table 3).

In this study, a statistically significant difference was found between the employment status of the patients and the EORTC QLQ-C30 global health status and physical functioning sub-dimension (p<0.05). The global health and physical functioning scores of those who were employed were higher than those unemployed (p=0.024; p<0.001). A statistically significant intergroup difference was found between the employment status and symptoms of fatigue and appetite loss in patients with lung cancer (p<0.05). The symptoms of fatigue and appetite loss were worse in

**Table 1.** Characteristics of patients (n=146)

| **Characteristics** | **Mean±SD** | |
|---|---|---|
| Age | 60.85±9.81 | |
| Diagnosis time of the patient (year) | 1.83±2.53 | |
| | **n** | **%** |
| **ECOG** | | |
| 0 | 39 | 26.7 |
| 1 | 72 | 49.3 |
| 2 | 21 | 14.4 |
| 3 | 14 | 9.6 |
| Gender | | |
| Female | 25 | 17.1 |
| Male | 121 | 82.9 |
| **Marital status** | | |
| Married | 138 | 94.5 |
| Single | 8 | 5.5 |
| Education status | | |
| Primary school | 111 | 76 |
| High school and above | 35 | 24 |
| **Smoking** | | |
| No | 35 | 24.0 |
| Yes | 10 | 6.8 |
| Quit smoking | 101 | 69.2 |
| **State of the disease** | | |
| Primary | 90 | 61.6 |
| Metastasis | 56 | 38.4 |
| **Surgical Treatment for lung cancer** | | |
| No | 113 | 77.4 |
| Yes | 33 | 22.6 |
| **Receiving radiotherapy for lung cancer** | | |
| No | 86 | 58.9 |
| Yes | 60 | 41.1 |
| **Income rate** | | |
| Poor | 7 | 4.8 |
| Middle | 125 | 85.6 |
| Good | 14 | 9.6 |
| **Employment status** | | |
| Employed | 21 | 14.4 |
| Unemployed | 125 | 85.6 |
| Health Assurance | 142 | 97.3 |
| Yes | 4 | 2.7 |
| No | | |

Mean±SD: Mean±standart deviation

**Table 2.** Distribution of patients' EORTC Qols-C30 quality of life and dyspnea perception mean scores (n=146)

| **EORTC QOL-C30/ DYSPNEA** | **Mean± SD** | **Median** | **Minimum** | **Maximum** |
|---|---|---|---|---|
| **EORTC QOL 30** | | | | |
| Global health status | 50.11±22.29 | 50.00 | 0.00 | 100.00 |
| **Functional status** | | | | |
| Physical functioning | 61.41±24.89 | 66.66 | 0.00 | 100.00 |
| Role functioning | 72.48±27.65 | 66.66 | 0.00 | 100.00 |
| Emotional functioning | 74.25±25.44 | 75.00 | 0.00 | 100.00 |
| Cognitive functioning | 82.87±20.43 | 83.33 | 0.00 | 100.00 |
| Social functioning | 70.43±27.52 | 66.66 | 0.00 | 100.00 |
| **Symptoms/items** | | | | |
| Fatigue | 48.47±27.05 | 44.44 | 0.00 | 100.00 |
| Nausea-vomiting | 21.68±24.94 | 16.66 | 0.00 | 100.00 |
| Pain | 34.01±29.74 | 33.33 | 0.00 | 100.00 |
| Dyspnea | 23.05±29.70 | .00 | 0.00 | 100.00 |
| Insomnia | 32.64±34.89 | 33.33 | 0.00 | 100.00 |
| Appetite loss | 39.26±33.60 | 33.33 | 0.00 | 100.00 |
| Constipation | 23.28±26.04 | .00 | 0.00 | 100.00 |
| Diarrhea | 16.89±26.04 | .00 | 0.00 | 100.00 |
| Economic difficulties | 25.34±26.92 | 33.33 | 0.00 | 100.00 |
| **Dyspnea** | | | | |
| Effort | 4.67±4.03 | 4.00 | 0.00 | 18.00 |
| Anxiety | 2.28±3.08 | 1.00 | 0.00 | 14.00 |
| Discomfort | 4.62±3.10 | 3.00 | 0.00 | 12.00 |
| Total | 26.33±6.15 | 25.00 | 12.00 | 46.00 |

Mean±SD: Mean±standart deviation

unemployed than in employed patients (p=0.017; p=0.024) (Table 3).

A statistically significant difference was found between the income levels of the patients and the EORTC QLQ-C30 diarrhea symptom sub-dimension (p<0.05). Diarrhea symptoms were worse in patients with high income than in those with middle or low income (p=0.026). A statistically significant difference was found between the income levels of the patients and the economic difficulty sub-dimension (p<0.05). The economic difficulties score was higher in patients with low income than in those with high and middle income (p=0.002) (Table 3). No statistically significant difference was found between the sociodemographic characteristics and dyspnea scores of patients with lung cancer (Table 3).

In this study; a statistically significant negative correlation was found between the dyspnea effort sub-dimension and EORTC QOL-C30 functional sub-dimension scores, including physical functioning (r=-0.443; p<0.001), role functioning (r=-0.395; p<0.001), emotional functioning (r=-0.284; p=0.001), cognitive functioning (r=-0.240; p=0.003), and social functioning (r=-0.372; p<0.001). A statistically positive significant correlation was found between the dyspnea effort subdimension and EORTC QOL-C30 symptom subdimension scores, including fatigue (r=0.289; p<0.001), pain (r=0.401; p<0.001), respiratory distress

**Table 3.** Comparison of some characteristics of patients with EORTC QOL-C30 quality of life scale and cancer dyspnea scale (n=146)

| EORTC QOL C30/ DYSPNEA | Gender | | | Employment status | | | Income rate | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **EORTC QOL 30** | **Female mean±SD** | **Male mean±SD** | ***p**** | **Employed mean±SD** | **Unemployed Mean±SD** | ***p**** | **Good Mean±SD** | **Middle Mean±SD** | **Poor Mean±SD** | ***p**** |
| Global Health Status | 46.33±21.09 | 50.27±22.61 | .950 | 59.52±21.93 | 48.53±22.04 | .024 | 51.19±23.07 | 50.46±22.55 | 41.66±15.95 | .430 |
| Functional Status | | | | | | | | | | |
| Physical Functioning | 52.53±27.71 | 63.25±23.99 | .073 | 78.73±13.76 | 58.50±25.19 | .000 | 62.85±17.67 | 62.02±25.09 | 47.61±32.53 | .469 |
| Role Functioning | 62.00±29.86 | 74.65±26.79 | .045 | 76.19±30.53 | 71.86±27.22 | .368 | 69.04±22.51 | 73.60±27.69 | 59.52±35.81 | .394 |
| Emotional Functioning | 72.66±27.69 | 74.58±25.06 | .891 | 72.22±30.42 | 74.60±24.63 | .919 | 74.25±25.44 | 73.86±25.47 | 73.80±22.78 | .664 |
| Cognitive Functioning | 82.00±17.29 | 83.05±21.08 | .442 | 86.50±16.34 | 82.26±21.03 | .500 | 85.71±17.11 | 82.66±20.88 | 80.95±20.24 | .892 |
| Social Functioning | 63.33±28.46 | 71.90±27.21 | .145 | 72.22±27.55 | 70.13±27.62 | .737 | 79.76±16.24 | 69.86±28.60 | 61.90±23.00 | .349 |
| **Symptoms/items** | | | | | | | | | | |
| Fatigue | 55.11±26.34 | 47.10±27.10 | .187 | 36.50±27.92 | 50.48±26.49 | .017 | 56.34±19.71 | 47.37±27.87 | 52.38±24.60 | .441 |
| Nausea-Vomiting | 30.66±28.33 | 19.83±23.89 | .054 | 23.01±27.11 | 21.46±24.66 | .871 | 30.95±28.38 | 20.40±25.03 | 26.19±8.90 | .169 |
| Pain | 44.00±30.38 | 31.95±29.31 | .055 | 30.15±27.69 | 34.66±30.12 | .566 | 30.95±25.19 | 34.26±30.40 | 35.71±29.54 | .958 |
| Dyspnea | 28.00±31.44 | 22.03±29.36 | .347 | 22.22±32.20 | 23.20±29.39 | .795 | 30.95±33.24 | 22.93±29.45 | 9.52±25.19 | .232 |
| Insomnia | 48.00±34.80 | 29.47±34.20 | .011 | 20.63±30.68 | 34.66±30.12 | .075 | 21.42±30.95 | 34.40±35.65 | 23.80±25.19 | .374 |
| Appetite Loss | 48.00±30.55 | 37.46±34.03 | .129 | 23.80±28.17 | 41.86±33.84 | .024 | 42.85±27.51 | 37.86±34.22 | 57.14±31.70 | .253 |
| Constipation | 17.33±29.05 | 24.51±30.66 | .213 | 19.04±32.61 | 24.00±30.11 | .280 | 21.42±30.95 | 23.46±30.23 | 23.80±37.08 | .966 |
| Diarrhea | 28.00±22.93 | 14.60±26.13 | .001 | 20.63±30.68 | 16.26±25.26 | .623 | 35.71±33.24 | 15.20±24.86 | 9.52±16.26 | .026 |
| Economic Difficulties | 30.66±28.73 | 24.24±26.52 | .277 | 28.57±30.34 | 24.80±26.40 | .645 | 11.90±16.57 | 25.06±26.65 | 57.14±25.19 | .002 |
| **DYSPNEA** | | | | | | | | | | |
| Effort | 5.00±4.66 | 4.60±3.91 | .867 | 4.23±3.60 | 4.74±4.11 | .700 | 6.00±3.39 | 4.49±4.03 | 5.14±5.14 | .260 |
| Anxiety | 2.68±3.53 | 2.20±2.99 | .706 | 1.85±2.61 | 2.36±3.16 | .695 | 2.42±2.68 | 2.30±3.11 | 1.71±3.72 | .498 |
| Discomfort | 4.16±3.18 | 4.71±3.09 | .313 | 4.09±3.11 | 4.71±3.10 | .425 | 5.78±2.77 | 4.59±3.11 | 2.85±3.02 | .070 |
| Total | 27.52±6.34 | 26.09±6.11 | .277 | 26.00±4.38 | 26.39±6.41 | .960 | 26.64±4.48 | 26.20±6.17 | 28.00±8.92 | .732 |

* Mann–Whitney U, ** Kruskal–Wallis analysis of variance

(r=0.660; p<0.001), insomnia (r=0.331; p<0.001), constipation (r=0.190; p=0.022), and economic difficulties (r=0.306; p<0.001) (Table 4). As the dyspnea effort subdimension of the patients worsened, their quality of life, global health status, functional status, and symptoms also worsened.

In this study, a statistically significant negative correlation was found between the dyspnea anxiety subdimension and the EORTC QOL-C30 global health status scores (r=0.217; p=0.009). A statistically negative significant correlation was found between the dyspnea anxiety sub-dimension and EORTC QOL-C30 functional sub-dimension scores, including physical functioning (r=-0.469; p<0.001), role functioning (r=-0.398; p<0.001), emotional functioning (r=-0.237; p=0.004), cognitive functioning (r=-0.248; p=0.003), and social functioning (r=-0.336; p<0.001). A statistically positive correlation was found between the dyspnea anxiety subdimension score and EORTC QOL-C30 symptom subdimension score, including fatigue (r=0.295; p<0.001), pain (r=0.407; p<0.001), respiratory distress (r=0.603; p<0.001), insomnia (r=0.274; p=0.001), appetite loss (r=0.178; p=0.032), and economic difficulties (r=0.262; p=0.001) (Table 4). As the dyspnea anxiety dimension of the patients worsened, so did their quality of life, global health status, functional status, and symptoms.

In the study, a statistically significant negative correlation was found between dyspnea discomfort sub-dimension score and EORTC QOL-C30 functional sub-dimension scores, including physical functioning (r=-0.327; p<0.001), role functioning (r=-0.272; p=0.001), emotional functioning (r=-0.235; p=0.004), cognitive functioning (r=-0.256; p=0.002), and social functioning (r=-0.209; p=0.012). A statistically positive correlation was found between the

**Table 4.** Comparison of the relationship between the EORTC QOL-C30 quality of life scale and the cancer dyspnea scale (n=146)

| EORTC QOL 30 | DYSPNEA | | | |
|---|---|---|---|---|
| | **Effort** | **Anxiety** | **Discomfort** | **Total** |
| Global health status | r= -.211<br>p= .010 | r= -.217<br>p= .009 | r= -.118<br>p= .154 | r= -.209<br>p= .011 |
| **Functional status** | | | | |
| Physical functioning | r= -.443<br>p= .000 | r= -.469<br>p= .000 | r= -.327<br>p= .000 | r= -.375<br>p= .000 |
| Role functioning | r= -.395<br>p= .000 | r= -.398<br>p= .000 | r= -.272<br>p= .001 | r= -.352<br>p= .000 |
| Emotional functioning | r= -.284<br>p= .001 | r= -.237<br>p= .004 | r= -.235<br>p= .004 | r= -.227<br>p= .006 |
| Cognitive functioning | r= -.240<br>p= .003 | r= -.248<br>p= .003 | r= -.256<br>p= .002 | r= -.183<br>p= .027 |
| Social functioning | r= -.372<br>p= .000 | r= -.336<br>p= .000 | r= -.209<br>p= .012 | r= -.331<br>p= .000 |
| **Symptoms/items** | | | | |
| Fatigue | r= .289<br>p= .000 | r= .295<br>p= .000 | r= .270<br>p= .001 | r= .220<br>p= .008 |
| Nausea-vomiting | r= .159<br>p= .055 | r= .139<br>p= .094 | r= .094<br>p= .259 | r= .159<br>p= .055 |
| Pain | r= .401<br>p= .000 | r= .407<br>p= .000 | r= .200<br>p= .016 | r= .350<br>p= .000 |
| Dyspnea | r= .660<br>p= .000 | r= .603<br>p= .000 | r= .479<br>p= .000 | r= .499<br>p= .000 |
| Insomnia | r= .331<br>p= .000 | r= .274<br>p= .001 | r= .170<br>p= .040 | r= .276<br>p= .001 |
| Appetite Loss | r= .130<br>p= .118 | r= .178<br>p= .032 | r= .120<br>p= .149 | r= .126<br>p= .128 |
| Constipation | r= .190<br>p= .022 | r= .155<br>p= .061 | r= .154<br>p= .063 | r= .122<br>p= .142 |
| Diarrhea | r= .096<br>p= .249 | r= .136<br>p= .103 | r= .105<br>p= .207 | r= .066<br>p= .427 |
| Economic Difficulties | r= .306<br>p= .000 | r= .262<br>p= .001 | r= .095<br>p= .252 | r= .317<br>p= .000 |

dyspnea discomfort subdimension score and EORTC QOL-C30 symptom subdimension scores, including fatigue (r=0.270; p=0.001), pain (r=0.200; p=0.016), respiratory distress (r=0.479; p<0.001), insomnia (r=0.170; p=0.040) (Table 4). As the dyspnea discomfort subdimension of the patients worsened, the quality of life, global health status, functional status, and symptoms also deteriorated.

In the study, a statistically significant negative correlation was found between the dyspnea scale total score and EORTC QOL-C30 global health status (r=-0.209; p=0.011), functional subdimension scores including physical functioning (r=-0.375; p<0.001), role functioning (r=-0.352; p<0.001), emotional functioning (r=-0.227; p=0.006), cognitive functioning (r=-0.183; p=0.027), and social functioning (r=-0.331; p<0.001). A statistically positive correlation was found between the dyspnea scale total score and EORTC QOL-C30 symptom subdimension scores, including fatigue (r=0.220; p=0.008), pain (r=0.350; p<0.001), respiratory distress (r=0.499; p<0.001), insomnia (r=0.276; p<0.001) and economic difficulties (r=0.317; p<0.001) (Table 4). As the patients' dyspneas symptoms worsened, so did their quality of life.

## DISCUSSION

In this study, the mean EORTC QOL-C30 global health status score of patients was moderate. It was determined that the patients obtained the highest score for cognitive functioning in the functional subdimension and the lowest score for physical functioning. In the symptom sub-dimension; the highest mean score was fatigue, and the lowest mean score was diarrhea. The three most common symptoms were fatigue, appetite loss, and pain. The total mean score of dyspnea was moderate. Çalışkan et al. (17) found that the EORTC QLQ-C30 global health status of patients was moderate, and the three most common symptoms were fatigue, anorexia, and insomnia. Damani et al. (26) reported that the main symptoms affecting quality of life were pain, anorexia, and respiratory distress. In a study conducted with patients with lung cancer, it was found that the EORTC QLQ-C30 global health status of the patients was moderate and they obtained the highest score in the functional sub-dimension on cognitive functioning. In the same study, the three most common symptoms were insomnia, financial difficulty, and fatigue (27). In a study of cancer patients receiving radiotherapy, it was shown that the cognitive and social domains of quality of life had the greatest impact, while tiredness and pain ratings were highest in the symptom subdimension (28). This situation can be explained by the fact that physical functioning along with quality of life of patients are affected by the symptoms associated with the treatment they receive as well as the disease.

Male patients who participated in this study had better quality of life role functioning scores than female patients. Female patients had worse insomnia symptoms than male patients. Altıparmak et al. (29), determined in their study that the quality of life of males was better than that of females with physical, role, emotional, cognitive, and social functioning. In a study examining symptoms and functionality among males and females with lung cancer; it has been reported that males have a better quality of life role functioning than females and that the most common symptom in males is insomnia (30). Cheun et al. (31), reported more nausea and anxiety in females than males and reported a worse quality of life in females than males. The results of our study are consistent with the literature. This situation can be explained by the fact that women generally have more household chores (cooking, cleaning, maintenance, etc.) than men, and the symptoms experienced by cancer patients prevent women from performing their role functioning.

In this study, the employed patients had better quality of life, global health, and physical functioning scores compared to the unemployed patients. At the same time, the symptoms of fatigue and appetite loss were worse in the unemployed than in the employed ones. Zimmermann et al. (32) reported that employed or retired patients have a higher quality of life than unemployed and disabled patients. In another study, it was stated that quitting cancer patients from their jobs negatively affected their quality of life scores (33). This condition may be explained by the fact that patients with cancer who have fewer symptoms are able to execute their bodily functions, employment, and tasks and thus have a higher quality of life.

In this study, individuals who stated that their income was good had more diarrhea symptoms than those who stated that their income was moderate or poor. At the same time, patients with a low income had worse economic difficulty scores than those with middle and high income. In a study conducted to determine the symptoms that occur due to chemotherapy treatment and the effect of these symptoms on quality of life, it was found that patients with high-income status have high quality of life scores (34). In the study of Altıparmak et al. (29) stated that those with sufficient income perception had better quality of life, global health status, and role functioning than those with low-income perception. Zimmermann et al. (32) found that low-income cancer patients had a lower quality of life. Gelin and Ulus. (33) observed that the higher the economic status of patients,

the higher the quality of life scores. Economic problems of individuals with poor health conditions due to health-related expenditures, care costs, etc. worsen the quality of life of people. At the same time, a high-income state makes individuals more comfortable with their purchasing power and nutrition, leading to the more frequent occurrence of certain symptoms (diarrhea, etc.) accordingly.

In this study, it was found that as dyspnea effort, anxiety, discomfort, and the total score increased, quality of life, global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning scores decreased. At the same time, this study found that as the effort, anxiety, discomfort, and total score increased, the symptoms of fatigue, pain, respiratory distress, and insomnia increased. In a study examining the symptom correlates of dyspnea in patients with advanced cancer, it was stated that tiredness, loss of appetite, depression, and anxiety were significant for the presence of moderate/severe dyspnea in patients (35). A study examining the characteristics and relationships of dyspnea in patients with advanced-stage cancer reported that dyspnea was positively correlated with fatigue, sleep, depression, anxiety, and feelings of well-being (36). In a study examining the emotional problems, quality of life, and symptom burden in patients with lung cancer, the severity of emotional problems increased, as did reported level of symptom burden, and those with more emotional problems reported having more frequent pain, greater pain severity, more dry coughing, more shortness of breath, and greater fatigue (13). It has been reported that the frequency of respiratory distress and insomnia symptoms is higher and quality of life is reduced in patients with advanced lung cancer (37). It has been reported that dyspnea is associated with many symptoms, such as fatigue, anxiety, and appetite loss causing poor quality of life in patients (26). It has been reported that patients with high dyspnea scores experience more severe physical symptoms, such as weakness, choking, tension, congestion, panic, and pain, and have higher anxiety levels (38). Because of the diagnosis of the disease and side effects of treatment, lung cancer patients experience respiratory distress, which is one of the basic functions of survival. This condition causes difficulties in performing other activities and negatively affects quality of life, along with other side effects.

### Limitation

Since the study was conducted with patients who applied to the medical oncology clinic of the faculty of medicine hospital between the study dates, met the inclusion criteria, and volunteered to participate, the research data can only be generalized to patients who are treated only in the institution where the study was conducted.

### Conclusion

In this study; it was found that dyspnea symptoms and quality of life in patients with lung cancer were moderate. The quality of life was worse among females with lung cancer, unemployed individuals, and those with low-income status. Quality of life decreased as dyspnea symptoms worsened. In conclusion, health professionals should evaluate the symptoms of dyspnea that individuals with lung cancer may experience due to diagnosis and treatment and provide individualized care. Nurses should ensure that patients benefit from physical and psychosocial support to reduce dyspnea symptoms. In addition, nurses should provide treatment, care, and counseling that will improve patients' quality of life by reducing their physical and psychosocial symptoms.

## ETHICS

**Ethics Committee Approval:** Approval from the Scientific Research Ethics Committee of the Tarakya University Faculty of Medicine and research permission were obtained from the institution where the study was conducted (08.01.2018/ TUTF-BAEK 2018/05).

**Informed Consent:** The purpose and scope of the study were communicated to the patients in the sample group before the study and their verbal consent was obtained.

### FOOTNOTES

### Authorship Contributions

Concept: S.K., S.U., Design: S.K., Data Collection or Processing: S.K., İ.Y.Ç., Analysis or Interpretation: S.K., S.U., Literature Search: S.K., S.U., İ.Y.Ç., Writing: S.K., S.U., İ.Y.Ç.

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Research

# Endoscopic Transsphenoidal Approach to Somatotroph Adenomas in Pediatric Patients

## Pediatrik Populasyonda Somatotrof Adenomlara Endoskopik Transsfenoidal Yaklaşım

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## ABSTRACT

**Objective:** Somatotroph adenomas account for approximately 5%-15% of pediatric pituitary adenomas and are more common in males. The aim of this study was to discuss the early and late outcomes of endoscopic pediatric growth hormone (GH)-secreting pituitary adenoma surgery performed at a high-volume tertiary hospital.

**Methods:** A total of 4875 consecutive patients underwent endoscopic transsphenoidal surgery between August 1997 and December 2022 in Kocaeli University Medical Faculty Neurosurgery Department and Pituitary Research Center. We reviewed the medical data, radiological images, and surgical videos of these patients and included 19 (0.39%) pediatric patients aged 18 years with pathologically identified GH-secreting pituitary adenoma.

**Results:** The data of 19 pediatric patients with GH-secreting pituitary adenoma were pathologically identified at our institution and retrospectively analyzed. 8 (42.1%) participants were male and 11 (57.9%) were female. Gross total resection (GTR) was performed in 10 (52.6%) patients, and subtotal resection was performed in 9 (47.4%) patients. 9 (47.4%) patients met the criteria for remission. Statistically significant results for adenoma size on GTR were obtained (p-value: 0.021). Sphenoid sinus pneumatization was not associated with resection rate (p-value 0.264). The absence of cavernous sinus invasion was significant as a positive predictive value for GTR, but it was not significant for remission (p-value:0.027-0.102, respectively).

**Conclusion:** Somatotroph adenomas in pediatric patients are rare and challenging lesions. Adenoma size and cavernous sinus invasion are effective for resection. Sphenoid sinus pneumatization does not affect the resection rate in experienced centers.

**Keywords:** Endoscopic surgery, somatotroph adenoma, pediatric

## ÖZ

**Amaç:** Somatotrof adenomlar pediatrik hipofiz adenomlarının yaklaşık %5-15'ini oluşturur ve erkeklerde daha yüksek insidans gösterir. Bu çalışmadaki amacımız yüksek volümlü üçüncü basamak merkezde gerçekleştirilen endoskopik pediatrik büyüme hormonu (GH) salgılayan hipofiz adenomu ameliyatlarının erken ve geç dönem sonuçlarını tartışmaktır.

**Gereç ve Yöntem:** Ağustos 1997-Aralık 2022 tarihleri arasında toplam 4875 hastaya endoskopik transsfenoidal cerrahi uygulandı. Bu hastaların tıbbi verilerini, radyolojik görüntülerini ve cerrahi videolarını inceledik ve patolojik olarak GH salgılayan hipofiz adenomu tespit edilen 18 yaşın altındaki 19 (%0,39) pediatrik hastayı çalışmaya dahil ettik.

**Bulgular:** Kurumumuzda patolojik olarak tanısı konan on dokuz pediatrik GH salgılayan hipofiz adenomu hastasının verileri retrospektif olarak analiz edildi. Hastaların 8'i (%42,1) erkek, 11'i (%57,9) kadındı. Hastaların 10'unda (%52,6) gross total rezeksiyon, 9'unda (%47,4) subtotal rezeksiyon gerçekleştirildi. 9 (%47,4) hasta remisyon kriterlerini karşılamıştır. Adenom boyutunun Gros total rezeksiyon (GTR) üzerindeki etkisinde istatistiksel olarak anlamlı sonuçlara ulaşılabildi (p-değeri: 0.021). Sfenoid sinüs pnömatizasyonu rezeksiyon oranları için anlamlı değildi (p-değeri 0.264). Kavernöz sinüs invazyonunun olmaması GTR için pozitif prediktif değer olarak anlamlıydı ancak remisyon için anlamlı değildi (sırasıyla p değeri: 0.027-0.102).

**Sonuç:** Pediatrik hastalarda somatotrof adenomlar nadir ve zor lezyonlardır. Adenom boyutu ve kavernöz sinüs invazyonu rezeksiyon oranları üzerinde etkilidir. Sfenoid sinüs pnömatizasyonu deneyimli merkezlerde rezeksiyon oranlarını etkilememektedir.

**Anahtar Kelimeler:** Endoskopik cerrahi, somatotrof adenom, pediatrik

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## INTRODUCTION

Pituitary adenomas rarely occur in childhood, accounting for approximately 3% of all supratentorial tumors (1). They represent 2-8.5% of all pituitary tumors in children (2). Although pituitary adenomas are benign lesions, they can cause endocrinopathy due to hormone hypersecretion and/or visual disturbances due to mass effects. The majority of these adenomas are sporadic and occur at a low rate in the context of genetic syndromes or familial isolated pituitary adenomas (3).

The latest developments in endoscopic transsphenoidal approaches and advances in tools have increased the effectiveness of endoscopic transsphenoidal surgery (4). There are few studies on the endoscopic transsphenoidal approach because of the low incidence of sellar tumors in pediatric patients (5-8).

Somatotroph adenomas account for approximately 5%-15% of pediatric pituitary adenomas and are more common in males (9). The aim of this study was to discuss the early and late outcomes of endoscopic pediatric GH-secreting pituitary adenoma surgery performed at a high-volume tertiary hospital.

## METHODS

### Patient Population

A total of 4875 consecutive patients underwent endoscopic transsphenoidal surgery between August 1997 and December 2022 in Kocaeli University Medical Faculty Neurosurgery Department and Pituitary Research Center. We reviewed the medical data, radiological images, and surgical videos of these patients and included 19 (0.39%) pediatric patients aged 18 years with pathologically identified growth hormone (GH)-secreting pituitary adenoma. Patients with pathologically identified other sellar region tumors like craniopharyngioma, chordoma, rathke cleft cyst, and other pituitary adenoma, were excluded from the study. The records of these patients were reviewed for age, sex, presenting symptoms, endocrinological findings, imaging studies, surgical outcomes, and follow-up data. Approval was obtained from Kocaeli University Non-Interventional Clinical Research Ethics Committee (decision no: KÜ GOKAEK-2024/12.20, date: 26.07.2024). Written informed consent was obtained from the families of all patients. written informed consent was obtained from the families and all patients.

### Magnetic Resonance Imaging (MRI) and Paranasal Sinus Tomography

Paranasal sinus tomography (evaluation of sphenoid sinus pneumatization and sellar type) and MRI were performed preoperatively in all patients.

Sphenoid sinus pneumatization was divided into 4 types (conchal, presellar, sellar, and postsellar) based on preoperative paranasal sinus tomography (Figure 1).

MRI was performed using 1.5-T or 3-T magnetic resonance equipment. Preoperative and postoperative (1st day, 3rd month, 1st year) MRI sequences included precontrast and postcontrast T1- weighted images in the sagittal and coronal planes, T2- weighted images and dynamic contrast-enhanced T1-weighted images in the coronal plane, and 3D volumetric neuronavigation studies.

Volumetric analyses were performed to determine preoperative and postoperative tumor volumes. One radiologist reviewed the MRI scans.

The MRI findings showed the following: gross total resection and subtotal resection were defined as no residual tumor and presence of residual tumor on postoperative MRI, respectively.

### Surgical Technique

All procedures were performed using standard endoscopic transsphenoidal approaches and, if necessary, extended endoscopic transsphenoidal approaches with an image-guided neuronavigation system. The details of the surgical procedure have been previously described (10,11). Standard techniques were used for intrasellar lesions. In the surgical approach, both nostrils were used. A 4- mm endoscope was used in all patients. In the standard approach, small sphenoidotomy is performed. The sellar base was drilled, and then the dura was opened. The aim of surgery is always to maximize the extent of resection; however, this is not possible in all cases.

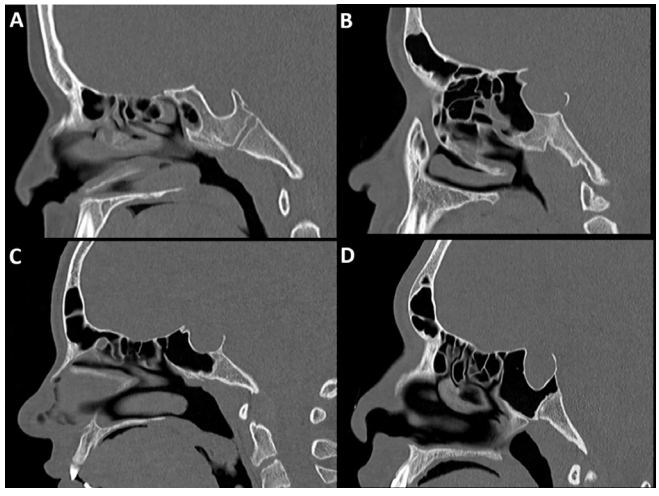


**Figure 1:** Sphenoid sinus pneumatization types: A) conchal type, B) prestellar type, C) sellar type, D) postsellar type

An extended endoscopic transsphenoidal approach is required for skull base lesions extending to the suprasellar area using the infrachiasmatic corridor (12). The difference between this approach and the previous one is that the sellar base opening is extended superiorly (Figure 2).

If intraoperative cerebrospinal fluid (CSF) leakage was observed, the multilayer closure technique was used. In cases where there was no CSF leak, reconstruction was not performed.

### Endocrine and Clinical Investigations

Endocrinological functions were evaluated before and after surgery on days 1, 3, and year 1 using conventional stimulation tests. Endocrinological outcomes were assessed according to the 2010 consensus criteria. Patients were determined to have a postoperative random GH level < 1 ng/ml or a baseline GH level < 0.4 ng/ml after OGTT suppression in combination with a normal insulin-like growth factor (IGF)-1 level.

Ophthalmological examination included assessments of visual acuity, visual field function (Goldmann perimetry, and ocular motility (Hess chart).

### Statistical Analysis

All statistical analyses were performed using IBM SPSS for Windows version 18.0 (SPSS, Chicago, IL, USA). A Shapiro-Wilk's or Kolmogorov-Smirnov tests were used to assess the assumption of normality. Continuous variables were presented depending on normal distribution with either mean±standard deviation or (in the case of non-normal distribution) median (interquartile range). Comparisons of continuous variables between groups were performed using an independent sample t-test. Associations between categorical variables were determined using the chi-square test. A p-value<0.05 was considered statistically significant.

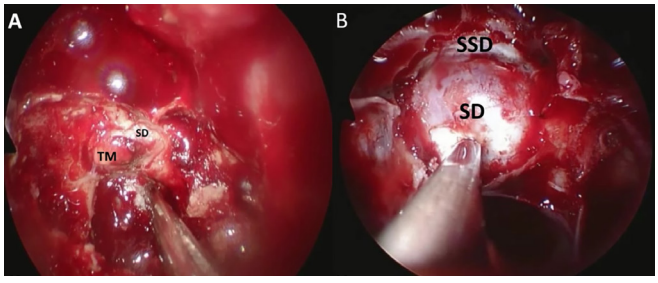


**Figure 2:** Sellar opening differences in different approaches. A) Intraoperative view of the standard endoscopic transsphenoidal approach. TM, tumor; SD, sellar dura. B) The sellar base opening is extended superiorly in the extended endoscopic transsphenoidal approach. SD; sellar dura; SSD, suprasellar dura.

## RESULTS

### Patients' characteristics

The data of 19 pediatric patients with GH-secreting pituitary adenoma who were pathologically identified at our institution were retrospectively analyzed. 8 (42.1%) participants were male and 11 (57.9%) were female. The mean age was 15.8±2.1 years (Table 1). 6 (31.6%) patients had GH+prolactin (PRL) cosecretion according to their endocrinological profiles. 1 (5.3%) of 19 patients had a history of surgery in another center.

### Clinical Presentation

Of all patients, 14 (73.7%) had hand-foot enlargement, 5 (26.3%) had headache, and 5 (26.3%) had visual field deficit (Table 2). 1 of all patients had a history of surgery in another center and were asymptomatic. During follow-up, surgical treatment was performed for the recurrent tumor.

All 6 patients with GH+PRL-secreting mixed adenoma had hand-foot growth, 3 (15.8%) had visual field deficit, 1 (5.3%) had menstrual irregularity.

### Radiology

1 (5.3%) patient had conchal type, 2 (10.5%) patients had presellar type, 11 (57.9%) patients had sellar type, and 5 (26.3%) had postsellar type sphenoid sinus pneumatization.

1 (5.3%) patient had microadenoma, and 18 (94.7%) had macroadenoma. There were 6 (31.6%) patients presented with unilateral cavernous sinus invasion, and 3 (15.8%) with bilateral cavernous sinus invasion (Figure 3).

### Surgery and Biochemical Evaluation

The standard endoscopic transsphenoidal approach was performed in 15 patients. The extended endoscopic transsphenoidal approach was performed in 4 patients in whom the tumor extended to the suprasellar area.

Total gross resection was performed in 10 (52.6%) patients, and subtotal resection was performed in 9 (47.4%) patients. 9 (47.4%) patients met the criteria for remission. 2 of the 9 patients were in the GH+PRL cosecretion group. 5 of 10 patients that among we could not achieve remission, GH and IGF-1 levels were reduced to normal limits with postoperative medical treatment.

**Table 1.** Demographic Findings of Patients

| | n | % |
|---|---|---|
| **Patients** | 19 | 100 |
| **Age at surgery, and years** | 15.8 ± 2.1 (11-18) | |
| **Sex** | | |
| **Female** | 11 | 57.9 |
| **Male** | 8 | 42.1 |

Statistically significant results for adenoma size on GTR were obtained (p value: 0.021). Sphenoid sinus pneumatization was not associated with resection rate (p-value 0.264). The absence of cavernous sinus invasion was significant as a positive predictive value for GTR, but it was not significant for remission (p-value: 0.027-0.102, respectively) (Table 3). Any complications, such as epistaxis and rhinorrhea, were not encountered in this series.

## DISCUSSION

In this study, we focused on the clinical outcomes of surgeries and the factors affecting the extent of tumor removal using the endoscopic transsphenoidal approach. Pediatric pituitary adenomas are rare but challenging lesions, especially somatotrophic adenomas. It is found in approximately 90% of patients at the time of diagnosis (9,13). It is also seen to be invasive in 30%-60% of cases (2,14). Likewise, in our study, the percentage of macroadenomas was 94.7%. The cavernous sinus invasion rate was 47.4%, similar to the literature. It is established that childhood pituitary adenomas are more aggressive than adult pituitary adenomas (9,13-15).

The most important goal in surgery for somatotroph adenomas is to achieve GTR and remission so that the patient does not need medication during the postoperative period. However, the fact that the majority of somatotroph

**Table 2.** Characteristic Features of Patients

| | | GH n:13 | GH+PRL n:6 | Total n:19 |
|---|---|---|---|---|
| **Preoperative symptoms** | Hand-foot enlargement | 8 (61.5%) | 6 (100%) | 14 (73,7%) |
| | Headache | 5 (38.4%) | | 5 (26,3%) |
| | Visual field deficit | 2 (15.4%) | 3 (50%) | 5 (26.3%) |
| | Menstrual irregularity | | 1 (16.7%) | 1 (5.3%) |
| **Tumor size** | Microadenoma | 1 (7.7%) | None | 1 (5.3%) |
| | Macroadenoma | 12 (92.3%) | 6 | 18 (94.7%) |
| | Giant | None | None | |
| **Sella type** | Conchal | 1 (7.7%) | None | 1 (5.3%) |
| | Presellar | 2 (15.4%) | None | 2 (10.5%) |
| | Sellar | 6 (46.1%) | 5 (83.3%) | 11 (57.9%) |
| | Postsellar | 4 (30.7%) | 1 (16.7%) | 5 (26.3%) |
| **CS invasion** | | 5 (38.4%) | 4 (66.7%) | 9 (47.4%) |

GH: Growth hormone, PRL: Prolactin, CS: Cavernous sinus

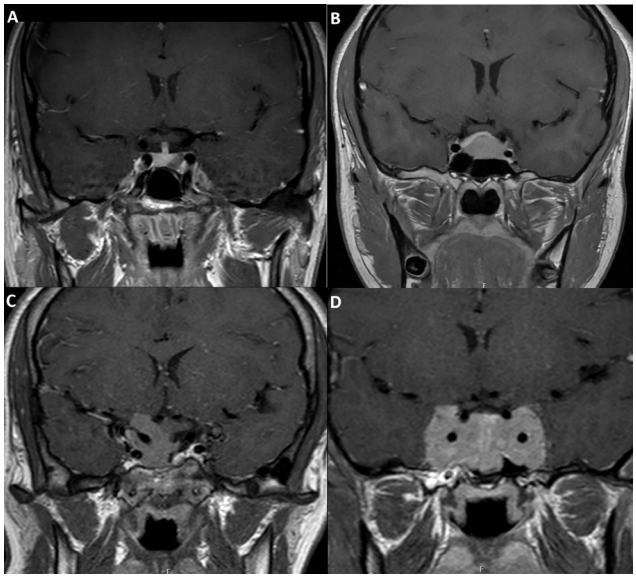


**Figure 3:** Radiology of adenomas. A) Microadenoma. B) Macroadenoma. C) Unilateral cavernous sinus invasion (Right) D) Bilateral cavernous sinus invasion.

**Table 3.** Gross total resection rates

| | n | % | p-value |
|---|---|---|---|
| **Number of patients** | 19 | 100 | |
| **CS invasion** | | | **0.027*** |
| **Yes** | 9 | 47.4 | |
| **No** | 10 | 52.6 | |
| **Sphenoid pneumatization rate of** | | | 0.264 |
| **Conchal** | 1 | 5.3 | |
| **Presellar** | 2 | 10.5 | |
| **Sellar** | 11 | 57.9 | |
| **Postsellar** | 5 | 26.3 | |
| **Adenoma size** | | | **0.021*** |
| **Microadenoma** | 1 | 5.3 | |
| **Macroadenoma** | 18 | 94.7 | |

*Statistically significant, CS: Cavernous sinus

adenomas in childhood are macroadenomas at the time of diagnosis and the frequent invasion of the cs decreases the GTR rate in surgical outcomes. Although we are an experienced and tertiary center in endoscopic surgery, we have shown that both are effective in this regard in the results of our study. We were able to obtain GTR results in approximately 50% of the patients.

Sphenoid sinus pneumatization did not affect GTR. There are two possible reasons for the results of our study. First, the youngest patient in our study was aged 11 years, indicating that the sphenoid sinus had already developed. Thus, a narrower and smaller sphenoid sinus was less common in our study. If younger patients could be included in the studies, more accurate results could be obtained. The second reason is that the total number of participants in this study is also small, and larger series are needed to overcome this.

In addition to GH hypersecretion, high PRL level was observed in these patients. This may be histopathologically relevant. Or loss of dopaminergic tone due to pressure on the pituitary stalk.

The only thought-provoking point in the study was that cavernous sinus invasion was not statistically significant on remission. However, the point that should be noted here is that pituitary adenomas are subtypes in the 2022 World Health Organization classification (16). Differences in subtypes affect remission. Since this subtyping was not considered in our study, the results were considered to be obtained like this.

Considering that surgical outcomes are even lower for recurrence of pituitary adenomas, surgery for pituitary adenomas, especially childhood somatotroph adenomas, should be performed by experienced surgeons at centers of excellence. Thus, better results can be achieved.

The limitation of our study is the small number of patients. Studies with higher patient numbers are needed. At the same time, studies that examine histopathological subtypes in detail are needed.

## CONCLUSION

Somatotroph adenomas in pediatric patients are rare and challenging lesions. The majority of these tumors are macroadenomas and invasive at the time of diagnosis. Adenoma size and cavernous sinus invasion are effective for resection. Sphenoid sinus pneumatization does not affect the resection rate in experienced centers. Further studies with a large number of patients are required.

### ETHICS

**Ethics Committee Approval:** Approval was obtained from Kocaeli University Non-Interventional Clinical Research Ethics Committee (decision no: KÜ GOKAEK-2024/12.20, date: 26.07.2024).

**Informed Consent:** Written informed consent was obtained from the families and all patients.

### FOOTNOTES

#### Authorship Contributions

Surgical and Medical Practices: M.Ç., S.C., Concept: M.Ç., S.C., Design: M.Ç., S.C., Data Collection or Processing: M.Ç., Analysis or Interpretation: M.Ç., Literature Search: M.Ç., Writing: M.Ç.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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

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Research

# Predictive Value of Plasma Zonulin Levels during Early Gestational Weeks in Gestational Diabetes Mellitus

## Erken Gestasyonel Haftalarda Değerlendirilen Plazma Zonulin Düzeylerinin Gestasyonel Diabetes Mellitus İçin Prediktif Değeri

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## ABSTRACT

**Objective:** This study aimed to determine the impact and predictive utility of serum zonulin levels measured between 11-14 weeks of gestation and 75-g oral glucose tolerance test (OGTT) testing between 24-28 weeks of gestation in predicting patients diagnosed with gestational diabetes mellitus (GDM).

**Methods:** The study included 209 pregnant women at 11-14 weeks of gestation. Among the pregnant women who presented to the Obstetrics and Gynecology Outpatient Department of İstanbul Medipol Mega Hospital, those who could not be reached due to the covid pandemic (69), aborted (4), diagnosed with chromosomal abnormalities in the fetus (3), and those who withdrew from the study (4) were excluded from the study. The study group included 48 pregnant women diagnosed with GDM at 24-28 weeks of gestation. On the other hand, the control group was formed by randomly selecting 40 pregnant women from 81 pregnant women who were not diagnosed with GDM due to the lack of a kit using a computer-based program. GDM was diagnosed using an OGTT performed between 24 and 28 weeks of gestation according to the International Association of Diabetes and Pregnancy Study Groups criteria. Plasma zonulin levels were measured using enzyme-linked immunosorbent assay.

**Results:** When zonulin (ng/mL) and body mass index (BMI) (kg/m$^2$) values were compared between the study and control groups, a significant correlation was found between zonulin (35.77±8.79 (ng/mL), 29.76±6.96 (ng/mL), p=0.01) and BMI (kg/m$^2$) (26.02±2.39, 24.78±2.7 (kg/m$^2$), p=0.032). In addition, a correlation analysis showed a significant positive correlation between plasma zonulin level and first-hour OGTT.

**Conclusion:** The findings of our research indicate that zonulin has the potential to function as a non-invasive biomarker of GDM development. More extensive research is required on this topic.

**Keywords:** Body mass index, gestational diabetes mellitus, zonulin

## ÖZ

**Amaç:** Bu çalışmada, 11-14. gebelik haftaları arasında ölçülen serum zonulin düzeylerinin ve 24-28. gebelik haftaları arasında yapılan 75 g oral glukoz tolerans testi (OGTT)'nin gestatsyonel diyabetes mellitus (GDM) teşhisi konulan hastaları öngörmedeki etkisini belirlemeyi amaçladık.

**Gereç ve Yöntem:** Çalışmaya 11-14 gebelik haftasındaki 209 gebe kadın dahil edilmiştir. İstanbul Medipol Mega Hastanesi Kadın Hastalıkları ve Doğum Polikliniğine başvuran bu gebelerden covid pandemisi nedeniyle ulaşılamayanlar (69), abortus yapanlar (4), fetüste kromozomal anormallik saptananlar (3) ve çalışmadan çekilenler (4) çalışma dışı bırakılmıştır. Çalışma grubuna 24-28. gebelik haftalarında GDM tanısı alan 48 gebe kadın dahil edildi. Buna karşılık, kontrol grubu ise GDM teşhisi konmamış 81 gebe içerisinden kit yetersizliğinden dolayı 40 gebe kadın bilgisayar tabanlı program kullanılarak rastgele seçilerek oluşturulmuştur. GDM tanısı, Uluslararası Diyabet ve Gebelik Çalışma Grupları Birliği kriterlerine göre 24-28. gebelik haftaları arasında yapılan bir OGTT ile konulmuştur. Plazma zonulin düzeyleri enzime bağlı immünosorbent testi ile ölçülmüştür.

**Bulgular:** Çalışma ve kontrol grupları arasında zonulin (ng/mL) ve vücut kitle indeksi (VKİ) (kg/m$^2$) değerleri karşılaştırıldığında, zonulin (35.77±8.79 (ng/mL), 29.76±6.96 (ng/mL), p=0.01) ve VKİ (kg/m$^2$) (26.02±2.39, 24.78±2.7 (kg/m$^2$), p=0.032) arasında anlamlı bir korelasyon bulunmuştur. Ayrıca, korelasyon analizi plazma zonulin düzeyi ile birinci saat OGTT arasında anlamlı bir pozitif korelasyon olduğunu göstermiştir.

**Sonuçlar:** Araştırmamızın bulguları, zonulinin GDM gelişimi için non-invaziv bir biyobelirteç olarak işlev görme potansiyeline sahip olduğunu göstermektedir. Bu konuda daha geniş ölçekli çalışmalara ihtiyaç vardır.

**Anahtar Kelimeler:** Gestasyonel diabetes mellitus, vücut kitle indeksi, zonulin

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## INTRODUCTION

Gestational diabetes mellitus (GDM) is a medical condition characterized by impaired tolerance to carbohydrates, which is observed specifically during pregnancy (1-4). Not only the infant but also the mother exhibits heightened vulnerability to complications during and after pregnancy. A global consensus on the diagnosis, screening, and treatment of GDM is yet to be reached. Added to this, there also remains a lack of consensus regarding the optimal timing for conducting screening, the appropriate thresholds to employ in screening, the population to target for screening (i.e., all pregnant women or solely those at high risk of GDM), and the preferred approach to the screening test (i.e., one-stage or two-stage) (5-9).

Zonulin serves as a significant noninvasive biomarker that indicates heightened intestinal permeability, and increased levels of zonulin indicate heightened impairment in the functioning of the intestinal barrier (10). Numerous studies have shown a correlation between increasing intestinal barrier dysfunction and elevated inflammatory markers [tumor necrosis factor, interleukin-6 (IL-6), etc.] and insulin resistance in women who are not pregnant (11, 12). Serum zonulin has been shown to correlate with dietary composition, suggesting a novel pathway through which diet could influence the development of metabolic disorders associated with inflammation (13). However, very few studies have investigated the relationship between GDM and zonulin (13, 14). To the best of our knowledge, this is one of the first studies to correlate circulating zonulin concentration (a marker and modulator of intestinal permeability) in patients in terms of risk groups and screening time for GDM.

In this study, we aimed to determine the impact and predictive utility of serum zonulin levels measured between 11-14 weeks of gestation and 75-g OGTT testing between 24-28 weeks of gestation in predicting patients diagnosed with GDM.

## METHODS

### Establishment of study groups

This study was conducted with the approval of the Ethics Committee for Noninterventional Research of Wma Declaration Of Helsinki-Ethical Principles Formedical Research Involving Human Subjects (date: 20.08.2020, decision number: 626). Following the distribution of the informed consent form to all participants, the purpose of the study was shared with them to secure their voluntary participation in the research. The cases in our study consisted of pregnant women who presented to our outpatient clinic at the Department of Obstetrics and Gynecology, İstanbul Medipol Mega Hospital Hospital between 20/08/2020 and 15/01/2022.

The study included 209 pregnant women at 11-14 weeks of gestation. Among these pregnant women, those who could not be reached due to the covid pandemic (69), aborted (4), diagnosed with chromosomal abnormalities in the fetus (3), and those who withdrew from the study (4) were excluded from the study. During the gestational period spanning from the 24$^{th}$ week to the 28$^{th}$ week, a total of 129 women were subjected to a 75-g oral glucose tolerance test (OGTT). The study group consisted of 48 pregnant women diagnosed with GDM based on the diagnostic criteria established by the International Association of Diabetes and Pregnancy Study Groups. Due to the lack of available kits, only 40 out of the total 81 pregnant women who had not received a GDM diagnosis were randomly allocated to the control group.

### The Blood Sample Collection Method

Women presenting to the obstetrics and gynecology outpatient clinic at İstanbul Medipol University Hospital were asked to observe a minimum fasting period of 8 hours. Following the acquisition of informed consent, a 5-cc blood sample was collected from pregnant women during the 11$^{th}$ to 13$^{th}$ weeks of gestation to measure zonulin levels. The blood was drawn into biochemical tubes and subsequently centrifuged at 3000 rpm. The plasma samples were collected and then stored at a temperature of -80 ⁰C until the day of analysis.

### Serum Zonulin Level Determination

Serum zonulin levels were determined by the ELISA (Enzyme-Linked Immunabsorbent Assay) method (Elabscience, catalog number: E- EL -H5560, Wuhan, Hubei Province, China). The coefficients of variation for both intra-assay and inter-assays were 10%.

### Statistical Analysis

The mean and standard deviation were used to express continuous quantitative variables, whereas qualitative variables were expressed using n and median. Normality tests for the variables were conducted using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Mann-Whitney rank sum test was used to analyze continuous variables comprising independent variables that did not exhibit a normal distribution. Receiver operating characteristic curve analysis was applied to determine values such as cut-off point, sensitivity, and specificity of continuous variables. Spearman's rho correlation test was used to determine the

degree of relationships between variables. We attributed significance to probability values less than 0.05. All data analyses were performed using the IBM SPSS Statistics 21 package.

## RESULTS

The mean standard deviation (unit) of the parameters studied among the pregnant women who participated in the study were age (28.875±3,45 years), BMI (25.45±2.59 (kg/m$^2$), fasting plasma glucose (FPG) (90.3±9.3 (mg/dL), OGTT 1$^{st}$ hour (163.16±32.877 (mg/dL), OGTT 2nd hour (123.53±24 (mg/dL), and zonulin (33.04±8.5 (ng/mL). 60.2% of the participating pregnant women were first-time pregnancies. Table 1 and Figure 1 present the standard deviation values for zonulin (ng/mL), age (years), BMI (kg/m$^2$), FPG (mg/dL),

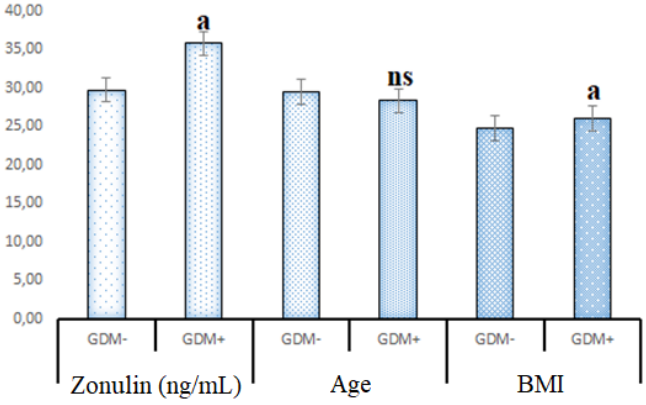


**Figure 1.** Zonulin, Age, and BMI of the study group (S) and control group (C)
BMI: Body mass index, GDM: Gestational diabetes mellitus

first-hour OGTT (mg/dL), and second-hour OGTT (mg/dL) in both the study and control groups. Serum zonulin levels were elevated in patients with GDM compared with the control group, which was determined to be of statistical significance (p<0.01). Although no significant correlation was found between age and GDM (p=0.645), there was a significant correlation was found between BMI (kg/m$^2$) and GDM (p=0.032). No statistically significant correlation was observed between gravidity and parity (p=0.148). However, a statistically significant difference was observed between the study and control groups about FPG scores (p<0.001).

In the correlation analysis, a significant positive correlation was found between serum zonulin and the first-hour OGTT (mg/dL) (p=0.009, r=0.278), whereas no significant correlation was found between serum zonulin and other parameters (Table 2).

The Youden index, the optimal cutoff value for serum zonulin, was ≥36.783 (ng/mL) in predicting GDM between the 24$^{th}$ and 28$^{th}$ months of pregnancy, with a sensitivity of 54.17% and a specificity of 87.5%. The area under the receiver operating characteristic (ROC) curve was 0.706 (95% CI: 0.6-0.799) (Figure 2).

## DISCUSSION

Zonulin is a novel circulatory marker of intestinal permeability (11, 15). Mokkala et al. (15) showed for the first time an association between increased serum zonulin levels in early pregnancy and GDM, suggesting that zonulin may serve as a predictive marker for GDM. In their study of women who were 12.8±2.5 weeks pregnant, they observed

**Table 1.** Demographic and laboratory characteristics of the control and gestational diabetes mellitus (GDM) groups

| Groups | Control (GDM-) | | | Group Work (GDM+) | | | p-value |
|---|---|---|---|---|---|---|---|
| | N | Mean | SD | N | Mean | SD | |
| Zonulin (ng/mL) | 40 | 29.76 | 6.96 | 48 | 35.77 | 8.79 | <0.01 |
| BMI (kg/m$^2$) | 40 | 24.78 | 2.03 | 48 | 26.02 | 2.392 | =0.032 |
| Age | 40 | 29.475 | 4.26 | 48 | 28.375 | 2.284 | =0.645 |
| FPG (mg/dL) | 40 | 83.92 | 5.25 | 48 | 95.72 | 8.6 | <0.001 |
| OGTT (1.Hour) (mg/dL) | 40 | 137.2 | 24.04 | 48 | 184.77 | 21.7 | <0.001 |
| OGTT (2.Hour) (mg/dL) | 40 | 110.15 | 18.34 | 48 | 134.68 | 23.05 | =0.550 |

BMI: Body mass index, FPG: Fasting plasma glucose, OGTT: Oral glucose tolerance test, SD: Standard deviation

**Table 2.** Correlation Analyses of the Study Groups

| | | | Y | BMI (kg/m$^2$) | FPG (mg/dl) | OGTT 1.H. (mg/dL) | OGTT 2.H. (mg/dL) |
|---|---|---|---|---|---|---|---|
| Spearman's rho | Zonulin (ng/mL) | r | .048 | .119 | .150 | .279** | .065 |
| | | p | .659 | .269 | .163 | .009 | .550 |

Significant difference compared with zonulin
**: p<0.001, BMI: Body mass index, FPG: Fasting plasma glucose, OGTT: Oral glucose tolerance test

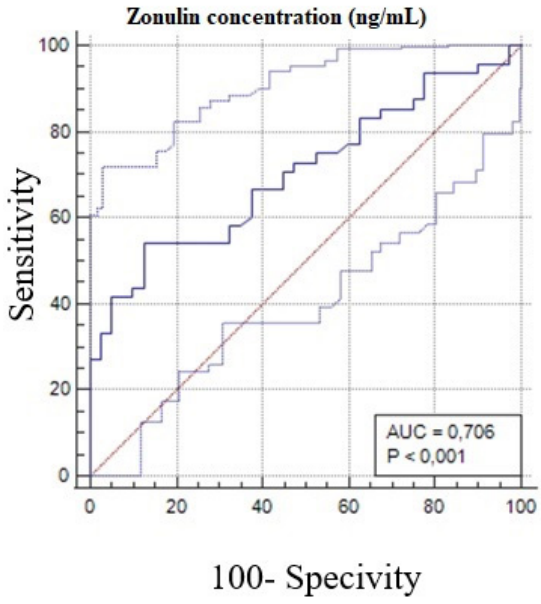


**Figure 2.** ROC curve for serum zonulin level for predicting GDM
ROC: Receiver operating characteristic, GDM: Gestational diabetes mellitus, AUC: Area under the curve

that those who developed GDM later in mid-pregnancy had higher serum zonulin levels in the early stages of pregnancy. Furthermore, a study using ROC curve analysis and the Youden index found that the optimal cutoff point for serum zonulin concentration to predict GDM in mid-pregnancy is ≥43.5 ng/mL, with a sensitivity of 88% (95% confidence interval (CI): 71-100%) and a specificity of 47% (95% CI: 33-58%) (15). The fact that the number of patients with GDM was only sixteen and the specificity score was low is a limitation of this study. Demir et al. (14) also reported elevated plasma zonulin levels in patients with GDM. The study population consisted of women between 24 and 28 weeks of pregnancy. They reported that in patients with plasma zonulin levels of 20 ng/mL, the sensitivity was 98.8%, specificity was 100%, positive predictive value (PPV) was 98.8%, and negative predictive value was 100%. They also found a significant correlation between plasma zonulin and the first hour of the OGTT ($p<0.001$, $r=0.568$) (14). Consistent with prior research (14, 15), our study found elevated plasma zonulin levels in pregnant women diagnosed with GDM. Furthermore, a remarkable positive correlation was found between plasma zonulin levels and the first hour of the OGTT ($p=0.009$, $r=0.279$). The differences observed in sensitivity and specificity may be accounted for by the timing of the test during pregnancy as well as the criteria for excluding participants from the study. The prevalence of pregnancy-related complications, including GDM, is progressively rising, as evidenced by previous studies. According to the results of our study, the sensitivity was 54.17% (95%) and the specificity was 87.5% (95%). Furthermore, the optimal threshold for serum zonulin concentration to predict the development of GDM between the 24$^{th}$ and 28$^{th}$ weeks of pregnancy was >36.783 (ng/mL).

Diet and lifestyle are significant risk factors for obesity and GDM. The observation that there has been a notable rise in the incidence of obesity among women in the age group capable of bearing children, reaching approximately 30%, and that a significant proportion of pregnant women face a heightened susceptibility to GDM should not be disregarded. Studies have suggested that the adoption of certain measures, including adhering to a nutritious diet before and during pregnancy, maintaining a BMI below 25 kg/m$^2$, engaging in physical activity exceeding 30 minutes per day, and refraining from smoking, can potentially reduce the incidence of GDM by approximately 45% (16), which offers the possibility of avoiding short- and long-term complications associated with GDM. Furthermore, the result of the measurement can serve expectant mothers as a valuable reference for adjusting their lifestyle.

Recent studies have indicated a correlation between dietary and serum zonulin concentrations (13). People who eat diets deficient in naturally occurring antioxidants, fiber, and omega-3 fatty acids from fruits, vegetables, and whole grains, while being abundant in refined starches, sugars, saturated fats, and trans fats, tend to have significantly elevated levels of pro-inflammatory cytokines and lower levels of anti-inflammatory cytokines (17). According to previous reports, the presence of chronic inflammation resulting from dietary habits in this particular situation can potentially contribute to adverse outcomes, including metabolic syndrome, obesity, cardiovascular disease (CVD), type 2 diabetes mellitus (DM), and cancer (18, 19). Previous studies have demonstrated a positive correlation between zonulin levels and the likelihood of experiencing inflammation, insulin resistance, elevated fasting blood glucose levels, and metabolic syndrome (11, 15, 20). A study by Mokkala et al. (15) revealed a correlation between metabolic endotoxemia, inflammation, glucose and lipid metabolism, and serum zonulin concentrations in obese pregnant women. The activation of metabolic processes by zonulin has deleterious effects on maternal and fetal health. By supporting the integrity of the intestinal barrier and modifying the composition of the diet, it is possible to prevent negative outcomes resulting from metabolic reactions (21). This objective can be achieved by adhering to a Mediterranean diet characterized by high fiber content (22), low glycemic load and index (23), and anti-inflammatory (24) and antioxidant properties (25). One

study found an association between plasma levels of zonulin and the consumption of various vitamins, minerals, omega-3 fatty acids, and dietary fiber, which affect the composition and diversity of the gut microbiota in obese pregnant women (13).

## CONCLUSION

GDM is a risk factor with acute and long-term fetal and maternal effects in the intrapartum and postpartum periods. The maternal effects can manifest as type 2 DM, hypercholesterolemia, and elevated susceptibility to CVD, whereas the fetal effects can manifest as abnormalities, DM, and increased accumulation of adipose tissue. To mitigate the acute and long-term impacts of GDM on both the mother and fetus, it is crucial to prioritize early identification and intervention, which requires a multidisciplinary approach encompassing the diagnosis, treatment, and subsequent monitoring of GDM. In the present study, the optimal threshold for serum zonulin concentration at 11-14. weeks of pregnancy was >36.783 (ng/mL) for predicting GDM. We suggest that serum zonulin levels should be used as a screening tool in the prenatal period or early pregnancy for biochemical determination of the association between serum zonulin levels and GDM. In addition to assessing zonulin levels, the incorporation of various biochemical parameters, such as insulin, C-reactive protein, high-density lipoprotein, low-density lipoprotein, cholesterol, interleukin-1, and IL-6, can also prove beneficial in the diagnostic process. In addition, it is recommended that larger cohorts of patients be included in future studies. However, in the postpartum period, patients with GDM should undergo a 75-g OGTT test within the first 6 months. Close follow-up and thorough observation are crucial to avoid short- and long-term complications associated with GDM. We also recommend that patients be carefully monitored simultaneously by a registered dietitian and an internal medicine specialist.

### ETHICS

**Ethics Committee Approval:** This study was conducted with the approval of the Ethics Committee for Noninterventional Research of Wma Declaration Of Helsinki-Ethical Principles Formedical Research Involving Human Subjects (date: 20.08.2020, decision number: 626).

**Informed Consent:** Following the distribution of the informed consent form to all participants, the purpose of the study was shared with them to secure their voluntary participation in the research.

### FOOTNOTES

#### Authorship Contributions

Surgical and Medical Practices: C.C., İ.A.Ö., Concept: C.C., L.H.A.T., V.Ü., İ.A.Ö., Design: C.C., L.H.A.T., V.Ü., İ.A.Ö., Data Collection or Processing: C.C., Analysis or Interpretation: C.C., M.C., Literature Search: C.C., M.C., Writing: C.C., M.C., İ.A.Ö.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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Research

# Functional and Radiological Comparison and Evaluation of Gustilo-Anderson Type 3 Open Tibia Fractures Treated with an Ilizarov External Fixator

## İlizarov Eksternal Fiksatörle Tedavi Edilen Gustilo-Anderson Tip 3 Açık Tibia Kırıklarının Fonksiyonel ve Radyolojik Değerlendirilmesi

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## ABSTRACT

**Objective:** This study aimed to evaluate and compare the functional and radiological results of Gustilo-Anderson (G-A) type 3 open tibial shaft fractures G-A treated with an Ilizarov external fixator (I-EF).

**Methods:** Sixty-one patients (7 female, 54 male) who matched these criteria were included in the study. Patients who were treated with the I-EF for a G-A type 3 tibial shaft fracture between January 2013 and December 2018 were included in this retrospective study. The patients were divided into three groups: subtype 3A (I), subtype 3B (II), and subtype (III). The radiological, functional, and demographic features were also evaluated.

**Results:** There were no statistically significant differences between G-A classification and age, gender, body mass index, full weight-bearing time, and rotational alignment ($p>0.05$). The G-A Subtype 3A Lower Extremity Functional Scale (LEFS) score was significantly higher than those of Subtypes 3B and 3C ($p<0.05$ respectively). The time to union was shorter in G-A Subtype 3A cases than in subtype 3C cases ($p<0.05$). Coronal and sagittal alignment angulations were significantly lower in G-A subtype 3A than in subtypes 3B and 3C ($p=0.022$, and $p<0.01$ respectively). The Johner-Wruhs Score was lower than that of subtype 3C in patients with G-A Subtype 3A patients ($p<0.05$).

**Conclusion:** Radiological and functional outcomes worsen as injury severity increases from subtype A to C in G-A type 3 open tibial shaft fractures.

**Keywords:** Ilizarov-external fixation, open tibia shaft fracture, Gustilo-Anderson type 3 fracture, lefs score

## ÖZ

**Amaç:** Bu çalışmada; ilizarov eksternal fiksatörü (I-EF) ile tedavi edilen Gustillo-Anderson (G-A) tip 3 açık tibia cisim kırıklarının fonksiyonel ve radyolojik değerlendirilmesi amaçlandı.

**Gereç ve Yöntem:** Ocak 2013 ile Aralık 2018 tarihleri arasında G-A tip 3 açık tibia şaft kırığı nedeniyle I-EF uygulanan hastalardan 61 hasta (7 kadın, 54 erkek) çalışmaya dahil edildi. Hastaların ortalama yaşı 38,20±9,63 (17-59 yıl) yıl, ortalama takip süresi 48,62±14,88 (26-96 ay) ay idi.

**Bulgular:** G-A sınıflandırması ile yaş, cinsiyet, vücut kitle indexi, tam yük verme süresi ve rotasyonel dizilim arasında istatistiksel olarak anlamlı fark yoktu ($p>0,05$). G-A Tip 3A alt ekstremite fonksiyonel skala (LEFS) skoru Tip 3B ve 3C'den anlamlı derecede yüksekti (sırasıyla $p<0,05$). G-A Tip 3A olgularında kaynama süresi Tip 3C olgularına göre daha kısaydı ( $p<0,05$). G-A Tip 3A'daki koronal ve sagittal dizilim açıları Tip 3B ve C'ye göre anlamlı derecede düşüktü (sırasıyla $p=0,022$ ve $p<0,01$). G-A Tip 3A hastalarında Johner-Wruhs Skoru Tip 3C'den düşük bulundu ($p<0,05$).

**Sonuç:** Bu çalışmada G-A tip 3 açık tibial cisim kırıklarında A'dan C'ye kadar olan yaralanma derecesi arttıkça radyolojik ve fonksiyonel sonuçların bozulduğu belirtilmektedir.

**Anahtar Kelimeler:** İlizarov eksternal fiksasyon, tibia şaft kırığı, Gustillo-Anderson tip 3 kırık, LEFS skoru

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## INTRODUCTION

Owing to its location and poor soft tissue coverage, open fractures of the tibia are more common than in other bones (1). Gustilo and Anderson. (2) (1976) proposed a system of classification for open fractures that relied on the size of the related laceration, the level of soft tissue damage, and the degree of contamination and vascular damage. Open tibial shaft fractures require immediate orthopedic treatment. The standard of care for open tibial shaft fractures includes early prophylactic antibiotic therapy, surgical wound debridement, and fracture stabilization. Moreover, they play a critical role in reducing long-term morbidity (3). After infection control, the treatment goals are to reduce the deformity, correct the deformity, and equalize the limb length (4). Intramedullary nailing (IMN), plate fixation, and external fixation(EF) (AO-EF and Ilizarov-EF) are some of the current treatment options. However, these techniques are associated with various complication rates (5, 6). Although different fixation methods with satisfactory results have been used for a long time, the IMN and EF methods have begun to be preferred because they reduce secondary damage to soft tissues and bone vascularity (7). The I-EF technique is a special type of external fixator. It is used for indirect or closed reduction with fine wires and small incisions that cause minimal soft tissue damage. The wires are stretched and circumferentially supported. This resulted in better mechanical performance than monolateral external fixator, which allowed for both early ROM and weight-bearing initiation (8, 9). Our study aimed to evaluate and compare the radiological and functional results according to the severity of soft tissue damage in patients with a history of Gustilo-Anderson (G-A) type 3 open tibial shaft fractures treated with the Ilizarov technique. We will base this on the extent of soft tissue damage. We hypothesized that the functional and radiological results would worsen as the degree of injury increased in patients who underwent the Ilizarov technique. Although the worst results of type 3 open injuries have been accepted in studies comparing open fracture results in the literature, the number of studies evaluating subtypes of type 3 injuries is limited. The current study aimed to evaluate the functional and radiological results of type 3 open tibial fractures.

## METHODS

Patients who underwent I-EF due to G-A type 3 tibial shaft fracture between January 2013 and December 2018 were retrospectively approved by Bakırkoy Dr. Sadi Konuk Egitim Ve Research Hospital Clinical Research Ethics Board (approval no: 2015/01/10, date: 04.01.2016). Among the patients treated with I-EF, those with a minimum follow-up period of 24 months and regular controls (1st day, 2nd, 6th, and 12th weeks, 6th month, 9th month, and 1st year) were included in the study. Closed fractures, conservative treatment, fixation with different implants, revision surgery with different implants, ipsilateral femur fractures, bilateral tibia fractures, patients with other injuries that made it impossible for them to move, intra-articular fractures, and not enough follow-up were excluded. In this period, 324 patients presented to the emergency orthopedic service with open tibial fractures. Of these, 228 were found to have type 1 and type 2 open fractures and were excluded from the study. AO-EF was applied to 25 of 96 patients presenting with type 3 open fractures and left for secondary surgery. Four of the 10 patients were amputated under emergency conditions, and six were amputated due to necrosis development during follow-up despite vascular injury repair (Figure 1). The study included sixty-one patients who met these criteria (7 females and 54 males). Patients with G-A type 3 open tibial injury were divided into three groups [G-A subtype 3A (I), subtype 3B (II), and subtype 3C (II)] (2). The radiological, functional, and demographic features were evaluated and compared.

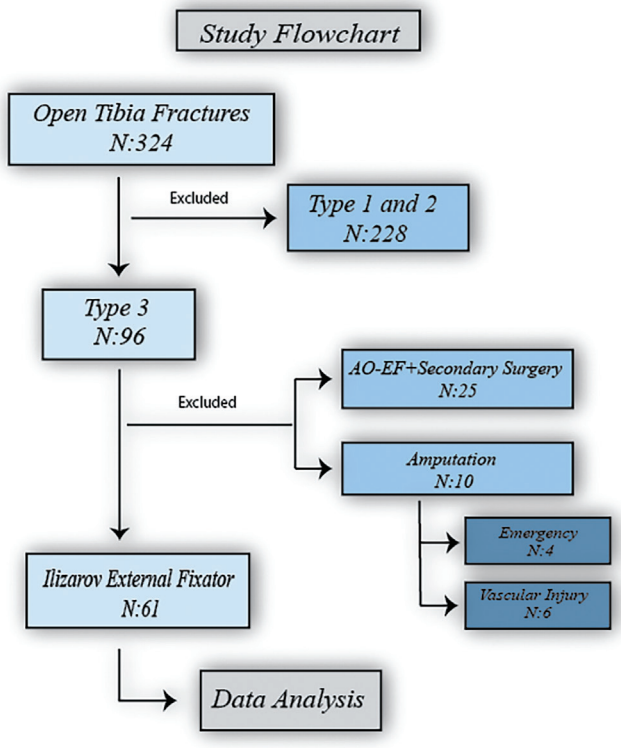


**Figure 1.** Study Flowchart (Include-Exclude Criteria)

AO-EF: Arbeitsgemeinschaft für Osteosynthesefragen-External fixator

### Surgical Procedure

The surgical procedure was performed in the supine position without the use of a tourniquet on a radiolucent table under general or spinal anesthesia. The fixation was performed using the technique described by Ilizarov (10). In addition, hybrid fixation was added to the classic Ilizarov technique. Hybrid methods using k-wire and Schanz screws were preferred for the Ilizarov frames. The wounds were covered with a wet dressing, and the patients were taken to the hospital. Tetanus prophylaxis was applied in the emergency department, as indicated in the literature (11). Preoperatively, 1 g of cefazolin was administered. Dual antibiotic therapy was administered during the postoperative period. Cefazolin 100 mg/kg/day (dose divided into three doses IV every 8 hours) and gentamicin 5-7.5 mg/kg/day (dose divided into three doses IV every 8 hours) were administered. In patients with penicillin allergy, clindamycin was administered on 15-40 mg/kg/day (dose divided into three and IV every 8 hours).

### Functional Evaluation

Hip, knee, and ankle range of motion (ROM) exercises and weight-bearing exercises are immediately recommended in the early postoperative period, as patients tolerate them. Patients were followed-up in the outpatient clinic with knee and ankle joint ranges of motion under control. The ROM of the joints was measured using a goniometer. Follow-up after the first year was performed at 3-month intervals, and after 2 years, annually. The LEFS score was used for clinical evaluation. LEFS has been shown to have good reliability and predictive correlation in assessing the lower extremity. In addition, it is a reliable and valid tool for monitoring healing in patients with tibial shaft fractures (12, 13). The patients' LEFS scores and coronal and sagittal alignment information were obtained from the medical records of the last postoperative controls. The rotational alignment information was collected and evaluated from the physical examination information in the patient files.

### Radiological Evaluation

Postoperative radiographs were obtained on the 1st day, 2nd, 6th, and 12th weeks, 6th month, 9th month, and 1st year. Two orthopedic specialists who were not involved in the study performed radiological evaluation. Coronal and sagittal alignments and Johner-Wruhs scores were evaluated from the last postoperative anteroposterior (AP) and lateral radiographs (14, 15). The radiological end result was graded as good when there was <1 cm of shortening, <50 of angulation, less than 10% of ad latus shift, and no clinically detectable rotational malunion. It was graded as satisfactory if there were 1-2 cm of shortening, <50 of angulation, and less than 10% lateral displacement. The radiological results were graded as poor, with a 1-2 cm shortening and/or 5-100 angulation (16). For rotational alignment evaluations, the line connecting the midpoint of the knee joint and the point between the malleoli in the ankle joint was compared with the line connecting the uninjured side when the patients were in the supine position (16). The ankle is normally in 12-150 external rotation. In comparative measurements with the uninjured side, 0-50 rotation was accepted as excellent, 5-100 was good, 10-150 rotation was fair, and >150 rotation was considered poor (16). Varus-Valgus angulations were evaluated on AP and lateral radiographs. 0-10 varus-valgus was accepted as excellent, 2-50 varus-valgus was good, 6-100 varus-valgus was fair, and >100 varus-valgus angulation was evaluated as poor (16). The angular results obtained on the long tape that included the knee and ankle were recorded. The union was decided by the Johner-Wruhs score. Patients were taken for AP and lateral X-rays, and at three points, cortex healing was accepted as a union. (Figure 2)

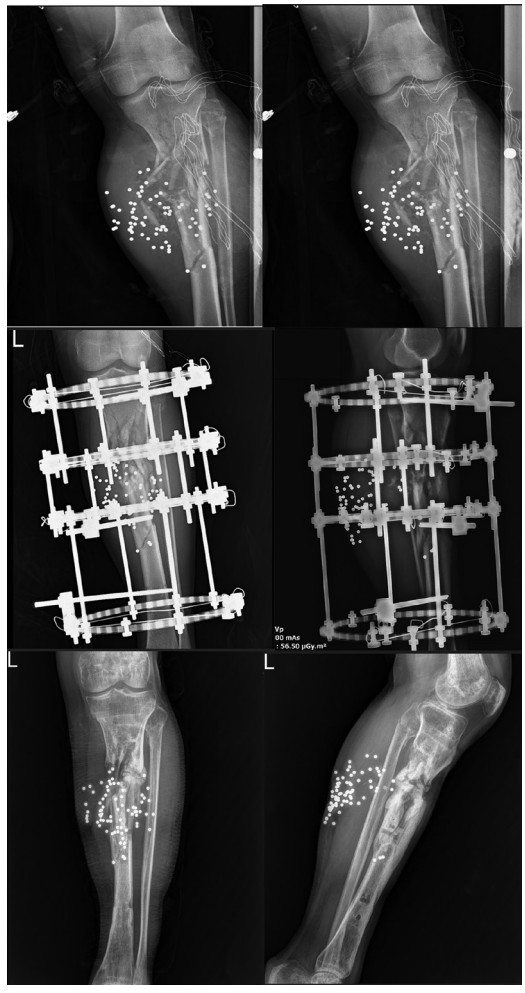


**Figure 2.** Ilizarov external fixator treatment. Patients underwent anteroposterior and lateral X-rays and at three cortex healing was accepted as a union

### Statistical Analysis

The Number Cruncher Statistical System 2007 (Kaysville, Utah, USA) software was used for statistical analysis. Descriptive statistical methods (median, first quarter, and third quarter) were used to evaluate the study data. The Shapiro-Wilk test and graphical examinations were used to assess whether quantitative data were suitable for normal distribution. The Kruskal-Wallis test and the Dunn-Bonferroni test were used to compare quantitative variables that did not show a normal distribution between more than two groups. The Pearson chi-squared test and the Fisher-Freeman-Halton test were used to compare qualitative data. Statistical significance was set as $p<0.05$.

## Results

The mean age of the patients was 38.20±9.63 (17-59) years, and the mean follow-up period was 48.62±14.88 (24-96) months. The demographic and clinical characteristics of the patients are presented in Table 1. No statistically significant difference was found between the distribution of age, time to surgery, length of hospital stay, operation time, and full load times according to the G-A classification ($p>0.05$). The LEFS scores differed significantly depending on the G-A classification ($p<0.01$). The group with G-A classification Type 3A had significantly higher LEFS scores than those with Types 3B and 3C ($p=0.017$; $p=0.001$; $p<0.05$). The union time was significantly different according to the G-A classification ($p<0.05$); the significance of the union time of the group with Type 3A was found to be significantly lower than the cases with Type 3C ($p = 0.008$; $p<0.05$). According to the G-A classification, gender and body mass index did not differ significantly ($p>0.05$). The coronal sequence differed significantly depending on the GA classification ($p<0.01$). The G-A Type 3A group had a significantly lower coronal alignment score than the Type 3B and 3C groups ($p=0.043$; $p=0.001$; $p<0.01$). There were significant differences in sagittal alignment based on the G-A classification ($p<0.01$).

**Table 1.** Demographic characteristics of the patients

| | | n | % |
|---|---|---|---|
| **Gender** | **Female** | 7 | 11.5% |
| | **Male** | 54 | 88.5% |
| **BMI (kg/m²)** | **Normal** | 31 | 50.8% |
| | **Overweighted** | 30 | 49.2% |
| **Side** | **Left** | 27 | 44.3% |
| | **Right** | 34 | 55.7% |
| **Vascular repair** | **None** | 50 | 82.0% |
| | **Artery** | 8 | 13.1% |
| | **Vein** | 3 | 4.9% |
| | **Nerve** | 1 | 1.6% |
| **Gustillo classification** | **3A** | 41 | 67.2% |
| | **3B** | 11 | 18.0% |
| | **3C** | 9 | 14.8% |
| **Graft/flap** | **None** | 52 | 85.2% |
| | **Graft** | 6 | 9.8% |
| | **Flap** | 3 | 4.9% |
| | | Mean±SD | Median (min-max) |
| Age | | 38,2±9,63 | 39 (17-59) |
| **Time to surgery (hours)** | | 13,38±12,28 | 9 (3-72) |
| **Operation time (minutes)** | | 75,21±15,86 | 71 (58-150) |
| **Hospitalization (days)** | | 5,41±5,65 | 4 (2-29) |
| **Follow-up time (months)** | | 48,62±14,88 | 49 (24-96) |
| **LEFS Score** | | 76,85±20,84 | 83,8 (22,5-100) |
| **Full weight-bearing time (weeks)** | | 8,89±2,72 | 8 (5-19) |
| **Union time (weeks)** | | 14,26±3,6 | 13 (11-26) |

LEFS: Lower Extremity Functional Scale

The sagittal alignment score of the G-A Type 3A group was much lower than that of the Type 3B and 3C groups (p=0.022; p=0.001; p<0.05). Johner-Wruhs Score was used to discuss union. The Johner-Wruhs score differed significantly according to the G-A classification (p<0.05); the significance of the Johner-Wruhs score of the G-A classification Type 3A group was found to be significantly lower than that of the Type 3C group (p=0.028; p<0.05). The rotation distributions according to the G-A classification do not show a statistically significant difference (p>0.05). Vascular injury and graft/flap application were performed in the G-A Type 3C subgroup (1 patient had only vein repair, 2 patients had both arterial and vein repair, and 6 patients had only arterial repair). Patients were assessed for full weight bearing when removing their crutches (Table 2).

## Discussion

The most significant finding of our research was that G-A subtype 3C fractures had worse functional and radiological outcomes than other types of fractures. Previous research has demonstrated that fractures of the G-A type 3 have been associated with high rates of chronic infection and non-union, with the former being 38% and the latter being 50% (17, 18). Complications, such as infection and non-union, make the treatment procedure more time-consuming and

**Table 2.** Relationship between demographic features, functional outcomes, and radiological outcomes in the G-A subgroups

| | | G-A Subtype 3 (A) | G-A Subtype 3 (B) | G-A Subtype 3 (C) | [a]p-value |
|---|---|---|---|---|---|
| **Age** | Mean±SD | 38.71±9.25 | 37.00±11.19 | 37.33±10.34 | **0.940** |
| | Median (min-max) | 38 (20-59) | 38 (20-52) | 39 (17-46) | |
| **LEFS Score** | Mean±SD | 83.70±18.94 | 69.27±15.12 | 54.87±17.73 | **0.001**** |
| | Median (min-max) | 88.8 (22.5-100) | 76.25 (42-87.5) | 55 (27.5-83.8) | |
| **Fully weight-bearing (weeks) Median (min-max)** | Mean±SD | 8.59±2.47 | 9.82±3.06 | 9.11±3.41 | **0.241** |
| | 8 (5-19) | 9 (6-18) | 8 (6-17) | | |
| **Union time (weeks) Median (min-max)** | Mean±SD | 13.15±2.02 | 14.73±4.45 | 18.78±4.74 | **0.011*** |
| | 13 (11-21) | 13 (12-26) | 21 (12-24) | | |
| | | **n (%)** | **n (%)** | **n (%)** | **p-value** |
| **Gender** | **Female** | 4 (9.8) | 2 (18.2) | 1 (11.1) | [b]**0.828** |
| | **Male** | 37 (90.2) | 9 (81.8) | 8 (88.9) | |
| **BMI (kg/m²)** | **Normal** | 21 (51.2) | 4 (36.4) | 6 (66.7) | [b]**0.404** |
| | **Overweight** | 20 (48.8) | 7 (63.6) | 3 (33.3) | |
| **Coronal alignment (Prasad et al. 19)** | **Excellent** | 35 (85.4) | 5 (45.5) | 0 (0.0) | |
| | **Good** | 6 (14.6) | 5 (45.5) | 6 (66.7) | |
| | **Mild** | 0 (0.0) | 1 (9.1) | 3 (33.3) | |
| | **Median (min-max)** | 1 (1-2) | 2 (1-3) | 2 (2-3) | [a]**0.001**** |
| **Sagittal alignment** | **Excellent** | 35 (85.4) | 5 (45.5) | 0 (0.0) | |
| | **Good** | 5 (12.2) | 3 (27.3) | 7 (77.8) | |
| | **Mild** | 1 (2.4) | 3 (27.3) | 2 (22.2) | |
| | **Median (min-max)** | 1 (1-3) | 2 (1-3) | 2 (2-3) | [a]**0.001**** |
| **Johner Wruhs Score** | **Excellent** | 28 (68.3) | 7 (63.6) | 2 (22.2) | |
| | **Good** | 11 (26.8) | 2 (18.2) | 5 (55.6) | |
| | **Mild** | 2 (4.9) | 2 (18.2) | 2 (22.2) | |
| | **Median (min-max)** | 1 (1-3) | 1 (1-3) | 2 (1-3) | [a]**0.03**** |
| **Rotational alignment (Prasad et al. 19)** | **Excellent** | 33 (80.5) | 7 (63.6) | 6 (66.7) | |
| | **Good** | 7 (17.1) | 4 (36.4) | 3 (33.3) | |
| | **Mild** | 1 (2.4) | 0 (0.0) | 0 (0.0) | |
| | **Median (min-max)** | 1 (1-3) | 1 (1-2) | 1 (1-2) | [a]**0.462** |

[a]Kruskal–Wallis test/Dunn-Bunferroni test, [b]Pearson Ki kare test/Fisher Freeman Halton test *p<0.05 **p<0.01
G-A: Gustilo-Anderson, SD: Standard deviation, Min-max: Minimum- maximum

have an impact on the patients' ability to function regularly and their quality of life (19).

Vascular injury and the need for soft tissue repair, such as grafts or flaps, are among the reasons for poor functional outcomes in G-A subtype 3C injuries (20). According to the findings of our research, patients with subtype 3C (group III) underwent surgical procedures, such as graft/flap application and vascular repair.

Kumar et al. (21) conducted a study and found that the results for G-A subtypes 3A to 3C deteriorated in open fractures of the tibia. According to the findings of our research, patients in group I (subtype 3A) had higher LEFS ratings than those in groups II (subtype 3B) and III (subtype 3C) who suffered tibial open fractures. The fact that this is the case shows that the long-term functional results are deteriorating in a way that is directly proportional to the degree of injury that was caused (from subtype 3A to subtype 3C). I-EF is often used for tibial fractures with open, infected, comminuted, or segmental bone loss (22). I-EF is often used for the management of tibial fractures that involve open, infected, comminuted, or segmental bone loss (20). Because I-EF offered a more biomechanically stable fixation, the patients were able to engage in effective weight-bearing during the early stages of treatment. There is evidence that early weight bearing has a beneficial effect on the soleus muscle. Stable fixation, early weight bearing, and the beginning of range-of-motion physical activity at an earlier stage have positive effects on mobilization and muscle function (23, 24). In our study, there was no statistically significant difference in the duration of full weight bearing between the groups. As a result of the steady fixation with the I-EF and the fact that it is a system that is capable of carrying weights in the early period, we think that the entire weight-bearing times are similar as well.

After open high-energy lower extremity trauma, the relationship between the length of time elapsed before surgical debridement and the risk of infection is in proportion (25-26). Westgeest et al. (27) reported a late union rate of 17% in a prospective analysis of 736 open fractures. The current study also found a correlation between union time and injuries to soft tissues. According to our findings, the union time in group I (G-A subtype 3A) was shorter than that in group II (G-A subtype 3C). The Johner-Wruhs score (15) and the criteria set up in the study conducted by Prasad et al. (16) showed that the radiological results of patients who were assigned to group I (G-A subtype 3A) were considerably superior to those of patients who were assigned to groups II and III.

In the treatment of compound tibial diaphyseal fractures, Mangukiya et al. (28) reported that the AO monolateral fixator had superior functional and radiological outcomes compared with the extremity reconstruction system. Bayrak et al. (29) showed that I-EF results were more positive in a study in which they compared the Ilizarov external fixator and monolateral external fixator in comminuted tibia fractures resulting from gunshot injury. According to the findings of our research, group I (G-A subtype 3A) had superior coronal and sagittal alignment compared to group III (subtype 3C). The belief that we have is that the deterioration of bone tissue integrity that occurs in type 3C fractures is the cause of the increase in alignment issues. We found that the results worsened than the severity of the injury and the damage to the soft tissue increased. This study is in addition to studies that are currently unavailable. The present study has several limitations, such as its retrospective design, lack of randomization, and relatively small number of patients. When I-EF is used for the treatment of GA type 3 open tibial shaft fracture, the study has a long follow-up period and a cohort of patients. These are two positive aspects of the study. Another aspect of the study is that it demonstrates the application of I-EF as a permanent treatment for wounded patients who have open fractures of the tibia shaft at the time of injury.

## CONCLUSION

In conclusion, although our findings were positive in the patients to whom we used the Ilizarov technique, we discovered that the clinical and radiological results were worse as the severity of the wound grew (G-A subtype A to C). This was the case even if our results were positive.

### ETHICS

**Ethics Committee Approval:** Patients who underwent I-EF due to G-A type 3 tibial shaft fracture between January 2013 and December 2018 were retrospectively approved by Bakırkoy Dr. Sadi Konuk Egitim Ve Research Hospital Clinical Research Ethics Board (approval no: 2015/01/10, date: 04.01.2016).

**Informed Consent:** Since this study was a retrospective study, patient consent was not required.

### FOOTNOTES

#### Authorship Contributions

Surgical and Medical Practices: M.Ç., A.B., M.C.A., Concept: M.Ç., V.Ö., Design: M.Ç., A.B., V.Ö., Data Collection or Processing: A.B., V.Ö., C.K., Analysis or Interpretation: M.Ç., A.B., V.Ö., C.K., Literature Search: M.Ç., A.B., M.C.A., Writing: M.Ç., V.Ö., M.C.A.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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Research

# The Importance of Hip Pathologies in Neurosurgery Practice: A Retrospective Analysis

## Nöroşirurji Pratiğinde Kalça Patolojilerinin Önemi: Retrospektif Analiz

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## ABSTRACT

**Objective:** Lumbar and leg pain is a common issue in neurosurgical practice. While physical examination and magnetic resonance imaging (MRI) are critical in diagnosis, differential diagnosis should also consider possible hip pathologies.

**Methods:** This retrospective study analyzed the hospital records of 970 patients who visited our outpatient clinic between 2013 and 2023 and underwent hip MRI along with standard assessments due to lumbar and leg pain. Data on the necessity of orthopedic hip surgery, lumbar spinal surgery, spinal epidural injections, and hip-related physical therapy and medical treatments were evaluated alongside demographic information, such as age and gender.

**Results:** Of 970 patients, 290 were male and 680 were female. The average age was 52.61 years, with males averaging 48.2 years and females averaging 54.5 years. Following hip MRI, orthopedic surgeries were performed in 18 patients with detected mass lesions and 32 patients with severe coxarthrosis. Neurosurgical interventions were performed in 215 patients, including 173 lumbar spinal surgeries and 42 spinal epidural injections. In addition, 385 patients received intra-articular hip injections and exercise therapy from the Physical Treatment and Rehabilitation. Medical treatment and lifestyle modification were recommended for 320 patients without further interventions.

**Conclusion:** This study underscores the frequent co-occurrence of spinal and hip pathologies, highlighting the need for multidisciplinary approaches in outpatient diagnostics. Mass lesions in the hip, which were observed in 1.85% of the cases, should be particularly noted. Future research will aim to further investigate physical examination findings and patient-reported pain characteristics to aid diagnosis.

**Keywords:** Lumbar disc, hip, coxarthrosis, orthopedics, physical therapy, differential diagnosis

## ÖZ

**Amaç:** Bel ve bacak ağrısı, nöroşirurji pratiğinde sık karşılaşılan sorunlar olarak izlenmektedir. Fizik muayene ve manyetik rezonans görüntüleme (MRG) tanıda hayati öneme sahipken, ayırıcı tanıda kalça patolojileri de göz önünde bulundurulmalıdır.

**Gereç ve Yöntem:** Bu retrospektif çalışma, 2013 ile 2023 yılları arasında polikliniğimizi ziyaret eden ve bel ve bacak ağrısı nedeniyle standart değerlendirmelerin yanı sıra kalça MRG istenen 970 hastanın hastane kayıtlarını analiz etmektedir. Ortopedik kalça cerrahisi, lomber omurga cerrahisi, spinal epidural enjeksiyonlar, kalça ile ilgili fizik tedavi ve tıbbi tedavilerin gerekliliği gibi veriler, yaş, cinsiyet gibi demografik bilgilerin yanı sıra değerlendirildi.

**Bulgular:** 970 hastanın 290'ı erkek, 680'i kadındı. Ortalama yaş 52,61 olup, erkeklerde ortalama 48,2, kadınlarda ise 54,5 yıl idi. Kalça MRG'si sonrasında, tespit edilen kitle lezyonları olan 18 hastaya ve şiddetli koksartrozlu 32 hastaya ortopedik cerrahi uygulandı. Nöroşirurjik müdahaleler 215 hastada gerçekleştirildi; bunların 173'ü lomber omurga cerrahisi, 42'si spinal epidural enjeksiyonuydu. Ayrıca, 385 hastaya fizik tedavi ve rehabilitasyon tarafından intra-artiküler kalça enjeksiyonları ve egzersiz tedavisi uygulandı. Ek müdahaleye gerek duyulmayan 320 hastaya medikal tedavi ve yaşam tarzı değişiklikleri önerildi.

**Sonuç:** Çalışma, omurga ve kalça patolojilerinin sık birlikte görüldüğünü vurgulayarak, ayakta tanı koymada multidisipliner yaklaşımların gerekliliğini ortaya koymaktadır. Vakaların %1,85'inde gözlenen kalça kitle lezyonları özellikle dikkate alınmalıdır. Gelecek araştırmalar, tanıda yardımcı olmak amacıyla fiziksel muayene bulguları ve hasta tarafından belirtilen ağrı özelliklerini daha detaylı araştırmayı hedeflemektedir.

**Anahtar Kelimeler:** Lomber disk, kalça, koksartroz, ortopedi, fizik tedavi, ayırıcı tanı

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## INTRODUCTION

One of the most common complaints of outpatient neurosurgery is low back pain. A recent study conducted in Turkey observed that although the majority of patients presenting at the neurosurgery outpatient clinic did not require surgical intervention, they predominantly reported complaints of spinal pain (1). This finding highlights the prevalence of nonsurgical spinal issues within the neurosurgical field.

Hip-related complaints are the most common issue among patients with low back pain (2). In this patient group, simultaneous complaints, such as groin, thigh, and knee pains, complicate the diagnosis. Although it is traditionally recognized that hip pathologies manifest primarily in the groin area, it has been observed that pain may also radiate to the groin (84%), gluteal region (76%), anterior thigh (59%), posterior thigh (43%), anterior knee (69%), anterior side of the leg (47%), and posterior side of the leg (29%) (3, 4). The widespread distribution of pain poses challenges in accurately identifying the underlying hip pathologies.

Considering that the general prevalence of osteoarthritis in Turkey is 11.2% according to 2022 data, a multidisciplinary approach to spinal patients is inevitable (5). This rate is 9.2% in the US (6) and 7% all over the world (7).

Diagnostic tests to distinguish hip pathologies from lumbar pathologies encompass examination-based assessments, such as the straight leg lift test, flexion, abduction, and external rotation, and flexion, adduction, and internal rotation, as well as imaging techniques, including plain radiography, Computed Tomography (CT), and Magnetic Resonance Imaging (MRI). However, the diagnostic intra-articular injection method is considered the most reliable approach for accurately identifying hip-related issues. (8)

The sensitivity of injections into the hip is 87%, with a specificity of 100%. This indicates a high level of accuracy when using this method to diagnose hip pathologies (9).

It is essential to determine which branch of medicine will oversee the follow-up and treatment of this patient group, which requires a detailed diagnostic examination. According to a study conducted in America, neurosurgeons specializing in spinal surgery perform spinal operations four times more frequently than their orthopedic colleagues in the same specialty. This highlights the significant role of neurosurgeons in the management of spinal conditions (10).

However, orthopedic physicians require additional examinations for the evaluation of hip pathologies at a rate of 52.6%, compared with 38.1% for neurosurgeons. Additionally, the success rates of orthopedic physicians and neurosurgeons in identifying hip pathologies that require treatment are 43.6% and 28.9%, respectively (10). These statistics indicate a higher level of proficiency among orthopedic physicians in both the diagnostic and treatment processes for hip-related issues.

Considering the differences in working conditions and specialty training across medical disciplines in Turkey, there is a lack of research on this subject. The study also noted that patients evaluated in the outpatient clinic were examined in terms of their need for interventions from neurosurgery, orthopedic, and physical therapy disciplines. This underscores the importance of a multidisciplinary approach to the assessment and management of such conditions.

## METHODS

The study was designed in accordance with the Standards for Reporting Qualitative Research guidelines, ensuring that the criteria were prepared to meet this standards (11). This adherence enhances the clarity, transparency, and rigor of the research process and reporting. In this study, patients who visited the neurosurgery outpatient clinic between 2013 and 2023 were retrospectively analyzed using hospital records. The basis for data collection was lumbar and hip MRI examinations requested during the same patient visit. The outpatient clinics of four different neurosurgeons were reviewed, and the sample size remained consistent because only consecutive applications were considered. This study was approved by the Istanbul Health Sciences University Ümraniye Training and Research Hospital Scientific Research Ethics Committee (number: B.10.1TKH.4.34.H.GP.0.01/157, date: 16.05.2024).

MRI was deemed appropriate for the study due to its consistency in reliability across different observers and its ability to be radiologically reported. The inclusion criteria for participants were having both lumbar and hip MRI images taken during the same hospital visit and being re-admitted to the hospital for the results after the MRI request. Patients who did not meet the inclusion criteria were excluded from the study. No other exclusion criteria were specified.

970 patients undergoing lumbar and hip MRI were analyzed in this study. Demographic variables, including gender and age, were also assessed. The cohort was categorized into six distinct subgroups based on the type of medical intervention required. For those requiring orthopedic intervention, patients were subdivided into those with hip mass lesions and those with severe coxarthrosis. Neurosurgical intervention was required for patients undergoing either lumbar spinal surgery or spinal epidural

injection. Additionally, a subgroup of patients requiring physical therapy and rehabilitation were identified who received intra-articular hip injections and exercise. Lastly, the conservative treatment group through medical management and lifestyle modification was delineated (Table 1).

### Statistical Analysis

The statistical analysis was conducted to evaluate the differences in treatment modalities and demographic characteristics among patients with low back and hip pain. Descriptive statistics were used to summarize demographic variables, including age and gender distributions, across the study cohort. Continuous variables are presented as means and standard deviations, whereas categorical variables are expressed as frequencies and percentages.

## Results

In this study involving 970 patients, the cohort consisted of 290 males and 680 females. The mean age of the entire group was 52.61 years, with a mean age of 48.2 years for men and 54.5 years.

Treatment modalities varied across disciplines, with 50 patients treated by orthopedic physicians, 215 by neurosurgeons, 385 by Physical Treatment and Rehabilitation (PTR), and 320 by conservative methods.

**Table 1.** Treatment Types

| | |
|---|---|
| Orthopedics | Surgery for mass lesion on the hip |
| | Surgery for severe coxarthrosis |
| Neurosurgery | Lumbar spinal surgery |
| | Spinal epidural injection |
| Physical therapy and rehabilitation | Intra-articular hip injection and exercise |
| Conservative | Medical treatment and lifestyle modifications |

Within the orthopedic treatment group, 18 patients underwent surgeries for mass lesions in the hip, while 32 patients were treated for severe coxarthrosis.

In the neurosurgery group, 173 patients underwent lumbar spinal surgery, and 42 underwent spinal epidural injection.

All 385 patients under the care of PTR received intra-articular hip injections. Additionally, 320 patients were managed conservatively, receiving medical treatment, and lifestyle modification (Figure 1).

## DISCUSSION

Lumbar and hip pain are significant concerns in the daily practice of neurosurgery. This study underscores that although these symptoms may often be attributed to underlying neurosurgical pathologies, the potential for orthopedic conditions should not be overlooked. Specifically, hip mass lesions, which occur in approximately 1.8% of cases, require orthopedic intervention. This highlights the importance of considering orthopedic causes when evaluating patients with these symptoms.

In the literature concerning the rate at which individuals consult a physician for low back pain, the female-to-male ratio typically ranges between 1.1 and 1.3. However, in this study, the female-to-male ratio was found to be 2.3, which is significantly higher than what is generally reported (12). Although bone-related pain intensifies in women during the postmenopausal period, the notably high female-to-male ratio observed in this study suggests that further investigation is warranted.

International publications indicate that approximately 15.76% of neurosurgical outpatients require surgical intervention, whereas domestic literature reports a slightly lower rate of 14.8% (1, 13) . In this study, 17.8% of patients received neurosurgical surgical treatment. This relatively high rate was attributed to patients presenting with substantial pain

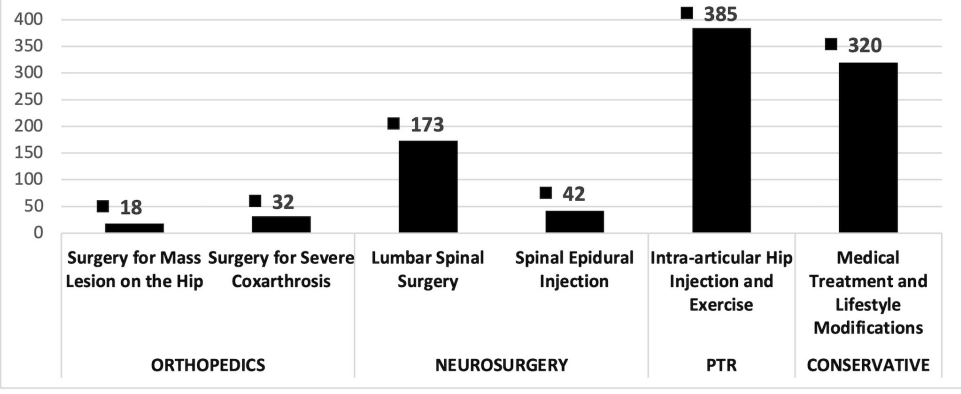


**Figure 1.** Treatment methods and number of patients

levels and clinical symptoms severe enough to necessitate hip imaging for differential diagnosis. Consequently, the findings underscore the importance of considering hip pathologies in neurosurgical practice. Such pathologies can significantly impact diagnosis and treatment strategies, highlighting the need for a thorough assessment of hip-related issues in patients with neurosurgical conditions.

Moreover, the need for a more integrated approach in medical training and practice is evident, with the aim of fostering deeper understanding and collaboration across specialties. This approach is not only crucial for enhancing diagnostic accuracy but also for ensuring that patients receive the most comprehensive and effective treatment. The study's emphasis on multidisciplinary treatment strategies confirms that addressing complex cases often requires insights from various medical fields, reinforcing the value of cross-disciplinary education and cooperation in clinical settings.

## CONCLUSION

Effective management of low back and hip pain requires a collaborative, multidisciplinary approach to ensure accurate diagnosis and appropriate treatment. This strategy enhances patient outcomes by integrating the expertise of neurosurgeons, orthopedic specialists, and rehabilitation specialists.

### ETHICS

**Ethics Committee Approval:** This study was approved by the Istanbul Health Sciences University Ümraniye Training and Research Hospital Scientific Research Ethics Committee (number: B.10.1TKH.4.34.H.GP.0.01/157, date: 16.05.2024).

**Informed Consent:** In this study, patients who visited the neurosurgery outpatient clinic between 2013 and 2023 were retrospectively analyzed using hospital records.

### FOOTNOTES

#### Authorship Contributions

Surgical and Medical Practices: M.U.E., A.E.K., L.Ş., A.F.R., Concept: F.A., A.E.K.,

Design: F.A., A.E.K., Data Collection or Processing: M.U.E., F.B.Ö., Z.G., L.Ş., G.G.Ö., Analysis or Interpretation: M.U.E., F.A., S.I., F.B.Ö., Z.G., G.G.Ö., Literature Search: M.U.E., S.I., L.Ş., Writing: M.U.E., A.F.R.

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Research

# Relationship between Immune Thrombocytopenic Purpura and Thyroid Diseases

## İmmün Trombositopenik Purpura ve Tiroid Hastalıkları Arasındaki İlişki

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## ABSTRACT

**Objective:** This study aimed to determine the frequency of thyroid diseases, the positivity rates of anti-thyroid peroxidase antibodies (Anti-TPO-Ab), anti-thyroglobulin antibodies (Anti-TG-Ab), antinuclear antibodies (ANA), and anti-double-stranded deoxyribonucleic acid antibodies (Anti-dsDNA-Ab), and variables related to the frequency of hypothyroidism in patients with immune thrombocytopenia (ITP).

**Methods:** This retrospective study was conducted between January 2015 and December 2021. A total of 320 patients with newly diagnosed ITP were included in the study. Demographic characteristics, comorbidity status, features of ITP and thyroid diseases, laboratory findings, and mortality information of the patients were retrospectively reviewed. After investigating the thyroid disease and autoantibody frequencies of the patients, we divided the patients into the hypothyroid and no thyroid disease groups.

**Results:** Fifty-nine (18.4%) patients had thyroid disorders. Anti-TG-Ab positivity was detected in 20.0%, Anti-TPO-Ab positivity in 29.4%, ANA positivity in 16.9%, and Anti-DsDNA-Ab positivity in 4.2% of ITP patients. In total, 42 (13.1%) patients had hypothyroidism. Patients with high age (p=0.024), female sex (p=0.006), and positive Anti-TPO-Ab (p=0.009) had a higher risk of hypothyroidism than other patients.

**Conclusion:** ITP disease and hypothyroidism may result from a standard pathophysiological process involving Anti-TPO antibodies. Advanced age and female sex also seem to support the coexistence of these two diseases.

**Keywords:** Immune thrombocytopenia, thyroid diseases, hypothyroidism, antithyroid antibodies, antinuclear antibody, anti-double-stranded deoxyribonucleic acid antibodies

## ÖZ

**Amaç:** Bu çalışma, immün trombositopeni (ITP) hastalarında tiroid hastalıklarının sıklığını, anti-tiroid peroksidaz antikorları (Anti-TPO-Ab), anti-tiroglobulin antikorları (Anti-TG-Ab), anti-nükleer antikorlar (ANA), anti-çift sarmallı deoksiribonükleik asit antikorları (Anti-dsDNA-Ab) pozitiflik oranlarını ve hipotiroidizm sıklığı ile ilişkili değişkenleri belirlemeyi amaçlamıştır.

Gerekçe ve Yöntem: Bu retrospektif çalışma Ocak 2015 ile Aralık 2021 tarihleri arasında gerçekleştirilmiştir. Yeni tanı almış 320 ITP hastası çalışmaya dahil edilmiştir. Hastaların demografik özellikleri, komorbidite durumları, ITP ve tiroid hastalıklarının özellikleri, laboratuvar bulguları ve mortalite bilgileri retrospektif olarak incelenmiştir. Hastaların tiroid hastalığı ve otoantikor sıklıkları araştırıldıktan sonra, hastalar hipotiroid grup ve tiroid hastalığı olmayan grup olarak ikiye ayrılmıştır.

**Bulgular:** Elli dokuz (%18,4) hastada tiroid hastalığı tespit edilmiştir. Anti-TG-Ab pozitifliği %20,0, Anti-TPO-Ab pozitifliği %29,4, ANA pozitifliği %16,9 ve Anti-DsDNA-Ab pozitifliği %4,2 olarak belirlenmiştir. Toplam 42 (%13,1) hasta hipotiroidizm tanısı almıştır. Yüksek yaş (p=0,024), kadın cinsiyet (p=0,006) ve pozitif Anti-TPO-Ab (p=0,009) olan hastalar, diğer hastalara göre hipotiroidizm riski daha yüksek bulunmuştur.

**Sonuç:** ITP hastalığı ve hipotiroidizm, Anti-TPO-Ab'nin de dahil olduğu ortak bir patofizyolojik sürecin sonucu olabilir. İleri yaş ve kadın cinsiyet de bu iki hastalığın bir arada bulunmasını destekleyen faktörler olarak görülmektedir.

**Anahtar Kelimeler:** İmmün trombositopeni, tiroid hastalıkları, hipotiroidizm, anti-tiroid antikorlar, anti-nükleer antikor, anti-çift sarmallı deoksiribonükleik asit antikorları

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## INTRODUCTION

Immune thrombocytopenia (ITP) is an acquired autoimmune disease characterized by isolated decreased peripheral platelet count, which is caused by insufficient platelet production and platelet destruction due to autoimmune antibodies that recognize platelet membrane glycoproteins (1-3). The incidence of ITP has been reported as approximately 1.9-6.4/100000 in children and 3.3-3.9/100000 in adults (4).

Due to changes in the immune response and the development of self-reactive antibodies, ITP and other autoimmune diseases may be present simultaneously (5). It has been shown in previous studies that autoimmune diseases such as antiphospholipid syndrome and systemic lupus erythematosus can coexist with ITP (1, 6). Additionally, various autoimmune thyroid diseases, such as Graves' disease and Hashimoto's thyroiditis, hyperthyroidism, and hypothyroidism, are associated with ITP (5, 7-9). More interestingly, it has been demonstrated that treatment of thyroid disease improves thrombocytopenia (5, 9). Positivity for antinuclear antibody (ANA), anti-double-stranded deoxyribonucleic acid antibodies (Anti-dsDNA-Ab), anti-thyroid peroxidase antibodies (Anti-TPO-Ab), and anti-thyroglobulin antibodies (Anti-TG-Ab)- the latter two defined as anti-thyroid antibodies (Anti-T-Abs)- are more common in patients with ITP than in the general population (10-13). It has been claimed that the presence of these antibodies in ITP patients affects the prognosis of ITP and increases the risk of some comorbidities (14, 15). Anti-T-Abs positivity in patients with ITP has been demonstrated to increase the risk of chronicity (15) and the development of autoimmune thyroiditis (11) and abnormal thyroid functions (8). However, the possible impact of these autoimmune markers on the prevalence, pathophysiology, and management of ITP is still unclear (11).

In this study, our aims were (i) to determine the frequency of thyroid diseases in patients with ITP, (ii) to determine the positivity rates of Anti-T-Abs, ANA, and Anti-dsDNA-Ab in patients with ITP, and (iii) to investigate whether the frequency of hypothyroidism in patients with ITP is associated with antibody positivity, demographic and clinical features, thyroid function tests (TFTs), and laboratory findings.

## METHODS

### Study Design and Population

This retrospective study was conducted between January 2015 and December 2021 at the Department of Hematology of University of Health Sciences Türkiye, Bakirkoy Dr. Sadi Konuk Training and Research Hospital. This retrospective study was conducted between January 2015 and December 2021 at the Department of Hematology of University of Health Sciences Türkiye, Bakirkoy Dr. Sadi Konuk Training and Research Hospital. The protocol for this study was approved by the Bakırkoy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (date: 06.12.2021, decision no: 2021-23-16).

A total of 320 patients aged >18 years with newly diagnosed ITP were included in the study. Patients younger than 18 years of age, those with secondary ITP associated with any cause other than thyroid disease(s), and those with known autoimmune diseases other than thyroid diseases were excluded from the study. Demographic characteristics, comorbidity status, ITP and thyroid disease characteristics, laboratory findings, and mortality information of the patients were recorded.

The diagnosis and treatment of ITP were based on the diagnostic criteria and treatment recommendations of relevant guidelines (3).

### Laboratory Analysis

Complete blood counts, liver and kidney function tests, and lactate dehydrogenase levels were measured using routine devices (Roche, Cobas 8000, ABD).

TFTs [free triiodothyronine (F-T3), free thyroxine (F-T4), thyroid-stimulating hormone (TSH)], Anti-TPO-Ab, Anti-TG-Ab, and anti-dsDNA-Ab were measured by a chemiluminescence microparticle immunoassay (Roche, Cobas 8000, ABD) according to the manufacturer's protocols.

ANA measurements were performed using an indirect immunofluorescence assay using the HEp-2 Test System (Ipro bıyosistem, Spain) (15).

The standard reference range for F-T3 was 1.58-3.91 pg/m,(16) F-T4 was 0.7-1.48 ng/d, (16) TSH was 0.35-4.94 mIU/L, (16) Anti-TPO-Ab was 0.00-5.61 IU/mL, (16) Anti TG-Ab was 0.00–4.11 IU/mL, (16) Anti-dsDNA-Ab was >35 IU/mL.(17)

A positive value of Anti-TPO-Ab was defined as Anti-TPO-Ab >5.61 IU/mL, (16) a positive value of Anti-TG-Ab was defined as Anti-TG-Ab >4.11 IU/mL, (16) a positive value of Anti-dsDNA-Ab was defined as Anti-dsDNA-Ab >35 IU/ml, (17) and a positive result for ANA was defined as a titer of ≥ 1:40. (15)

When selecting laboratory results for inclusion in the study, the time of diagnosis of ITP was taken as a reference.

First, the laboratory results that were studied at the time of ITP diagnosis were used. If absent, the most recently studied laboratory findings before or after the diagnosis of ITP were used.

### Thyroid Disease-related Definitions

An F-T4 level lower than the reference range was defined as overt hypothyroidism, and an F-T4 level higher than the reference range was defined as overt hyperthyroidism (18). Subclinical hypothyroidism was defined as TSH levels higher than the reference range with normal serum F-T4 and F-T3 levels in the absence of clinical signs or symptoms (5, 18). Subclinical hyperthyroidism was defined as a normal serum F-T4 and F-T3 level without clinical signs or symptoms and TSH levels lower than the reference range (5, 18).

Patients with single or multiple nodules of 1 cm or more in the thyroid gland on ultrasonography or computed tomography were defined as patients with thyroid nodules (19).

The diagnosis of Hashimoto's thyroiditis was made based on the presence of either Anti-TPO-Ab positivity or decreased echogenicity, heterogeneity, hypervascularity, and small cysts on thyroid ultrasonography, in addition to the clinical symptoms of thyroid dysfunction (20).

### Grouping

The "hypothyroidism" group was formed from patients with overt and subclinical hypothyroidism, except for thyroid nodules, thyroid cancer, and thyroidectomy.

### Statistical Analysis

All analyses were performed on SPSS v25 (SPSS Inc., Chicago, IL, USA). Histograms and Q-Q plots were used to determine whether continuous variables were normally distributed. Data are given as mean±standard deviation or median (1st quartile-3rd quartile) for continuous variables according to distribution normality and as frequency (percentage) for categorical variables. Between-group analysis of continuous variables was performed using Student's t-test or Mann-Whitney U test, depending on the normality of distribution. Categorical variables were compared between groups using chi-square tests or Fisher's exact test. Multivariable logistic regression analysis was performed to calculate odds ratios (ORs) adjusted for age and sex. The statistical significance was set as $p<0.05$.

## RESULTS

The patients' ages ranged from 19 to 92 (mean age 48.40±18.54), and 231 (72.2%) were female (Table 1).

**Table 1.** Summary of patient characteristics and laboratory measurements

| | |
|---|---|
| Age | 48.40±18.54 |
| **Sex** | |
| Female | 231 (72.2%) |
| Male | 89 (27.8%) |
| Duration of ITP: years | 6 (4-8) |
| Lymphoproliferative disease | 1 (0.3%) |
| Thyroid disease | 59 (18.4%) |
| Subclinical hypothyroidism | 4 (1.3%) |
| Overt hypothyroidism | 38 (11.9%) |
| Subclinical hyperthyroidism | 6 (1.9%) |
| Overt hyperthyroidism | 4 (1.3%) |
| HT with euthyroidism | 2 (0.6%) |
| Thyroid nodule | 3 (0.9%) |
| Thyroid cancer | 1 (0.3%) |
| Thyroidectomy | 1 (0.3%) |
| Duration of thyroid disease | 6.49 ± 4.18 |
| **Comorbidities** | |
| Diabetes mellitus | 51 (15.9%) |
| Hypertension | 76 (23.8%) |
| Malignancy (non-hematological) | 6 (1.9%) |
| Hyperlipidemia | 20 (6.3%) |
| Coronary artery disease | 26 (8.1%) |
| COPD | 13 (4.1%) |
| Rheumatic disease | 11 (3.4%) |
| Other | 78 (24.4%) |
| Glucose (mg/dL) | 102 (91 - 125) |
| Urea (mg/dL) | 28 (21 - 38) |
| Creatinine (mg/dL) | 0.68 (0.60 - 0.80) |
| Aspartate aminotransferase (U/L) | 19 (15 - 25) |
| Alanine aminotransferase (U/L) | 17 (12 - 26) |
| Lactate dehydrogenase (IU/L) | 210 (172 - 261) |
| Hemoglobin (g/dL) | 12.77 ± 2.08 |
| Hematocrit (%) | 38.50 ± 5.76 |
| MCV (fL) | 84.29 ± 6.61 |
| WBC ($x10^3$) | 8.05 (6.26 - 10.00) |
| Neutrophil ($x10^3$) | 4.95 (3.68 - 6.83) |
| Lymphocyte ($x10^3$) | 2.10 ± 0.96 |
| Eosinophil ($x10^3$) | 0.10 (0.04 - 0.19) |
| Platelet ($x10^3$) | 34.5 (11.0 - 71.5) |
| TSH (mIU/L) | 1.77 (1.04 - 3.00) |
| F-T4 (ng/dL) (n = 276) | 1.09 (0.87 - 1.29) |
| F-T3 (pg/mL) (n = 196) | 2.77 ± 0.97 |
| Anti-TG Ab positivity (n = 40) | 8 (20.0%) |
| Anti-TPO-Ab positivity (n = 51) | 15 (29.4%) |
| ANA positivity (n = 160) | 27 (16.9%) |
| Anti-dsDNA-Ab positivity (n = 120) | 5 (4.2%) |
| Mortality | 16 (5.0%) |

Data are presented as mean±standard deviation or median (1st quartile-3rd quartile) for continuous variables according to distribution normality and as frequency (percentage) for categorical variables.
ANA: Antinuclear antibody, Anti-dsDNA-Ab: Anti–double-stranded deoxyribonucleic acid antibodies, Anti-TG-Ab: Anti-thyroglobulin antibodies, Anti-TPO-Ab: Anti-thyroid peroxidase antibodies, COPD: Chronic obstructive pulmonary disease, F-T3: Free triiodothyronine, F-T4: Free thyroxine, HT: Hashimoto's thyroiditis, ITP: Immune thrombocytopenia, MCV: Mean corpuscular volume, TSH: Thyroid-stimulating hormone, WBC: White blood cells

Fifty-nine (18.4%) patients were diagnosed with thyroid-related diseases. Anti-TG-Ab positivity was detected in 20.0%, anti-TPO-Ab positivity in 29.4%, ANA positivity in 16.9%, and anti-dsDNA-Ab positivity in 4.2% of the patients.

In total, 42 (13.1%) patients had hypothyroidism, 38 (11.9%) of which were defined as overt hypothyroidism, and 4 (1.3%) were subclinical hypothyroidism. The mean age of patients with hypothyroidism was 54.45±17.61 years, whereas it was 47.38±18.71 years in those without any thyroid disease (p=0.023). 90.5% of patients with hypothyroidism and 68.6% of patients without any thyroid disease were females (p=0.006). In the hypothyroidism group, the percentage of those with hyperlipidemia (p=0.033) and the percentage of those with positive Anti-TPO-Ab (p=0.039) were significantly higher than those without any thyroid disease (Table 2).

**Table 2.** Comparison of patient characteristics and laboratory measurements between groups

| | **Groups** | | |
|---|---|---|---|
| | **No thyroid disease (n=261)** | **Hypothyroidism (n=42)** | **p-value** |
| Age | 47.38±18.71 | 54.45±17.61 | **0.023** |
| **Sex** | | | |
| Female | 179 (68.6%) | 38 (90.5%) | **0.006** |
| Male | 82 (31.4%) | 4 (9.5%) | |
| Duration of ITP: Years | 6 (4-8) | 6 (5-7) | 0.726 |
| Lymphoproliferative disease | 0 (0.0%) | 1 (2.4%) | 0.139 |
| **Comorbidities** | | | |
| Diabetes mellitus | 40 (15.3%) | 9 (21.4%) | 0.441 |
| Hypertension | 56 (21.5%) | 15 (35.7%) | 0.067 |
| Malignancy | 2 (0.8%) | 2 (4.8%) | 0.094 |
| Hyperlipidemia | 13 (5.0%) | 6 (14.3%) | 0.033 |
| Coronary artery disease | 19 (7.3%) | 6 (14.3%) | 0.133 |
| COPD | 12 (4.6%) | 0 (0.0%) | 0.384 |
| Rheumatic disease | 6 (2.3%) | 3 (7.1%) | 0.114 |
| Other | 61 (23.4%) | 10 (23.8%) | 1.000 |
| Glucose (mg/dL) | 102 (91-126) | 106.5 (95 - 116) | 0.479 |
| Urea (mg/dL) | 27.1 (21-38) | 31.5 (22 - 40) | 0.240 |
| Creatinine (mg/dL) | 0.68 (0.59-0.8) | 0.73 (0.61 - 0.82) | 0.438 |
| Aspartate aminotransferase (U/L) | 19 (15-25) | 21 (16 - 25) | 0.785 |
| Alanine aminotransferase (U/L) | 18 (12-27) | 15.5 (12 - 25) | 0.544 |
| Lactate dehydrogenase (IU/L) | 214 (179-258) | 204.5 (178 - 272) | 0.924 |
| Hemoglobin (g/dL) | 12.82±2.14 | 12.60 ± 1.67 | 0.514 |
| Hematocrit (%) | 38.65±5.94 | 38.15 ± 4.69 | 0.603 |
| MCV (fL) | 84.44±6.65 | 83.58 ± 6.41 | 0.434 |
| WBC ($x10^3$) | 8.13 (6.26-10.20) | 7.89 (6.60 - 9.43) | 0.676 |
| Neutrophil ($x10^3$) | 5.02 (3.76-7.13) | 4.86 (3.60 - 6.35) | 0.385 |
| Lymphocyte ($x10^3$) | 2.09±0.98 | 2.15 ± 0.77 | 0.638 |
| Eosinophil ($x10^3$) | 0.10 (0.04-0.19) | 0.11 (0.05 - 0.19) | 0.738 |
| Platelet ($x10^3$) | 31 (11-69) | 39.5 (14 - 81) | 0.552 |
| Anti-TG-Ab positivity | 6 (24.0%) | 1 (12.5%) | 0.652 |
| Anti-TPO-Ab positivity | 6 (20.0%) | 8 (53.3%) | **0.039** |
| ANA positivity | 20 (15.2%) | 6 (33.3%) | 0.089 |
| Anti-dsDNA-Ab positivity | 3 (3.1%) | 2 (15.4%) | 0.104 |
| Mortality | 13 (5.0%) | 2 (4.8%) | 1.000 |

Data are presented as mean±standard deviation or median ($1^{st}$ quartile-$3^{rd}$ quartile) for continuous variables according to distribution normality and as frequency (percentage) for categorical variables.
ANA: Antinuclear antibody, Anti-dsDNA-Ab: antidouble-stranded deoxyribonucleic acid antibodies, Anti-TG-Ab: antithyroglobulin antibodies, Anti-TPO-Ab: antithyroid peroxidase antibodies, COPD: Chronic obstructive pulmonary disease, ITP: Immune thrombocytopenia, MCV: Mean corpuscular volume, WBC: White blood cells

**Table 3.** Odds ratios for hypothyroidism based on multivariable logistic regression analysis

| | Hypothyroidism | |
|---|---|---|
| | **OR (95% CI)** | **p-value** |
| Age[1] | 1,021 (1,003-1,039) | **0.024** |
| Sex, Female[2] | 4,424 (1,521-12,872) | **0.006** |
| Duration of ITP, years[3] | 0.958 (0.875-1,049) | 0.351 |
| Anti-TG-Ab positivity[3] | 0.753 (0.066-8,631) | 0.820 |
| Anti-TPO-Ab positivity[3] | 9,995 (1,783-56,020) | **0.009** |
| ANA positivity[3] | 2,493 (0.825-7.535) | 0.106 |
| Anti-dsDNA Ab positivity[3] | 5,615 (0.796-39.601) | 0.083 |

[1]Adjusted for sex, [2]Adjusted for age, [3]Adjusted for age and sex, ANA: Antinuclear antibody, Anti-dsDNA-Ab: antidouble-stranded deoxyribonucleic acid antibodies, Anti-TG-Ab: antithyroglobulin antibodies, Anti-TPO-Ab: antithyroid peroxidase antibodies, CI: Confidence interval, ITP: Immune thrombocytopenia, OR: Odds ratio

High age was associated with hypothyroidism (p=0.024) after adjusting for sex. Females had a 4.424-fold higher risk of hypothyroidism than males (OR: 4.424, 95% CI: 1.521-12.872; p=0.006) after adjusting for age. Patients with anti-TPO-Ab positivity had a 9.995-fold higher risk for hypothyroidism than other patients (OR: 9.995, 95% CI: 1.783-56.020; p=0.009) after adjusting for age and sex (Table 3).

## DISCUSSION

The main findings of the current study were as follows: (i) among patients with ITP, 18.4% had thyroid disease, and 13.2% were found to have hypothyroidism (without any known cause); (ii) Anti-TG-Ab positivity was detected in 20.0%, Anti-TPO-Ab positivity in 29.4%, ANA positivity in 16.9%, and anti-dsDNA-Ab positivity in 4.2% of ITP patients; (iii) advanced age, female sex, and Anti-TPO-Ab positivity were determined as independent risk factors for ITP and hypothyroidism to occur in the same patients.

Because autoimmune diseases result from disrupted self-tolerance, the pathophysiological process that causes ITP formation may also trigger other autoimmune or immune diseases, seven and vice-versa. In this context, the most investigated thyroid-related diseases were Graves' disease and Hashimoto's thyroiditis, which are autoimmune diseases of the thyroid (5, 21). In the present study, the incidence of any thyroid disease in patients with ITP was 18.4%, and the incidence of hypothyroidism alone was 13.2%. In a similar study, among patients with ITP, it was reported that the percentage of patients with any thyroid disease was 21.4%, while more specifically, Graves' disease was diagnosed in 3.77%, Hashimoto's thyroiditis in 6.67%, subclinical hyperthyroidism in 0.87%, and subclinical hypothyroidism in 10.1% (5). Although the relationship between autoimmune thyroid diseases and ITP has been investigated (5, 7), the pathophysiological and prognostic link between these diseases is unknown. One study emphasized that autoimmune thyroiditis was not a prognostic risk factor for chronicity of ITP in the pediatric age (11). A prospective study showed that thyroid dysfunction was not correlated with the duration of ITP or response to treatment (8). The present study specifically examined the relationship between ITP and hypothyroidism, demonstrating a notable association between the conditions. Investigating causal relationships between thyroid dysfunction frequency in patients with ITP compared with the average population may help elucidate the unknown pathophysiological aspects of these disorders.

Anti-TPO-Ab attacks a component of the smooth endoplasmic reticulum of thyroid cells (22). They are the most frequently detected autoantibodies in Hashimoto's thyroiditis and Graves' disease and less frequently in nodular goiter or thyroid carcinoma, and their titers have been used as markers to assess disease activity (23). Anti-TG-Ab recognizes the thyroglobulin molecule. It can often be detected in autoimmune thyroiditis (in 70-80% of patients with Hashimoto's thyroiditis and 30-40% of patients with Graves' disease) and in 10%-15% of patients with non-thyroid autoimmune diseases (21). These two autoantibodies can be detected at varying percentages in many patients with various non-thyroid diseases, including ITP and the healthy population (24, 25). In addition to these two antibodies, we investigated the incidence of ANA and Anti-dsDNA-Ab positivity in ITP patients. The frequency of Anti-TG-Ab positivity was 20.0%, Anti-TPO-Ab positivity was 29.4%, ANA positivity was 16.9%, and Anti-dsDNA-Ab positivity was 4.2% in all ITP patients. Interestingly, these frequencies were 24.0%, 20.0%, 15.2%, and 3.1%, even in those with no thyroid disease. Since there was no healthy control group, we could not compare the findings with the general population's conclusions. Still, our reported percentages are considerably higher than prior data from healthy populations (10, 12, 13). Anti-T-Abs positivity in

patients with ITP ranges from 11.6% to 38% (11). In one study investigating the frequency of autoimmune antibody positivity in ITP patients, 77% of the patients were reported to be positive for at least one of the following autoantibodies: ANA, red blood cell direct antiglobulin test, Anti-TPO-Ab, anticardiolipin antibodies, rheumatoid factor, and lupus anticoagulant. In the same study, the most common positive antibodies were ANA (65%), Anti-TPO-Ab (31%), and red blood cell direct antiglobulin tests (29%) were identified as the most common positive antibodies (15). In summary, it is feasible to suggest that patients with ITP have an increased likelihood of having ANA, Anti-TPO-Ab, Anti-TG-Ab, and Anti-dsDNA-Ab positivity compared with healthy individuals, even if they do not have clinical signs of other autoimmune diseases. The results of the present study support these findings. We believe that if the roles of these markers in the pathophysiology of ITP can be clarified, significant advances in the management of ITP can be achieved.

We also investigated the risk factors for hypothyroidism in patients with ITP. For this purpose, we compared the data of patients with ITP and hypothyroidism (before, simultaneously, or after ITP) with those who had ITP but not thyroid disease. Consequently, advanced age, female sex, and Anti-TPO-Ab positivity were found to be independent risk factors for hypothyroidism in patients with ITP. In this retrospective study, pediatric patients diagnosed with chronic ITP were examined. It was reported that no significant correlation was observed between the positivity of Anti-T-Abs and clinical phenotype and biochemical profile (immunoglobulin levels, bleeding diathesis, frequency of immunosuppressive therapy, hypothyroidism, and duration of chronicity) in chronic ITP patients (11). In another retrospective study, female sex and ANA positivity were found to be associated with the presence of thyroid disease in patients with ITP (5). Mousa et al. (24) reported a significant relationship between Anti-T-Ab positivity and the development of relapse and the presence of low platelet count. However, no significant results were reported concerning the effects of sex and age. In another study, none of the participants with Anti-TPO-Ab positivity were found to have clinically apparent thyroid disease at baseline or during follow-up. However, thrombosis was significantly associated with lupus anticoagulant and ANA positivity, while a lower likelihood of remission was associated with Anti-TPO-Ab positivity (15). In another study, no significant difference was found between the Anti-T-Ab levels of patients with newly diagnosed ITP, persistent ITP, and chronic ITP; however, Anti-T-Ab positivity was determined to be associated with low platelet count at baseline and ITP relapse risk during 1-year follow-up in children with ITP (24). Many immunological factors play a role in the pathophysiology of ITP. Some autoantibodies in patients with ITP appear to affect the clinical severity, transient or permanent nature of ITP, or development of other diseases. Advanced age and female sex may also affect the course of ITP and its association with comorbid disorders like hypothyroidism. ITP and hypothyroidism may be caused by a common pathogenic mechanism, possibly through the involvement of Anti-TPO antibodies. Further investigation of this possible pathophysiological scenario could contribute to the management of both diseases. It may be beneficial to recommend that patients with ITP, especially elderly individuals and women with anti-TPO-Ab positivity, be followed up with TFTs and Anti-T-Ab measurements to prevent the development of overt hypothyroidism.

Several limitations of this study should be considered when interpreting the results. First, given the retrospective nature of the study, test results for all markers and TFT were unavailable for all patients. Thus, there was a lack of homogeneity in the testing of autoimmune markers and TFT. Alcohol use and smoking status were not assessed and may have affected the results. The timing of antibody quantification was not consistent in all patients. Because autoantibody levels may change over time, (11) future studies may benefit from performing measurements in a prospectively planned manner. The absence of a healthy control group without ITP is also a limitation that prevents reliable comparisons with healthy subjects. Lastly, to establish a cause-effect relationship between ITP and hypothyroidism, the longitudinal relationship between the diseases should be evaluated, which necessitates prospective designs or highly accurate record keeping.

## CONCLUSION

Data from the current study revealed that the overall frequency of thyroid diseases and hypothyroidism and the percentages of positivity for Anti-TG-Ab, Anti-TPO-Ab, ANA, and Anti-dsDNA-Ab were higher in ITP patients than in the literature in which healthy subjects were examined. We also determined that advanced age, female sex, and Anti-TPO-Ab positivity were independently associated with hypothyroidism in ITP patients. Further studies are required to confirm our findings and identify common pathophysiological pathways and autoimmune markers of ITP and thyroid-related diseases. These relationships could contribute to the better management of ITP and related autoimmune thyroid diseases.

## ETHICS

**Ethics Committee Approval:** The protocol for this study was approved by the Bakırkoy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (date: 06.12.2021, decision no: 2021-23-16).

**Informed Consent:** Since this study was retrospective, patient consent was not required.

## FOOTNOTES

### Authorship Contributions

Surgical and Medical Practices: D.Y., E.G., F.A., Concept: D.Y., E.G., K.A., F.A., Design: D.Y., E.G., K.A., F.A., Data Collection or Processing: K.A., F.A., Analysis or Interpretation: E.G., F.A., Literature Search: E.G., Fa.A., F.A., Writing: E.G., Fa.A.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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Research

# Is Submuscular Plating as Effective and Safe as Elastic Stable Intramedullary Nailing for Pediatric Diaphysial Fractures of the Femur?

## Pediyatrik Femur Diyafiz Kırıklarında Submusküler Plaklama, Elastik Çivileme Kadar Etkili ve Güvenli midir?

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## ABSTRACT

**Objective:** The aim of this study was to compare outcomes of submuscular plating (SMP) and elastic stable intramedullary nailing (ESIN) techniques in pediatric diaphysial fractures of the femur. We hypothesize that SMP technique is as safe and effective as ESIN technique for treating diaphysial fractures of the femur.

**Methods:** Hospital database was searched for surgically treated diaphysial femur fracture patients between January 2018 and January 2022. Patients were separated into two groups. Group A (n=23) consisted of patients treated with SMP technique and Group B (n=26) consisted of patients treated with ESIN technique. Age, gender, injury mechanism, length of hospital stay, union, complications, shortening, operation time and surgical techniques were evaluated. In order to assess post-operative outcomes, criteria described by Flynn were used [9]. In order to evaluate functional outcomes, hip and knee range of motion (ROM) were measured.

**Results:** Median values of age, gender and injury mechanism distributions as well as mean hospital stay, union ratio, open reduction ratio and mean time of surgery were similar. Time to visible callus and subsequent mobilization was significantly less in group A (3.7 weeks) compared to group B (4.3 weeks). (p<0.001). Clinical, functional and radiological outcomes were statistically similar.

**Conclusion:** Our study demonstrates that both SMP and ESIN methods provide high rates of union with satisfying clinical, radiological and functional outcomes. SMP is associated with earlier callus formation and patient mobilization. SMP technique may be as safe and as effective as ESIN technique for pediatric diaphysial fractures of femur.

**Keywords:** Elastic nailing, Femoral fracture, Submuscular plating

## ÖZ

**Amaç:** Pediyatrik femur şaft kırıklarının tedavisinde submusküler plaklama (SMP) ve elastik çivileme (ESIN) tekniklerini karşılaştıran yayınlar azdır. Pediyatrik femur şaft kırıklarının tedavisinde SMP tekniğinin de ESIN tekniği kadar etkili ve güvenilir bir tedavi yöntemi olduğu hipotezini kurduk.

**Gereç ve Yöntem:** Hastane veritabanı cerrahi olarak tedavi edilmiş pediyatrik femur şaft kırıkları açısından Ocak 2018 ve Ocak 2022 yılları arasını içermek üzere tarandı. Hastalar iki gruba ayrıldı. Grup A (n=23), SMP tekniği ile tedavi edilen hastalardan oluşurken grup B (n=26) ise ESIN tekniği ile tedavi edilen hastalardan oluşmaktaydı. Yaş, cinsiyet, yaralanma mekanizması, hastanede kalış süresi, kaynama, komplikasyonlar, kısalma, ameliyat süresi ve cerrahi teknikler değerlendirildi. Ameliyat sonrası sonuçları değerlendirmek için Flynn tarafından tanımlanan kriterler kullanıldı. Fonksiyonel sonuçları değerlendirmek amacıyla kalça ve diz hareket açıklığı ölçüldü.

**Bulgular:** Yaş, cinsiyet ve yaralanma mekanizması dağılımlarının median değerleri ile ortalama hastanede kalış süresi, kaynama oranı, açık redüksiyon oranı ve ortalama ameliyat süresi benzerdi. Görünür kallus ve mobilizasyona kadar geçen süre, grup B'ye (4-3 hafta) kıyasla grup A'da (3-7 hafta) anlamlı derecede daha kısaydı. (p<0,001). Klinik, fonksiyonel ve radyolojik sonuçlar istatistiksel olarak benzerdi.

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## ÖZ

**Sonuç:** Çalışmamız, hem SMP hem de ESIN yöntemlerinin tatmin edici klinik, radyolojik ve fonksiyonel sonuçlarla birlikte yüksek oranda kaynama sağladığını göstermektedir. SMP, daha erken kallus oluşumu ve hasta mobilizasyonu ile ilişkilidir. Pediatrik femur diyafiz kırıklarında SMP tekniği, ESIN tekniği kadar güvenilir ve etkili olabilir.


**Anahtar Kelimeler:** Elastik çivileme, submusküler plaklama, femur kırığı

## INTRODUCTION

Diaphysial fractures of the femur are among the most common pediatric fractures, representing approximately 2% of all childhood fractures (1). The most common injury mechanisms are falling from a height and motor vehicle accidents (2). These fractures can be unstable and challenging to treat due to strong deforming forces acting on the diaphysial region of the femur (3).

Several fixation methods have been defined for these fractures (4). Elastic stable intramedullary nailing (ESIN) fixation is the most commonly used treatment method for pediatric femoral shaft fractures (5). On the other hand, submuscular plating (SMP), which is a minimally invasive bridge plating technique, has been a standing out alternative treatment method for these fractures. Various institutions have different treatment choices that may depend on the patient's age and weight (6). However, high-quality evidence is lacking, and the ideal fixation method is highly debated among authors (7). In addition, the literature does not provide adequate information regarding the preference of a particular method among all (8).

Throughout the current literature, very few studies have compared the out-comes of SMP and ESIN. We hypothesized that the SMP technique would be as safe and effective as the ESIN technique for treating diaphysial fractures of the femur. We aimed to retrospectively compare the radiological, clinical, and functional outcomes of SMP and ESIN.

## METHODS

İstanbul Health Sciences University Kanuni Sultan Süleyman Training and Research Hospital permission was obtained (number: 2023.08.98, date: 08.10.2023). Patient-related information was gathered anonymously from the hospital database. In this study, evaluations were performed by neutral orthopedic surgeons who were not the attending surgeons of the patients and did not take any part in any of the procedures.

In this retrospective study, a hospital database was searched for patients with surgically treated diaphysial femur fracture between January 2018 and January 2022. Radiological data was obtained from Picture Archiving and Communications System, surgical data was gathered from operational notes, and clinical and functional data were acquired through out-patient clinic notes. Surgical interventions utilizing techniques other than SMP and ESIN were excluded. Fractures were classified according to the AO/OTA classification system. Patients with fractures other than AO/OTA 32A and AO/OTA 32B fractures were excluded. Pathological fractures, segmented fractures, open fractures, polytrauma patients, patients with additional ipsilateral lower extremity fracture, patients without proper follow-up, patients weighing more than 50 kg, and patients older than 18 and younger than 5 years were excluded from the study. The remaining patients were divided into two groups. Group A (n=23) consisted of patients treated with the SMP technique, and Group B (n=26) consisted of patients treated with the ESIN technique.

### Data Collection and Evaluation Criteria

Patient information was obtained from the hospital database. The following parameters were evaluated: Age, gender, injury mechanism, length of hospital stay, union, complications, shortened operation time, and surgical technique. In order to assess postoperative outcomes, the criteria described by Flynn were used (9). Radiographic presence of a callus on three of four cortices on anteroposterior and lateral views in addition to absence of pain at the fracture site was defined as a successful union. To evaluate functional outcomes, hip and knee range of motion (ROM) were measured.

### Surgical Procedure

Surgery was performed by surgeons with at least 5 years of experience. All surgeries were performed under general anesthesia with preoperative cefazolin administration. Routine preoperative planning was performed in accordance with standard fracture surgical planning techniques (10). The surgical technique utilized was according to the surgeon's preference, due to the variety of experience and training backgrounds. The SMP technique requires closed reduction and proper alignment of the fracture using fluoroscopy. In this technique, 3.5- or 4.5-mm low-contact dynamic compression plates [tuberculin skin test (TST), İstanbul, Türkiye] are used. Relative stability is the goal rather than correct fixation and compression. This technique achieves proper alignment and adequate length-stability. The plate is

placed laterally using adequate-sized mini-incisions distally and proximally without exposing the fracture site. The plate is introduced to the fracture site, where it enters from the distal femur and advances to the proximal femur. The plate should be advanced submuscularly without disrupting the periosteum. At least six cortices must be fixed to the plate at both the proximal and distal sides of the fracture site to begin early mobilization. (Figure 1). The ESIN technique requires titanium elastic nails [titanium elastic nail (TEN), TST, İstanbul, Türkiye]. Two TENs are introduced from stab incisions laterally and medially at the supracondylar region of the distal femur, followed by cortical entry just above the physical line, while closed reduction and proper alignment of the fracture are maintained. Stability is achieved by the expansile acting forces created by the TENs, which contribute to achieving proper alignment while minimizing length stability (Figure 2).

### Statistical Analysis

In this study, patiens' demographic and clinical data were evaluated by orthopedic surgeons other than the attending surgeons using descriptive statistical analyses (number, percentage, average, standard deviation etc.). The Mann-Whitney U test was used to compare the following parameters between the SMP and ESIN groups: Age, Knee ROM, hip ROM, and qualities of the surgical treatment. Furthermore, the chi-square test was utilized to compare the following parameters between the two groups: Gender, injury mechanism, and outcomes of the surgical intervention. In addition, multivariate binary logistic regression analysis was used to assess the factors affecting treatment success. For all analyses, significancy was designated as $p<0.05$. Compliance with normal distribution was assessed using kurtosis and skewness values (±1,5). The IBM SPSS Statistics 26 (IBM, Chicago, IL, USA) software was used for statistical analyses.

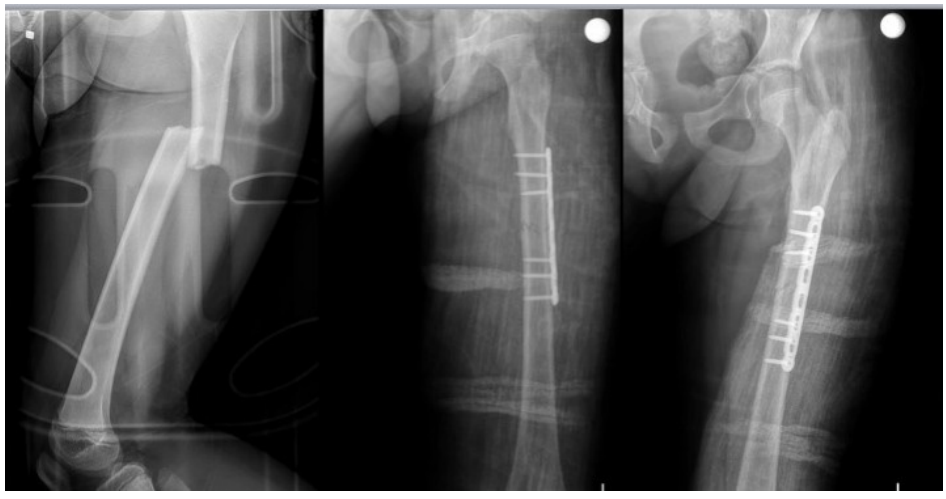

**Figure 1.** Preoperative and postoperative radiographic views of submuscular plating

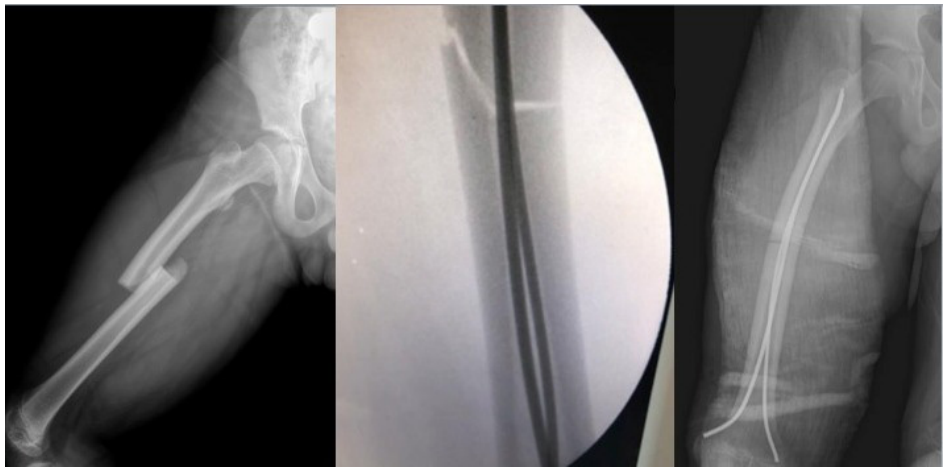

**Figure 2.** Preoperative and postoperative radiographic views of elastic stable intramedullary nailing

## RESULTS

The initial screening included 462 patients. After applying the inclusion and exclusion criteria, 49 patients were found eligible for the study. The mean age of the included patients was 9 (5-16). Thirty of the patients were male and 19 were female. According to the AO/OTA classification system, 26 patients (53%) had AO/OTA 32A fracture and 23 patients (47%) had an AO/OTA 32B fracture. The mechanism of injury was fall from a height in 34 patients (69%), motor vehicle accident in 10 patients (20 %), and other trauma mechanism in 5 patients (11%). Patients were divided into two groups depending on the surgical technique used. According to the Mann-Whitney U test, median age was similar between the two groups (p=0.384). According to the chi-square test, gender (p=0.962) and injury mechanism (p=0.765) distributions were similar between the two groups. (Table 1)

Group A consisted of 23 patients (47%) who underwent surgery using the SMP technique and group B consisted of 26 patients (53%) who underwent surgery using the ESIN technique. 13 patients in group A had an AO/OTA 32A type fracture, whereas 10 patients sustained an AO/OTA 32B type fracture. On the other hand, AO/OTA 32A-type fractures were identified in 14 patients and AO/OTA 32B-type fractures were seen in 12 patients in group B. The mean length of hospital stay was 3.3 days in Group A and 3.4 days in Group B (p=0.653). Union was achieved within 12 weeks in all patients in both groups. According to the chi-square test, no significant difference was identified regarding open reduction, as it was necessary in 6 patients (26%) in group A and in 13 patients (50%) in group B (p=0.086). According to the Mann-Whitney U test, no significant difference was identified regarding the mean time of surgery, as it was 73.9 minutes in group A and 88 minutes in group B (p=0.801). On the other hand, according to the Mann-Whitney U test, the time to visible callus and subsequent mobilization was significantly shorter in group A (3.7 weeks) than in group B (4.3 weeks). (p<0.001). (Table 2)

Postoperative outcomes were evaluated according to the Flynn criteria. These criteria consisted of leg length discrepancy (LLD), angular deformity, pain, and presence of complications. Each criterion was graded as excellent, satisfactory, or poor (8). Regarding LLD, overall excellent results were obtained in 23 patients (100%) in group A and 25 patients (96.2%) in group B (p=0.342). Regarding angular deformity, overall excellent results were obtained in 22 patients (95.7%) in group A and 24 patients (92.3%) patients in group B (p=0.626). Regarding pain, overall excellent results were obtained in 21 patients (91.3%) in group A and 25 patients (96.2%) in group B (p=0.558). Regarding complications, overall excellent results were obtained in 19 patients (82.6%) in group A and 22 patients (84.6%) patients in group B (p=0.850). These results did not show a significant difference between the two groups. (Table 3)

In order to thoroughly evaluate postoperative outcomes using the Flynn criteria, treatment results were divided into two groups entitled as "entirely excellent results" and "others". "Others" was defined as having an inferior

**Table 1.** Comparison of age, sex, and injury mechanism between the SMP and ESIN groups

| | | SMP | | ESIN | | p |
|---|---|---|---|---|---|---|
| Age (Med./25-75%) | | 9.00 | 7.00-12.00 | 8.00 | 7.00-10.00 | 0.384[a] |
| Gender (n/%) | Female | 9 | 39.1 | 10 | 38.5 | 0.962[b] |
| | Male | 14 | 60.9 | 16 | 61.5 | |
| Injury mechanism (n/%) | FFH | 16 | 69.6 | 18 | 69.2 | 0.765[b] |
| | MVA | 4 | 17.4 | 6 | 23.1 | |
| | OTHER | 3 | 13.0 | 2 | 7.7 | |

FFH: Fall from height, MVA: Motor vehicle accident, SMP: Submuscular plating, ESIN: Elastic stable intramedullary nailing, Med.: Median, a: Mann-Whitney U test, b: Chi-square test

**Table 2.** Comparison of the clinical outcomes of surgical techniques

| | | SMP | | ESIN | | p |
|---|---|---|---|---|---|---|
| Hospital stay (days) (Med./%25-75) | | 3.00 | 3.00-4.00 | 3.00 | 3.00-4.00 | 0.653[a] |
| Union (n/%) | Yes | 23 | 100.0 | 26 | 100.0 | - |
| Open reduction (n/%) | No | 17 | 73.9 | 13 | 50.0 | 0.086[b] |
| | Yes | 6 | 26.1 | 13 | 50.0 | |
| Time of surgery (Med./25-75%) | | 65.00 | 60.00-85.00 | 87.50 | 50.00-125.00 | 0.801[a] |
| Time to callus and mobilization (weeks) (Med./25-75%) | | 3.50 | 3.00-4.00 | 4.25 | 4.00-5.00 | **<0.001[a]** |

SMP: Submuscular plating, ESIN: Elastic stable intramedullary nailing, Med.: Median, [a]: Mann-Whitney U test, [b]: Chi-square test

**Table 3.** Comparison between the SMP and ESIN groups according to the outcomes related to the Flynn criteria

| | | SMP | | ESIN | | |
|---|---|---|---|---|---|---|
| | | n | % | n | % | p |
| LLD (cm) | Excellent | 23 | 100.0 | 25 | 96.2 | 0.342 |
| | Poor | 0 | 0.0 | 1 | 3.8 | |
| Angular deformity (degrees) | Excellent | 22 | 95.7 | 24 | 92.3 | 0.626 |
| | Satisfactory | 1 | 4.3 | 2 | 7.7 | |
| Pain | Excellent | 21 | 91.3 | 25 | 96.2 | 0.558 |
| | Poor | 1 | 4.3 | 1 | 3.8 | |
| | Satisfactory | 1 | 4.3 | 0 | 0.0 | |
| Complication | Excellent | 19 | 82.6 | 22 | 84.6 | 0.850 |
| | Satisfactory | 4 | 17.4 | 4 | 15.4 | |

Chi-square test result.
SMP: Submuscular plating, ESIN: Elastic stable intramedullary nailing, LLD: Leg length discrepancy

**Table 4.** Evaluation of the parameters affecting treatment success

| | B | SE | Wald | df | p | Odds Ratio | 95% CI | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | LL | UL |
| Age | .169 | .162 | 1.083 | 1 | .298 | 1.184 | .862 | 1.626 |
| Gender (Female) | -.341 | .873 | .152 | 1 | .696 | .711 | .129 | 3.936 |
| Open reduction (No) | -.584 | .810 | .520 | 1 | .471 | .558 | .114 | 2.727 |
| Surgical technique (ESIN) | -.109 | .827 | .017 | 1 | .895 | .897 | .177 | 4.536 |

R2: 0.06, X2: 1.76, p: 0.780, ESIN: Elastic stabile intramedullary nailing, Multivariate Binary Logistic Regression Analysis, n: 49, Nagekkerke

**Table 5.** Comparison of knee and hip ROM between the SMP and ESIN groups

| | SMP | | ESIN | | |
|---|---|---|---|---|---|
| | Med. | 25-75% | Med. | 25-75% | p |
| Knee Rom | 135.00 | 135.00-140.00 | 135.00 | 135.00-140.00 | 0.786 |
| Hip Rom | 140.00 | 135.00-140.00 | 135.00 | 135.00-140.00 | 0.271 |

Mann-Whitney U test. ROM: Range of motion, SMP: Submuscular plating, ESIN: Elastic stable intramedullary nailing, Med.: Median

clinical status compared to the "entirely excellent result" group, therefore being the less successful group. Next, these two groups were analyzed using multivariate binary logistic regression analysis. According to this analysis, the parameters designated in the model had no significant effect on treatment success (p>0.05). (Table 4)

Functional outcomes were evaluated by examining the knee and hip ROM using the Mann–Whitney U test. The mean range of knee flexion-extension in group A was 136.3, whereas it was 136.5 in group B (p=0.786). The mean range of hip flexion-extension in group A was 138, whereas it was 137.1 in group B (p=0.271) (Table 5).

There were two cases of superficial skin infection in the SMP group and two cases of superficial infection and two cases of skin irritation at the nail entry points in the ESIN group. The superficial skin infections of the SMP patients resolved with antibiotic therapy without the need for additional surgical intervention, whereas the ESIN patients healed after implant removal. There was a need for prolonged open surgery for two SMP patients who sought implant removal after 1 year of absence because the plate was covered up with overgrown bone tissue.

## DISCUSSION

In this study, we identified several outcomes. First, there was no significant difference in the demographic data of the SMP and ESIN groups. Second, clinical evaluation demonstrated no significant difference between the two groups, except for the time to callus and mobilization. Third, no statistically significant difference was identified between the SMP and ESIN groups according to the Flynn criteria (8). Finally, statistically similar results were obtained by evaluating the knee and hip ROM in both groups.

The main concern with both methods is malalignment due to the closed reduction technique. Edwards et al.

(11) concluded that plating diaphysial fractures of the femur in pediatric populations provides better clinical results compared with the ESIN technique. Abdelgawad et al. (12) also reported less malalignment with the SMP technique. Kanlic et al. (13) demonstrated no symptomatic malalignment in their study with 51 patients and reported excellent union in all fractures treated with the SMP technique. In contrast, Flynn et al. (9) reported excellent outcomes with the ESIN technique regarding alignment (including rotational). In our study, we found no statistically significant difference in alignment between the two groups regarding alignment (p=0.626).

Furthermore, various clinical outcomes have been reported in the literature. Regarding operation time, Allen et al. (14) reported a shorter operation time with ESIN. Caglar et al. (15) also reported longer mean operation times for SMP than for ESIN. However, we found statistically similar results when we evaluated the operation times for the two techniques (p=0.801). Regarding hospital stay, Wang et al. (16) reported a shorter duration of hospital stay. On the contrary, we found no statistically significant difference between the two groups (p=0.653). Regarding union, Reddy et al. (17) demonstrated earlier radiologic union with the ESIN technique. Interestingly, we found statistically similar results of radiologic union between the two groups. The need for open reduction was evaluated by Milligan et al. (18) in a retrospective study including 28 patients, and they found no significant difference between the SMP and ESIN groups. Our study also demonstrated similar results regarding the need for open reduction (p=0.086).

In addition, the Flynn criteria (8) were evaluated by most of the studies in the literature. Xu et al. (19) compared 39 patients treated using the ESIN technique with 28 patients treated with plate fixation and demonstrated statistically similar, excellent, and good results for both groups in their study. Sanjay et al. [20] also performed a similar evaluation using the Flynn criteria (8) in their retrospective study involving 40 patients. Our results regarding the Flynn criteria matched with the literature and we came up with statistically similar results (p=0.342 for LLD, p=0.626 for angular deformity, p=0.558 for pain and p=0.850 for complication).

Functional outcomes were also evaluated for both groups. Hip and knee ROM were measured in both patient groups by various authors. Xu et al. (19) evaluated hip and knee ROM and found similar results. In our study, all patients in both groups achieved knee and hip ROM within the functional limits. In addition, the results were statistically similar between the two groups (p=0.786 for knee ROM and p=0.271 for hip ROM).

Complication data for SMP and ESIN techniques were also evaluated by various authors. Xu et al. (19) reported similar rates of complications. Ho et al. (21) showed 22% complication rate of 22% for ESIN. In our study, the cases of superficial skin infection in both groups resolved with antibiotic therapy without the need for additional surgical intervention, whereas the ESIN patients healed after implant removal. We report similar complication rates for both techniques (p=0.850).

We believe that we have elaborated on a widely debated topic in the literature. The functional and radiological outcomes of this study may help surgeons select appropriate surgical treatment. The major limitation of this study was its retrospective nature. More objective and significant results can be obtained from randomized controlled prospective studies. Another limitation of this study was the low number of patients due to the rarity of this fracture. The number of patients can be increased by running multiple centered studies.

## CONCLUSION

The selection of surgical techniques for the treatment of pediatric diaphysial fractures is challenging. The results of this study demonstrate that both SMP and ESIN provide high union rates. Both techniques are associated with satisfactory clinical, functional, and radiological out-comes. However, according to the results of our study, SMP was associated with earlier callus formation and patient mobilization. We believe that the SMP technique may be as safe and effective as the ESIN technique for pediatric diaphysial fractures of the femur.

### ETHICS

**Ethics Committee Approval:** İstanbul Health Sciences University Kanuni Sultan Süleyman Training and Research Hospital permission was obtained (number: 2023.08.98, date:).

**Informed Consent:** In this retrospective study, a hospital database was searched for patients with surgically treated diaphysial femur fracture between January 2018 and January 2022.

### FOOTNOTES

#### Authorship Contributions

Surgical and Medical Practices: G.Ç., C.E., Concept: G.Ç., C.E., Design: G.Ç., C.E., Data Collection or Processing: O.Ç., Y.E., Analysis or Interpretation: O.Ç., Y.E., Literature Search: O.Ç., Y.E., Writing: G.Ç., O.Ç., Y.E., C.E.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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Research

# Research on the Endoplasmic Reticulum Stress-mediated Protective Effect of Melatonin against Cardiotoxicity Following Cisplatin Treatment

## Sisplatinin Oluşturacağı Kardiyotoksisiteye Karşı Melatoninin Endoplazmik Retikulum Stresi Aracılı Koruyucu Etkisinin Araştırılması

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## ABSTRACT

**Objective:** Cisplatin (CP) is a chemotherapeutic drug that causes cardiotoxicity. Melatonin (MEL) is secreted by the pineal gland throughout the night. This study aimed to investigate the protective effect of MEL against cardiotoxicity associated with CP exposure.

**Methods:** Physiological saline was applied to Group 1 (control) throughout the experiment. A single dose of CP (7 mg/kg) was administered to Group 2 on the 5th day of the experiment. Group 3 received MEL (10 mg/kg) for 7 days and CP (7 mg/kg) on day 5. MEL (10 mg/kg) was administered to group 4 for 7 days. On the 8th day of the experiment, the hearts were removed under anesthesia. Sections taken from heart tissue samples were stained with hematoxylin and eosin for histopathological evaluation. Additionally, heart tissue sections were immunohistochemically stained for 78-kDa glucose-regulated protein (GRP-78), growth arrest and DNA damage-inducible gene 153 (GADD 153), and connexins (Cx 43) expression.

**Results:** CP application caused cellular damage and disrupted heart tissue tissue integrity. At the same time, CP application caused an increase in the expression of GRP-78 and GADD 153, whereas it caused a decrease in the expression of Cx43. MEL application heals cell damage and impaired tissue integrity. However, while reducing GRP-78 and GADD153 expression; CX had an effect of increasing expression.

**Conclusion:** MEL may have a protective effect against CP-induced cardiotoxicity in rats.

**Keywords:** Cardiotoxicity, cisplatin, endoplasmic reticulum stress, melatonin, rat.

## ÖZ

**Amaç:** Sisplatin (CP), kardiyotoksisiteye neden olan kemoterapötik bir ilaçtır. Melatonin (MEL) epifiz bezinden gece boyu salgılanan bir moleküldür. Bu çalışmada CP'nin sebep olacağı kardiyotoksisteye karşı MEL'in koruyucu etkisinin araştırılması amaçlandı.

**Gereç ve Yöntem:** Grup 1'e (kontrol) deney boyunca serum fizyolojik uygulandı. Grup 2'ye deneyin 5. gününde tek doz CP (7 mg/kg) uygulandı. Grup 3'e 7 gün boyunca MEL (10 mg/kg) ve 5. günde CP (7 mg/kg) uygulandı. Grup 4'e 7 gün boyunca MEL (10 mg/kg) uygulandı. Deneyin 8. gününde aneztezi altında sıçanların kalpleri çıkarıldı. Kalp dokularından alınan kesitler histopatolojik değerlendirme için hematoksilen&eosin ile boyandı. Ayrıca kalp dokusu kesitleri GRP 78, GADD 153 ve Cx 43 ekspiresyonlarını değerlendirmek için immünohistokimyasal olarak boyandı.

**Bulgular:** CP uygulaması kalp dokusunda hücresel hasar ve doku bütünlüğünü bozucu etki göstermiştir. Aynı zamanda CP uygulaması GRP 78 ve GADD 153 ekspireyonunun artmasına sebep olurken Cx 43 ekpiresyonunun azalmasına sebep olmuştur. MEL uygulaması hücre hasarı ve

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## ÖZ

bozulmuş doku bütünlüğünü iyileştirici etki göstermiştir. Bununla birlikte GRP 78 ve GADD 153 ekspiresyonunu azaltırken; CX ekspiresyonunu artırıcı etki göstermiştir.

**Sonuç:** Sonuçlarımıza göre sıçanlarda CP'nin sebep olacağı kardiyotoksisiteye karşı MEL koruyucu etki gösterebilir.


**Anahtar Kelimeler:** Endoplazmik retikulum stresi, kardiyotoksisite, melatonin, sıçan, sisplatin

## INTRODUCTION

Cisplatin (CP) (cis-diamminodichloroplatinum II) is an antitumor agent used against various types of cancer (1). CP is effective against various tumors, such as head and neck, testicular, ovarian, cervix, bladder, and lung cancers. Despite its antitumoral effects, side effects, such as dose-related nephrotoxicity, hepatotoxicity, spermotoxicity, and cardiotoxicity, limit its clinical application (1-3). It is believed that the cytotoxic effect of CP occurs through the formation of covalent adducts between the platin compound in its structure and DNA bases (4). Studies have reported that acute and cumulative cardiovascular complications, a common side effect of CP, affect quality of life after treatment. These complications include arrhythmias, myocardial ischemia, heart failure, and ventricular hypertrophy (4, 5). These changes, which are difficult to reverse, may directly or indirectly cause patient death. Therefore, studies on the molecular mechanisms reducing CP-induced cardiotoxicity are necessary.

It is known that endoplasmic reticulum (ER) stress induces CP-induced cardiotoxicity (6). ER stress initiates myocardial cell damage associated with protein accumulation in the cell. This event is mediated by the ER chaperone 78-kDa glucose-regulated protein (GRP-78). Cells sequester GRP-78 from membrane receptors to regulate protein folding and accumulation. GRP7-8 aims to restore normal ER function by activating the unfolded protein response. If ER stress does not persist or ER homeostasis is disrupted, apoptotic cell death may occur. Apoptotic death caused by ER stress is involved in the pathophysiology of many cardiovascular diseases, as well as Huntington's disease and Alzheimer's disease (7, 8). One ER stress-mediated apoptotic pathway component is growth arrest and DNA damage-inducible gene 153 (GADD 153) (9). GADD 153, also known as Chop, is expressed at low levels under normal conditions. However, GADD 153, a leucine zipper transcription factor, is strongly expressed in response to stress. Agents that stop cell growth or damage DNA disrupt ER homeostasis by inducing the expression of GADD 153 (10). Treatment with CP increases GADD 153 expression (11). Gap junctions allow electrical connections between adjacent cardiomyocytes. These structures are formed by connexins (CX) (12). CX43 is by far the most abundant CX isoform and is widely expressed among atrial and ventricular myocyte (13).

Melatonin (MEL) was discovered by Aaron Lerner in 1958 by isolating it from the bovine pineal gland. It is chemically named 5-methoxy-N-acetyltryptamine (14). MEL is secreted at night under normal physiological conditions. MEL is an indoleamine molecule produced by the pineal gland by activation of the suprachiasmatic nucleus of the hypothalamus. It has sleep-inducing effects. It also regulates seasonal and circadian rhythms. MEL functions as a chronobiotic or endogenous synchronizer. Moreover, it induces numerous biological activities with potent antioxidant, anti-stimulant, anti-inflammatory, immunomodulatory, vasomotor, and metabolic properties. It is known that MEL plays therapeutic and protective roles against human health and diseases. These findings have made MEL an important research topic in cardiovascular research (15-17).

It has been shown in many studies that CP causes cardiotoxicity. However, studies on the protective effects of this damage are insufficient. In our study, we aimed to observe the protective effect of MEL against cardiotoxicity using histopathological and immunohistochemical methods, unlike other studies. The results of our study showed that MEL had a protective effect against CP-induced cardiotoxicity.

## METHODS

### Animals and Drug Administration

The experimental procedure was approved by Erciyes University Animal Experiments Local Ethics Committee (decision no: 23/259). The rats used in the study were obtained from Erciyes University Experimental Animal Laboratory. Forty adult male Wistar albino rats were used as subjects in the study. The weight of the rats was between 150 and 220 g, and their age was between 8 and 10 weeks. Rats were housed at 20°C–22°C under a 12:12 light/dark photoperiod and fed pellet-type feed.

### Experimental procedure

Control group (n=10): Daily intraperitoneal (i.p) isotonic solution (0.1 mg/kg).

CP group (n=10): On day 5 single dose i.p. CP (7 mg/kg) (1).

CP+MEL group (n=10): Daily i.p. MEL (10 mg/kg) + on the 5$^{th}$ day single dose i.p. CP (7 mg/kg).

MEL group (n=10): Daily i.p. MEL (10 mg/kg) (17).

Animals were sacrificed under anesthesia on the 8th day. Heart tissue samples were collected for histological and immunohistochemical examination.

### Hematoxylin&eosin (H&E) staining

Routine histological tissue monitoring was performed for histopathological evaluation. Tissues were embedded in paraffin blocks. 5 µm sections were obtained from the paraffin blocks. Sections were spread on slides. Paraffin was removed from the slides using xylol. The slides were then diluted by passing them through a series of gradually decreasing alcohol solutions. Slides were prepared using H&E staining. After staining, the slides were passed through a series of gradually increasing alcohol. Then, xylene was added. After applying the occlusion medium, the preparations were examined under a microscope (Olympus BX51, Tokyo, Japan) (18). H&E dyes were purchased from Nanotek Lab (Kayseri, Türkiye).

### Immunohistochemical staining

Immunohistochemistry was used to investigate GRP78 (bs-1219R, Bioss), GADD153 (sc-56107, SantaCruz Biotechnology, USA), and Cx43 (E-AB-30999, Elapscience, USA) immunoreactivities in heart tissue. 5 µm sections were obtained from paraffin blocks and placed on lysine slides. The sections were placed in an oven at 60 °C to remove the paraffin and were then kept. Paraffin was removed from the sections using xylol. The sections were then diluted by passing them through a series of gradually decreasing alcohol solutions. Sections were placed in sterile urine cups containing 0.01 M citrate buffer and heated in a microwave oven at 350 W for antigen retrieval. The sections were kept in phosphate buffered saline (PBS) (repeated 3 times). Sections were maintained in 3% (wt/vol) $H_2O_2$. Thus, endogenous peroxidase activity was blocked. The sample was washed with PBS. Ultra-V block solution was added to the tissues. Then, GRP-78, GADD 153, and Cx43 antibodies were added to the tissues and incubated at 4°C overnight. Tissues were washed again 3 times with PBS. The secondary antibody (TA-125-HDX, Thermo Fisher Scientific, Waltham, MA, USA) was applied at room temperature. The sample was then washed with PBS. The immune reaction was enhanced by the streptavidin-avidin-peroxidase complex. Sections were visualized using 3,30-β-diaminobenzidine tetrahydrochloride (TA-060-HDX, Thermo Fisher Scientific, Waltham, MA, USA). Gill hematoxylin was then applied. Finally, the Sections were passed through a series of gradually increasing alcohol. Then, xylene was added. After applying the occlusion medium. Images were obtained using a light microscope during preparation. The ImageJ program was used to evaluate antibody expression in the obtained images (19, 20).

### Statistical Analysis

All quantitative data were statistically analyzed using GraphPad Prism v8.0 for MacOS (GraphPad Software, La Jolla, California, USA). To determine the data's normal distribution, the D'Agostino-Pearson omnibus test was performed. The quantitative variables were compared using Kruskal-Wallis and Tukey's post hoc test. $P<0.05$ was used to determine statistically significant differences.

## RESULTS

### Microscopic Examination

In our study, histological evaluations of the heart tissue of the experimental groups were performed using H&E-stained preparations. Normally structured tissue sections are observed in the heart tissue sections of the control group. In the heart tissue sections in the group in which we applied CP, intense eosinophilic staining of cardiomyocytes, vacuolization-like cytoplasmic spaces and disorganization of muscle bundles were observed ($p<0.0001$). In the heart tissues of the group in which we applied CP and MEL, eosinophilic staining of cardiomyocytes, vacuolization-like cytoplasmic spaces, and disorganization in muscle bundles were significantly reduced ($p<0.0001$). Heart tissue sections in the group in which only MEL was applied had a normal appearance, similar to the control group. H&E-stained sections of heart tissue and histopathological scoring chart are shown in Figure 1.

### Immunohistochemical Examination

In our study, the immunoreactivity of GRP-78, GADD 153, and CX43 antibodies in sections obtained from cardiac tissues was measured. The obtained data were statistically compared. When the CP group was compared with the control group; CX43 ($p<0.01$) immunoreactivity decreased. However, GRP78 ($p<0.01$) and GADD 153 ($p<0.0001$) immunoreactivity increased. When the CP+MEL group was compared with the CP group; CX43 ($p>0.05$) immunoreactivity increased. However, GRP78 ($p<0.01$) and GADD 153 ($p<0.0001$) immunoreactivity decreased. There were no significant differences in the immunoreactivities of GRP-78, GADD 153, and CX43 between the control and MEL groups. Immunohistochemical staining showing GRP-78, GADD 153, and CX43 expression is shown in Figure 2. GRP-78, GADD 153, and CX43 immunoreactivity measurements are presented in Figure 3.

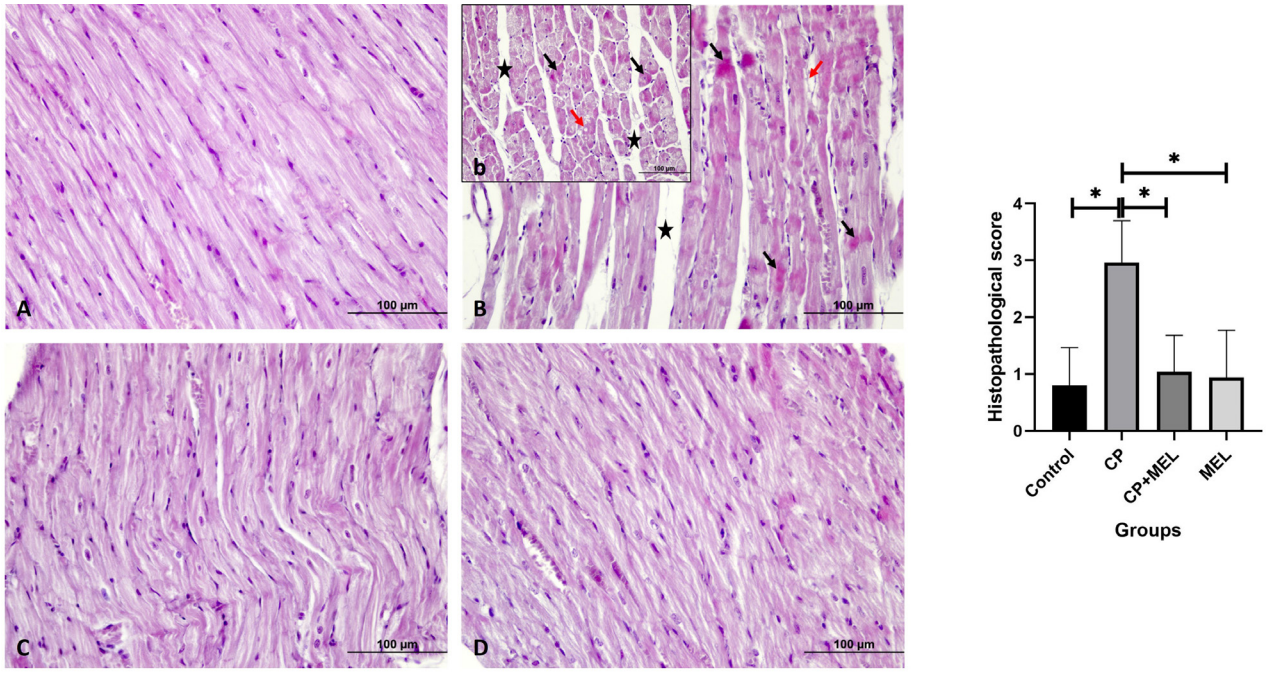


**Figure 1:** Light microscopic images taken from the hearts of the experimental groups and histopathological scoring graph. Regularly located cardiomyocytes were observed in the Control, CP+MEL, and MEL groups. In the CP group, intense eosinophilic staining of cardiomyocytes (black arrow), vacuolization-like cytoplasmic spaces (red arrow) and disorganization of muscle bundles (star) are observed. Inset photo (b) shows a cross-section of a different area belonging to the CP group. **A:** Control; **B:** CP; **C:** CP + MEL; **D:** MEL. (Hematoxylin&Eosin Staining) Olympus microscope, 400x. *p<0.0001

CP: Cisplatin, MEL: Melatonin

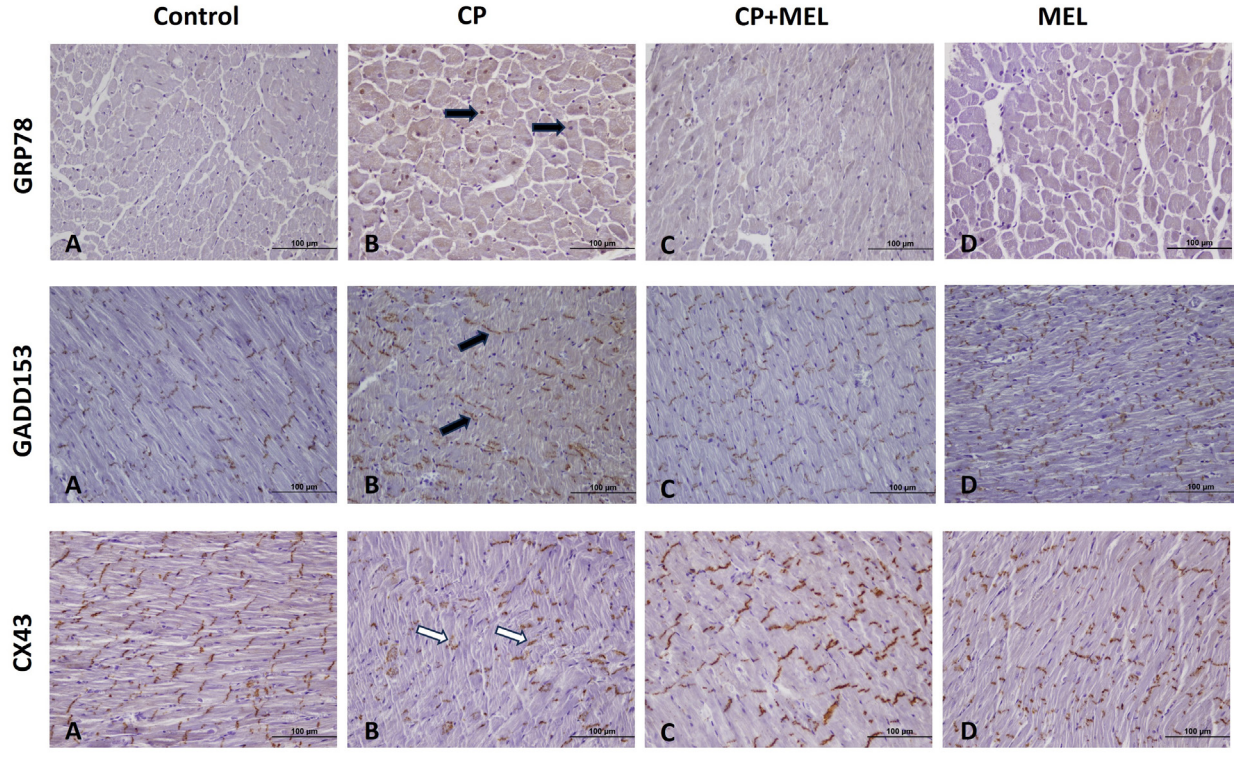


**Figure 2:** Immunohistochemical staining of GRP-78, GADD 153, and CX43 in experimental groups. The black arrow indicates immunohistochemically stained structures. The white arrows indicate structures that are not or are understained immunohistochemically. **A:** Control; **B:** CP; **C:** CP + MEL; **D:** MEL. Immunohistochemical staining, Olympus microscope, ×400.

CP: Cisplatin, MEL: Melatonin, GRP-78: 78-kDa glucose-regulated protein, GADD 153: Growth arrest and DNA damage-inducible gene 153

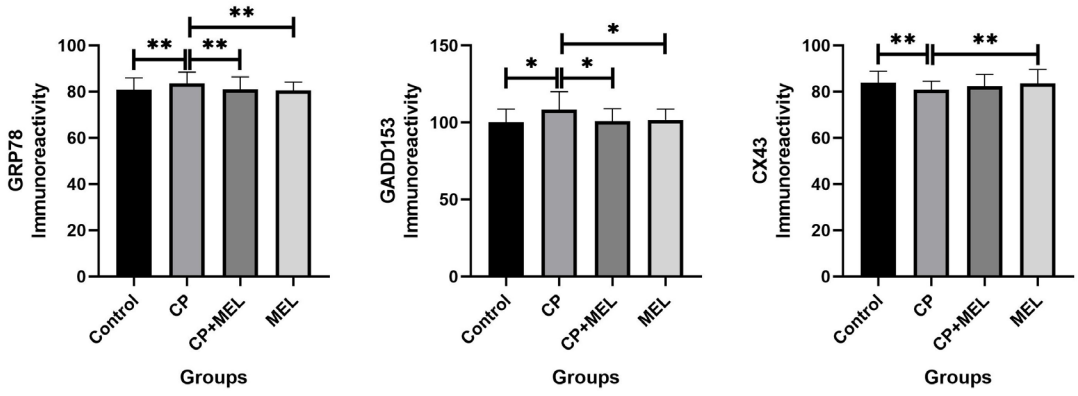


**Figure 3:** Statistical analysis of the immunoreactivity of GRP-78, GADD 153, and CX43 in the experimental groups. *p<0.0001 **p<0.01. GRP-78: 78-kDa glucose-regulated protein, GADD 153: Growth arrest and DNA damage-inducible gene 153

## DISCUSSION

Cardiac toxicity is a significant problem and a burden in patients with cancer. Cardiotoxicity induced by CP, which is used in various cancer treatments, occurs by triggering ER stress and causing damage to CXs. These changes may also disrupt the functionality of the heart by triggering apoptosis (7, 21). The aim of this study was to investigate the potential protective role of MEL against CP-induced cardiac toxicity in rats, focusing on the pathophysiological pathways. For this purpose, in our study, we performed histopathological and immunohistochemical evaluations to investigate the protective effect of MEL against CP-induced cardiotoxicity.

Various studies have shown that CP has a damaging effect on cardiomyocytes. In a study conducted on rat experimental models with a single dose of CP, acidophilic stained sarcoplasm and degenerated and separated muscle fibers were observed (21). In a study in which CP was applied chronically, muscle fibers were shown to degenerate and separate. Additionally, in the same study, cardiomyocytes had irregular or shrunken nuclei and cytoplasmic vacuoles were formed in some areas (6). Studies have revealed that CP application causes cardiomyocyte damage and muscle fiber separation. Similar to other studies, in our study, intense eosinophilic staining of cardiomyocytes was observed in the heart sections of CP-treated rats. In addition, vacuolization-like cytoplasmic spaces and disorganization of muscle bundles are observed in heart sections. These damages were significantly reduced in the heart tissue sections of CP-treated rats treated with MEL. These results show that MEL protects against histopathological damage caused by CP in the heart. At the same time, the mechanism underlying this protective effect needs to be elucidated. For this purpose, we also evaluated the immunoreactivities of GRP-78, GADD 153, and CX43 in our study.

CP-induced cardiotoxicity is associated with ER stress. ER stress induces apoptotic cell death. Excessive GRP78 and GADD153 expression triggers ER stress and ultimately causes apoptotic cell death (6, 7, 9). Saleh et al. (7), in their study in which they applied a single dose of CP, stated that GRP78 activation increased and therefore the cells would tend to undergo apoptosis. Chowdhury et al. (22) reported that single-dose CP treatment increased GRP78 expression in the heart and apoptotic cell death occurred through ER stress. Various studies have reported that CP induces ER stress-mediated apoptotic cell death in the heart. In our study, it was shown immunohistochemically that GRP-78 expression increased with CP application. The decrease in GRP-78 activation in rats treated with MEL as a protective agent indicates that ER stress will decrease. These findings indicate that the tendency of cells to undergo apoptosis will also decrease.

Another apoptotic pathway component that disrupts ER stress is GADD-153. GADD-153, a DNA damage susceptibility gene, can be highly induced by genotoxic agents. The levels of GADD-153, which is also a transcription factor, increase in response to stress (10, 23). An in vitro study showed that cardiomyocytes tend to undergo apoptosis under mechanical stress, and GADD-153 expression increases in these cells (24). According to D'Abrosca et al., protein folding can be significantly disrupted under certain physiological and pathological conditions, leading to ER stress. GADD-153 activation increased ER stress and induced apoptosis (25). In our study, we immunohistochemically determined the expression of the transcription factor GADD-153, which causes the initiation

of apoptosis in cardiomyocytes. We found that GADD-153 expression increased in the heart tissue of rats treated with CP and that MEL treatment reduced this expression level. These findings show that MEL exerts a protective effect against GADD-153- mediated apoptosis caused by CP.

As mentioned above, preventing CP-mediated apoptotic cell death is an important treatment approach for heart tissue. In addition, gap junction connections are required to ensure interaction between cardiomyocytes and to preserve tissue integrity. The structure of these channels that transmit action potentials consists of CX proteins. The most common isoform in the heart is CX43. Damage to CX43 may cause a decrease in the conduction velocity (26). In fact, Cx43 abnormalities are common in all cardiovascular diseases with impaired rhythms and conduction (27). This abnormality in cardiovascular diseases encouraged us to investigate whether there is a change in CX43 expression with CP application. In this study, we demonstrated that CX43 expression in heart tissue decreased with CP application. In diseased heart tissue, CX43 is downregulated and impairs heart function (13). CP-induced damage to CX43, which is common in atrial and ventricular myocyte, also indicates that cardiac functions and electrical stability will be impaired (21). The MEL dose used in our study improved CX43-related damage to a certain extent. However, different doses of MEL to be used in future studies may lead to a more effective improvement of CX43.

In conclusion, previous studies have shown that MEL has therapeutic effects in many tissues (28-30). In this study, MEL was applied to prevent CP from damaging rat heart tissue. There was improvement in the cardiomyocytes in the heart tissue of rats administered MEL together with CP and in the disorganization of muscle bundles. In addition, MEL prevented ER stress, a mediator that causes apoptosis. However, it can also protect against damage that may occur at gap junctions.

As a result, we determined that CP affects many organs and causes serious histopathological damage to the heart tissue. It has been shown that MEL, given for preventive purposes to prevent this damage, may protect the heart. Some mechanisms of this protective effect were revealed in our study. More research is needed to uncover the exact mechanism of MEL's protective effect on the heart.

## ETHICS

**Ethics Committee Approval:** The experimental procedure was approved by Erciyes University Animal Experiments Local Ethics Committee (decision no: 23/259, date: 07.12.2023).

**Informed Consent:** Since this research was conducted on animals, patient consent was not required.

## FOOTNOTES

### Authorship Contributions

Surgical and Medical Practices: T.C., M.Ü., E.K., A.T.A., N.K., D.K., Concept: T.C., M.Ü., B.Y., Design: T.C., M.Ü., B.Y., Data Collection or Processing: T.C., E.K., A.T.A., N.K., Analysis or Interpretation: T.C., M.Ü., E.K., A.T.A., N.K., D.K., B.Y., Literature Search: T.C., M.Ü., D.K., B.Y., Writing: T.C., M.Ü., D.K., B.Y.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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Research

# Single-center Surgical Outcomes of Arteriovenous Fistula Aneurysms in Patients with Chronic Renal Failure

## Kronik Böbrek Yetmezliği Hastalarında Arteriyovenöz Fistül Anevrizmalarının Tek Merkezli Cerrahi Sonuçları

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## ABSTRACT

**Objective:** To evaluate the surgical outcomes of arteriovenous fistula (AVF) aneurysm repair in patients with chronic renal failure (CRF) at a single center.

**Methods:** This retrospective study included 87 patients with CRF and AVF aneurysms treated between January 2012 and January 2023. Data on demographic characteristics, comorbid conditions, aneurysm characteristics, surgical procedures, and postoperative outcomes were collected. The primary endpoints were early (0-48 hours) and late (>48 h) complications, in-hospital mortality, and length of hospital stay.

**Results:** The mean age of the participants was 53.2±10.1 years, with 60.9% being male. The mean AVF flow rate was 897.6±328.9 ml/min. True aneurysms constituted 83.9% of the cases, with a mean diameter of 41.9±3.9 mm. The most common types of AVF aneurysm were radiocephalic (69.0%) and brachiocephalic (25.3%). Surgical indications included hand edema/skin laceration (41.4%), asymptomatic (26.1%), and extremely threatening ischemia (7.2%). No mortality was observed, and the average length of hospital stay was 2.4±0.9 days. Early complications included hematoma (2.3%) and bleeding (2.3%), whereas late complications included stenosis/thrombosis (4.6%), high-flow (2.3%), arterial steal syndrome (2.3%), and infection (3.4%).

**Conclusion:** Surgical treatment of AVF aneurysms in patients with CRF is effective and safe, with low complication rates and no in-hospital mortality. The most common types of AVF aneurysm were radiocephalic and brachiocephalic. Further multicenter prospective studies are needed to validate these findings and explore their long-term outcomes.

**Keywords:** AVF aneurysm, CRF, hemodialysis access, postoperative complications, surgical outcomes

## ÖZ

**Amaç:** Bu çalışmanın amacı, kronik böbrek yetmezliği (KBY) olan hastalarda arteriyovenöz fistül (AVF) anevrizma onarımının cerrahi sonuçlarını değerlendirmektir.

**Gereç ve Yöntem:** Bu retrospektif çalışma, Ocak 2012 ile Ocak 2023 arasında AVF anevrizması tedavi edilen 87 KBY hastasını içermektedir. Demografik veriler, eşlik eden hastalıklar, anevrizma özellikleri, cerrahi işlemler ve postoperatif sonuçlar hakkında veriler toplanmıştır. Birincil sonuç ölçütleri erken (0-48 saat) ve geç (>48 saat) komplikasyonlar, hastane mortalitesi ve hastanede kalış süresiydi.

**Bulgular:** Katılımcıların yaş ortalaması 53,2±10,1 yıl olup, %60,9'u erkekti. Ortalama AVF akış hızı 897,6±328,9 ml/dak idi. Gerçek anevrizmalar olguların %83,9'unu oluşturmakta olup, ortalama çapları 41,9±3,9 mm idi. En yaygın AVF anevrizma tipleri radiosefalik (%69,0) ve brakiosefalik (%25,3) idi. Cerrahi endikasyonlar arasında el ödemi/cilt yaralanması (%41,4), asemptomatik (%26,1) ve ekstremiteyi tehdit eden iskemik (%7,2) durumlar bulunmaktaydı. Hastane mortalitesi gözlenmemiş olup, ortalama hastanede kalış süresi 2,4±0,9 gündü. Erken komplikasyonlar hematom (%2,3) ve kanama (%2,3) iken, geç komplikasyonlar stenoz/tromboz (%4,6), yüksek akım (%2,3), arteriyel çalma sendromu (%2,3) ve enfeksiyon (%3,4) olarak kaydedilmiştir.

**Sonuç:** KBY hastalarında AVF anevrizmalarının cerrahi tedavisi etkili ve güvenlidir, düşük komplikasyon oranları ve hastane mortalitesi yoktur. En yaygın AVF anevrizma tipleri radiosefalik ve brakiosefaliktir. Bu bulguları doğrulamak ve uzun dönem sonuçları araştırmak için daha fazla çok merkezli prospektif çalışmalara ihtiyaç vardır.

**Anahtar Kelimeler:** AVF anevrizması, KBY, hemodiyaliz erişimi, ameliyat sonrası komplikasyonlar, cerrahi sonuçlar

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## INTRODUCTION

An arteriovenous fistula (AVF) is the most commonly used vascular access site for hemodialysis in patients with chronic renal failure (CRF). Approximately 60-70% of CRF patients undergoing routine hemodialysis worldwide utilize AVFs because of their superior long-term patency and lower rates of complications compared with other vascular access options, such as central venous catheters and grafts (1). AVFs are preferred because they offer a reduced risk of infection and thrombosis over extended periods, which are critical factors in the management of patients requiring chronic hemodialysis (2).

Although AVFs are beneficial for long-term hemodialysis, they are associated with certain complications (3). A significant complication is aneurysm formation, which is characterized by localized vessel wall dilations that can lead to severe morbidity if not adequately managed (4). Aneurysm formation in AVFs is associated with high blood flow rates, repeated needle insertions, and pre-existing vascular pathology in patients with CRF (5). These aneurysms present risks, including rupture, thrombosis, and infection, which necessitate timely surgical intervention to preserve AVF patency and functionality. Studies have reported that aneurysms develop in up to 25% of patients with AVF, emphasizing the need for continuous monitoring and proactive management (6).

The Valenti and Balaz typing systems are used to categorize AVF aneurysms, with each providing a structured approach to assess aneurysms based on various clinical parameters. The Valenti typing system focuses on the morphological characteristics of the aneurysm, including the size, location, and extent of the arterial wall. In contrast, the Balaz typing system emphasizes hemodynamic aspects, such as blood flow dynamics within the aneurysm, and the potential risks of rupture or thrombosis (7). These typing systems are crucial for guiding the selection of appropriate surgical interventions and ensuring that the chosen technique is best suited to the specific characteristics of the aneurysm. Incorporating these classifications into clinical decision-making helps optimize patient outcomes by tailoring surgical strategies to individual needs of patients with AVF aneurysms.

Surgical repair of AVF aneurysms is a critical procedure to prevent life-threatening complications and ensure continued use of the fistula for hemodialysis (8). Various surgical techniques, such as aneurysmectomy and vascular reconstruction, have been used to address this issue. However, the outcomes of these interventions can vary significantly based on patient-specific factors, the size and location of the aneurysm, and the presence of comorbid conditions (9). Standardized treatment protocols and comprehensive studies are required to evaluate the efficacy of different surgical approaches and optimize patient outcomes (10).

The primary objective of this study was to evaluate the surgical outcomes of AVF aneurysm repair in patients with CRF treated at our center. We aimed to identify factors associated with successful surgical outcomes and to analyze the incidence and types of postoperative complications. Additionally, we sought to establish guidelines for the optimal management of AVF aneurysms based on our findings to enhance the safety and efficacy of surgical interventions in this high-risk patient population.

## METHOD

### Study Location and Ethics Approval

This study was conducted at the Department of Cardiovascular Surgery, which is a tertiary center. This study was approved by the Bakırkoy Dr. Sadi Konuk Training & Research Hospital (decision no: 2023-24-19, date: 18.12.2023).

### Study Design and Population

This retrospective study analyzed the medical records of patients with CRF and AVF aneurysms treated between January 2012 and January 2023. A total of 87 patients with CRF who developed AVF aneurysms were included in the study.

Patients were included if they had an AVF aneurysm with a diameter greater than 35 mm, had not previously undergone aneurysm surgery, did not have aneurysms in other arteries or veins, and were between the ages of 20 and 65 years. The exclusion criteria were AVF aneurysm diameter 35 mm, history of aneurysm surgery, presence of aneurysms in other arteries or veins, and an age outside the 20 to 65-year range.

### Data Collection

The retrospective data collection included demographic data (age, sex, body weight, and height), comorbid conditions (diabetes mellitus, chronic obstructive pulmonary disease, peripheral artery disease (PAD), coronary artery disease), laboratory values, and body mass index. AVF aneurysms were categorized as radiocephalic, brachiocephalic, brachiobasilic, or snuff box. Indications for AVF aneurysm repair included a pulsatile mass, coldness, and numbness in the hand, hand edema, and skin laceration; heart failure; rupture; limb-threatening ischemia; embolism; and aneurysm infection.

### Surgical Details

The documented surgical procedures included plication, arteriotomy constriction and plication, aneurysm excision (Figure 1) and new AVF creation, saphenous vein or graft interposition, and ligation with AVF creation. The location, method, technique, and duration of each surgical intervention were described in detail.

Patients who experienced late complications, such as stenosis or thrombosis, occurred, the patients underwent surgical revision. In cases where thrombosis was detected, embolectomy was performed, while stenosis was managed by reparation of the affected AVF site. These treatment approaches ensure successful management of vascular complications and preservation of AVF function. For patients undergoing AVF revision, temporary dialysis catheters were inserted to maintain dialysis access during the revision period. This approach ensured that patients were able to continue their necessary dialysis treatments without interruption until the revised AVF was fully functional.

The selection of surgical procedure was primarily guided by our extensive experience with aneurysm repair. The decision-making process involved evaluating whether the aneurysm was infected or not. An infection requires a more aggressive surgical approach, whereas non-infected aneurysms are managed with standard repair techniques.

**Figure 1.** Total aneurysm excision

### Postoperative Data

Postoperative data collection focused on early complications (within the first 48 h), such as hematoma, thrombosis, and bleeding, and late complications (after 48 h), including stenosis and thrombosis, high flow, arterial steal syndrome, and infection. The Valenti and Balaz classifications were used to classify AVF aneurysms. Additionally, postoperative laboratory values, length of hospital stay, presence of wound infections, hematoma, neurological damage, and ischemia were recorded.

### Ethical Considerations

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This comprehensive evaluation aimed to enhance the understanding of AVF aneurysm management in patients with CRF and improve clinical outcomes through evidence-based practices.

### Statistical Analysis

Statistical analysis of the data was performed using the Statistical Package for the Social Sciences version 27.0. Continuous variables are expressed as mean±standard deviation, and categorical variables are presented as numbers and percentages (%). Demographic data, clinical characteristics, surgical procedures, and postoperative outcomes are summarized in tables, providing a statistical overview of data distribution. These analyses provided a comprehensive profile of surgical outcomes in patients with CRF undergoing AVF aneurysm repair.

## RESULTS

Participants had a mean age of 53.2±10.1 years. Of the participants, 53 were male, representing 60.9% of the study population. The majority of participants (n=58 ) reported smoking. Hypertension (4) was observed in 35 participants (40.2%), whereas 53 (60.9%) had diabetes mellitus (10). Chronic obstructive pulmonary disease (COPD) was present in 36 participants (41.4%), PAD in 43 (49.4%), and coronary artery disease (CAD) in 34 (39.1%). In addition, 46 participants (52.9%) had hypercholesterolemia (Table 1).

The mean flow rate of AVF aneurysms was 897.6±328.9 ml/min. Among the aneurysms, 73 (83.9%) were classified as true and 14 (16.1%) as false. The mean diameter of the aneurysms was 41.9±3.9 mm. The types of AVF aneurysms were radiocephalic (69.0%), brachiocephalic (25.3%), brachiobasilic (3.4%), and snuffbox (2.3%). Regarding

indications for AVF aneurysm repair, 26.1% of the patients were asymptomatic, 5.4% had a pulsatile mass, 4.5% had hand coldness and numbness, and 41.4% had hand edema/skin laceration. Heart failure, extremity-threatening ischemia, embolism, and aneurysm infection were present in 4.5 %, 7.2%, 7.2%, and 3.6% (Table 2).

In the Valenti classification, Type 1a was observed in 3 patients (3.4%), Type 1b in 4 patients (4.6%), Type 2a in 41 patients (47.1%), Type 2b in 17 patients (19.5%), Type 3 in 8 patients (9.2%), and Type 4 in 14 patients (16.1%). According to the Balaz classification, type 1 aneurysms were the most common (58 patients (66.7%). Type 2a was observed in six patients (6.9%), type 2b in seven patients (8.0%), type 2c in two patients (2.3%), type 2d in five patients (5.7%), and type 3 in nine patients (10.3%). No type 4 aneurysms were observed (Table 3).

Local anesthesia was used in 33 patients (37.9%), general anesthesia in 49 patients (56.3%), and upper extremity nerve block in 5 patients (5.7%). Regarding surgical procedures, plication was performed in 22 patients (25.3%), arteriotomy constriction and plication in six patients (6.9%), aneurysm excision with the creation of a new AVF in 52 patients (59.8%), saphenous vein/graft interposition in three patients (3.4%), and ligation with AVF creation in four patients (4.6%) (Table 4).

Hospital mortality was not observed in any of the patients, and all 87 patients (100.0%) survived. The mean length of hospital stay was 2.4±0.9 days. In terms of early complications (0-48 hours), 83 patients (95.4%) had no complications, whereas hematoma occurred in two patients (2.3%) and bleeding occurred in two patients (2.3%). Thrombosis was not observed in any patient during the study period. Seventy-six patients (87.4 %) experienced no late complications (after 48 h). Stenosis or thrombosis was noted in four patients (4.6%), high flow in two patients (2.3%), arterial steal syndrome in two patients (2.3%), and infection in three patients (3.4%) (Table 5).

**Table 1.** Baseline characteristics of the study population

| | Mean±SD/N (%) |
|---|---|
| **Age** | 53.2±10.1 |
| **Gender (male)** | 53 (60.9) |
| **Smoke** | 58 (66.7) |
| **HT** | 35 (40.2) |
| **DM** | 53 (60.9) |
| **COPD** | 36 (41.4) |
| **PAD** | 43 (49.4) |
| **CAD** | 34 (39.1) |
| **Hypercholesterol** | 46 (52.9) |

Values are expressed as mean±standard deviation and number (percentage). HT: Hypertension:, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, PAD: Peripheral artery disease, CAD: Coronary artery disease, SD: Standard deviation

**Table 2.** Characteristics and Indications for AVF aneurysm repair

| | | Mean±SD/N (%) |
|---|---|---|
| **Flow Rates (ml/min)** | | 897.6±328.9 |
| **Type Of Aneurysm** | True | 73 (83.9) |
| | False | 14 (16.1) |
| **Diameter of the aneurysm (9)** | | 41.9±3.9 |
| **AVF Aneurysm Types** | Radiocephalic | 60 (69.0) |
| | Brachiocephalic | 22 (25.3) |
| | Brachiobasilic | 3 (3.4) |
| | Snuffbox | 2 (2.3) |
| **AVF Aneurysm Repair Indications** | Asymptomatic | 29 (26.1) |
| | Pulsatile Mass | 6 (5.4) |
| | Hand Coldness and Numbness | 5 (4.5) |
| | Hend Eudema/Skin Laceration | 46 (41.4) |
| | Heart Failure | 5 (4.5) |
| | Rupture | 0 (0) |
| | Extremity-threatening ischemia | 8 (7.2) |
| | Embolism | 8 (7.2) |
| | Aneurysm Infection | 4 (3.6) |

Values are expressed as mean±standard deviation and number (percentage). AVF: Anterior venous fistula, SD: Standard deviation

**Table 3.** Classification of fistula aneurysms

| | | Count | Column N % |
|---|---|---|---|
| **Valenti Classification of fistula aneurysms** | Type 1a | 3 | 3.4% |
| | Type 1b | 4 | 4.6% |
| | Type 2a | 41 | 47.1% |
| | Type 2b | 17 | 19.5% |
| | Type 3 | 8 | 9.2% |
| | Type 4 | 14 | 16.1% |
| **Balaz Classification of Fistula Aneurysms** | Type 1 | 58 | 66.7% |
| | Type 2a | 6 | 6.9% |
| | Type 2b | 7 | 8.0% |
| | Type 2c | 2 | 2.3% |
| | Type 2d | 5 | 5.7% |
| | Type 3 | 9 | 10.3% |
| | Type 4 | 0 | 0.0% |

Values are expressed as number (percentage). AVF: Anterior venous fistula

**Table 4.** Anesthesia types and surgical procedures

| | | Count | Column N % |
|---|---|---|---|
| **The type of Anesthesia** | Local | 33 | 37.9% |
| | General | 49 | 56.3% |
| | Upper extremity nerve bloc | 5 | 5.7% |
| **Surgical Procedure** | Plication | 22 | 25.3% |
| | Arteriotomy constriction and plication | 6 | 6.9% |
| | Aneurysm excision and new AVF creation | 52 | 59.8% |
| | Saphenous Vein/graft interposition | 3 | 3.4% |
| | Ligation/AVF creation | 4 | 4.6% |

Values are expressed as number (percentage). AVF: Anterior venous fistula,

**Table 5.** Hospital mortality, hospitalization duration, and complications

| | | Mean±SD/N (%) | |
|---|---|---|---|
| **Hospital Mortality** | No | 87 | 100.0% |
| | Yes | 0 | 0.0% |
| **Hospitalization (day)** | | 2.4±0.9 | |
| **Early Complications (0-48 h)** | No | 83 | 95.4% |
| | Hematoma | 2 | 2.3% |
| | Thrombosis | 0 | 0.0% |
| | Bleeding | 2 | 2.3% |
| **Late Complications (>48 h)** | No | 76 | 87.4% |
| | Stenosis/thrombosis | 4 | 4.6% |
| | High flow | 2 | 2.3% |
| | Arterial stealing | 2 | 2.3% |
| | Infection | 3 | 3.4% |

Values are expressed as mean±standard deviation and number (percentage). AVF: Anterior venous fistula, SD: Standard deviation

## DISCUSSION

The creation of AVFs in patients with CRF is crucial for effective hemodialysis treatment. However, long-term use of AVFs can lead to serious complications, such as aneurysm. This study aimed to provide a detailed analysis of the repair and outcomes of AVF aneurysms conducted at a single center. Our findings offer significant insights into the early and late complications associated with the management of AVF aneurysms, hospital mortality rates, and length of hospital stay. In addition, the identification of AVF aneurysm types and repair indications contributes to the understanding of critical factors in patient management. These results expand the current knowledge regarding the surgical treatment of AVF aneurysms in patients with CRF and provide guidance for clinical practice.

In this study, significant findings were obtained regarding the surgical repair of AVF aneurysms in patients with CRF. Postoperative AVF aneurysm repair did not cause hospital mortality, and patients had an average hospital stay of 2.4 days. Early complications included hematoma and bleeding as the most common issues, whereas late complications were dominated by stenosis/thrombosis, high-flow arterial steal syndrome, and infection. The most frequent indications for AVF aneurysm repair were hand edema and skin laceration. However, serious indications, such as pulsatile mass and extremity-threatening ischemia, are also significant. Among the AVF types, radiocephalic aneurysms were the most common. These findings highlight critical points to be considered in the surgical management of AVF aneurysms and contribute to improving patient care.

In a study published by İnan et al. (11) in 2014, surgical treatment of AVF aneurysms in 24 patients with CRF was evaluated. Most patients had radiocephalic and brachiocephalic AVF aneurysms. Similarly, in our study, the most common AVF aneurysms were radiocephalic and brachiocephalic. In a study by İnan et al. (11), complications such as wound infection, hematoma, neurological damage, and ischemia were not observed postoperatively. Consistent with our findings, no in-hospital mortality was observed following surgical intervention, and early postoperative complications were minimal. In a 2023 study by Isik and Tanyeli. (12), six different surgical methods for AVF aneurysm repair were evaluated, with a focus on early outcomes. The most commonly used surgical methods include plication, arteriotomy constriction, and plication; aneurysm excision with new fistula creation; and saphenous vein or synthetic graft interpositioning. This study did not report postoperative fistula loss or minimal early complications. Similarly, in our study, no in-hospital mortality was observed after AVF aneurysm repair, and early complications were reduced.

In a retrospective study by Yan et al. (13), open surgical interventions for AVF aneurysm repair were found to have high success rates, with lower early thrombosis rates in single-stage repair. Similarly, our study observed low early complication rates following surgical intervention, which supports the efficacy of these surgical methods.

In 2023, Corr et al. (14) discussed the management of AVF aneurysms in kidney transplant recipients. This study highlighted the importance of preserving AVFs in transplant recipients for potential future hemodialysis needs in cases of graft failure. Additionally, high-flow AVFs were associated with increased cardiac output and left ventricular remodeling. In our study, the mean flow rate following surgical repair of AVF aneurysms in patients with CRF was measured at 897.6±328.9 ml/min, emphasizing the significance of managing high flow rates. Corr et al. (14) also evaluated various surgical options for treating AVF aneurysms, such as ligation and repair. Similarly, our study used different surgical techniques to achieve successful outcomes.

The findings of this study are in significant parallel with the existing literature. In a study by Płoński et al. (15) showed that classical, endovascular, and hybrid methods for the surgical treatment of AVF aneurysms were both safe and effective. Similarly, in our study, high success and low complication rates were observed following surgical intervention. In a study by Ecevit et al. (16), the mid-term outcomes of primary repair, saphenous vein interposition, and PTFE graft interposition in the surgical treatment of AVF aneurysms were examined. The patency rates were 80% and 60% at 12 and 24 months, respectively, in patients who underwent PTFE graft interposition. Consistent with these findings, our study also achieved high success and low complication rates using various surgical methods. Ecevit et al. (16) also reported short hospital stays and the absence of serious postoperative complications, which is consistent with our findings. Pasklinsky et al. (17) focused on the management of true aneurysms in hemodialysis access fistulas. Their study found that the various surgical techniques used for AVF aneurysm treatment were safe and effective. Similarly, our study observed low complication and high success rates following surgical intervention. Additionally, Pasklinsky et al. (17) reported that serious complications were rare during long-term follow-up, and most fistulas were successfully salvaged, which is consistent with our findings (17).

This study has several limitations. First, this was a retrospective study using data collected from patient records. This can lead to potential bias in data quality and accuracy. Additionally, our study was conducted at a single center, and the findings may not be generalizable to other centers. The sample size was also limited, and further validation of the findings is needed with larger patient groups in prospective studies. Furthermore, our study lacks long-term follow-up data, and more information on the long-term outcomes of surgical treatment of AVF aneurysms.

Surgical treatment of AVF aneurysms in patients with CRF is effective and safe, as demonstrated in our single-center study. The most common types of AVF aneurysms are radiocephalic and brachiocephalic. Our findings showed no in-hospital mortality and a short hospital stay (2.4 days. Early and late complications, including hematoma, bleeding, stenosis, and infection, were minimal. These results are consistent with those of the existing literature and highlight the importance of tailoring surgical techniques. Further multicenter prospective studies with larger cohorts are needed to validate and expand upon these findings.

### ETHICS

**Ethics Committee Approval:** This study was conducted at the Department of Cardiovascular Surgery, which is a tertiary center. This study was approved by the Bakırkoy Dr. Sadi Konuk Training & Research Hospital (decision no: 2023-24-19, date: 18.12.2023).

**Informed Consent:** Since this study was retrospective, patient consent was not required.

### FOOTNOTES

#### Authorship Contributions

Surgical and Medical Practices: H.T., Y.K., Concept: H.T., G.T., Design: H.T., A.A.Y., S.T., Data Collection or Processing: H.T., S.T., G.T., Analysis or Interpretation: H.T., G.T., H.B., Literature Search: H.T., G.T., H.B., Writing: H.T., A.A.Y.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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Research

# Newly Identified Preventable Risk Factors for Neonatal Clavicle Fractures

## Yenidoğan Klavikula Kiriklari için Yeni Önlenebilir Risk Faktörleri

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## ABSTRACT

**Objective:** Despite its excellent prognosis, neonatal clavicular fracture often leads to complaints regarding the proficiency of the delivery process and increased obstetrician frustration. It is considered an unavoidable complication of birth because most risk factors are uncontrollable. This retrospective study aimed to determine the obstetric and neonatal characteristics associated with neonatal clavicular fracture at our institution.

**Methods:** The data that obtained from the medical records of newborns delivered by spontaneous vaginal delivery and clinically diagnosed with clavicular fracture along with an x-ray confirmation were retrospectively evaluated. For each infant with a clavicular fracture, a healthy infant delivered by the same obstetrical team was enrolled as the control. Fetal, maternal, and delivery factors were evaluated in the fracture and control groups.

**Results:** Among the 106 newborn clavicle fracture cases, only 75 met the inclusion criteria and were enrolled in this study. Following the inclusion criteria, 75 healthy newborns were enrolled as controls. Birth weight and fetal distress were identified as fetal risk factors. Smoking during pregnancy, maternal hypothyroidism, and complications during pregnancy were maternal risk factors. Epidural anesthesia and instrumental delivery were identified as delivery risk factors

**Conclusion:** Smoking during pregnancy, maternal hypothyroidism, and epidural anesthesia have not been identified as risk factors for neonatal clavicle fracture. The risk factors that are mostly mentioned are uncontrollable. However, smoking and epidural anesthesia are risk factors that can be prevented.

**Keywords:** Neonatal clavicle fracture, ribosomal factors, epidural anesthesia, maternal smoking, maternal hypothyroidism

## ÖZ

**Amaç:** İyi prognozuna rağmen, neonatal klavikula kırığı genellikle doğum sürecinin yeterliliği hakkında şikayetlere ve kadın doğum uzmanları için artmış strese neden olur. Bu kırıklar normal doğumun doğumun kaçınılmaz bir komplikasyonu olarak düşünülür, çünkü risk faktörlerinin çoğu kontrol edilemez. Bu retrospektif çalışmada, kuruluşumuzdaki neonatal klavikula kırığı ile ilişkilendirilen obstetrik ve neonatal özellikleri belirlemeyi amaçladık.

**Gereç ve Yöntem:** Spontan vajinal doğum (SVD) ile doğan ve klinik olarak klavikula kırığı tanısı konulan ve Röntgen ile konfirme edilen bebeklerin tıbbi kayıtlarından elde edilen veriler retrospektif olarak değerlendirildi. Klavikula kırığı olan her bebek için, aynı obstetrik ekibin doğurduğu sağlıklı bir bebek kontrol olarak alındı. Fetal faktörler, maternal faktörler ve doğum faktörleri kırık ve kontrol grupları için değerlendirildi.

**Bulgular:** SVD'ler arasında, 106 yeni doğan klavikula kırığı olgusunun sadece 75'i kriterleri karşıladı ve çalışmaya dahil edildi. Kriterleri karşılayan 75 sağlıklı yenidoğan kontrol olarak alındı. Doğum ağırlığı ve fetal sıkıntı fetal risk faktörleri olarak bulundu. Gebelik sırasında sigara içme, maternal hipotiroidizm ve gebelik sırasında komplikasyonlar yaşama maternal risk faktörleri olarak bulundu. Epidural anestezi ve enstrümantal doğum doğum risk faktörleri olarak bulundu.

**Sonuç:** Bildiğimiz kadarıyla, gebelik sırasında sigara içme, maternal hipotiroidizm ve epidural anestezi neonatal klavikula kırığı için risk faktörleri olarak şimdiye kadar belirlenmemiştir. Daha önce bahsedilen risk faktörlerinin çoğu kontrol edilemezdi. Ancak sigara içme ve epidural anestezi önlenebilir risk faktörleridir.

**Anahtar Kelimeler:** Neonatal klavikula kırığı, risk faktörleri, epidural anestezi, maternal sigara içme, maternal hipotiroidizm

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## INTRODUCTION

Clavicula is considered the most common bone fracture occurring during the delivery process, accounting for 0.2-2.9% of all births (1, 2, 3, 4). Newborn clavicular fracture generally has a good outcome, and it almost always heals spontaneously without any intervention (1, 2, 5, 6). Although it has an excellent prognosis, clavicular fracture is a cause of anxiety among parents and often leads to complaints regarding the proficiency of the delivery process and increased obstetrician frustration. In addition, it may be a source of medico legal problems for doctors, midwives, or other medical staff, considering the increasing trend of litigation in obstetrics practice.

It is thought that difficult deliveries requiring considerable traction can result in neonatal fractures (7). In addition, it is suggested that this fracture results from the compression of the fetal shoulder against the maternal symphysis pubis (2). Although the exact mechanism of clavicular fracture during delivery remains unclear, a consensus is birth trauma.

Risk factors for neonatal clavicular fracture during delivery have been previously reported. Among these risk factors; birth weight, gestational age, Apgar score, prolonged labor, shoulder dystocia, instrumental vaginal delivery, maternal age, and obesity were well decumented (1-3, 5, 8). Neonatal clavicle fracture is an unpredictable and unavoidable complication of normal birth because most risk factors are uncontrollable (9, 10). This retrospective study aimed to determine the obstetric and neonatal characteristics associated with neonatal clavicular fracture at our institution.

## METHODS

The present study retrospectively evaluated data for all neonates who had a clavicle fracture during delivery at İstanbul Medicine Hospital, Turkey, between March 2012 and March 2018. The study was approved by the medical İstanbul Atlas University Non-Interventional Scientific Research Ethics Committee of thehe affiliated university and was conducted in accordance with the principles of the Declaration of Helsinki (date: 03.05.2024, number: E-22686390-050.99-41975).

Data were obtained from the medical records of a computerized database. The variables evaluated for the study and control groups were;

**Fetal factors:** Sex, birth weight, head circumference, length, fracture side (right-left), Apgar score at 1 and 5 min, presence of neurovascular damage or other birth fractures, fetal distress findings (asfixia, sepsis, respiratuar distress syndrome…).

**Maternal factors:** Age, parity, gravidity, weight at birth, weight gain during pregnancy, comorbidities [such as diabetes mellutus (DM), thyroid problems, epilepsi…], drug treatment during pregnancy, smoking or alcohol consumption during pregnancy,pregnancy complications (gestational DM, preeclampsia, infection, hypertension…).

**Delivery factors:** Gestational age, mode of delivery (vaginal or caesarian section), epidural anesthesia, performance of episiotomy, need for oxytocic induction, presentation (vertex or Breech), and presence or absence of instrumental delivery.

A cross-check was made with the discharge notes from the obstetric records, newborn baby room or (neonatal intensive care unit) NICU and discharge notes from the orthopedic department.

All newborns were examined by attending staff in the delivery suite and again by neonatologists before discharge from the hospital. The diagnosis of clavicular fracture was established by physical examination (pseudoparalysis af an extremity, asymmetry or crepitation of the clavicular bones, edema, agitation by palpation) and confirmed radiologically (clavicular anteroposterior x-ray).

The inclusion criteria consisted of newborns delivered by spontaneous vaginal delivery and those clinically diagnosed with clavicular fracture along with an x-ray confirmation.

Newborns with brachial plexus injury, birth fractures other than clavicular or pathologic fractures, such as those observed in osteogenesis imperfecta, incomplete medical recordings, missed x-ray recordings, and those delivered by Cesarian section were excluded.

Among the spontaneous vaginal deliveries, of the 106 newborn clavicle fracture cases identified, only 75 met the inclusion criteria and were enrolled in the study. For each infant with a clavicular fracture, a healthy baby born immediately before or after surgery and delivered by the same obstetrical team was selected as the control.

### Statistical Analysis

Number Cruncher Statistical System 2007 (Kaysville, Utah, USA) program was used for statistical analysis. While evaluating the study data, Student's t-test was used in the comparison of descriptive statistical methods (Mean, Standard Deviation, Median, Frequency, Ratio, Minimum, Maximum) for two groups of variables that showed normal distribution, and Mann-Whitney U test in two group comparisons of variables that did not show normal distribution. Logistic Regression Analysis was also performed to identify risk factors associated with clavicle

fracture. Pearson's chi-square test was used to compare qualitative data. Significant differences were evaluated at least at p<0.05 level.

## RESULTS

Of 3747 spontaneous live vaginal deliveries at our medical center during the study period, 106 infants were diagnosed with clavicular fracture, with an incidence of 2,8%.

Following the inclusion criteria, the study comprised a total of 150 infants (75 with clavicular fractures and 75 health newborns. Fifty-two infants (n=78) were female, and 48 % (n=72) were male.

The fracture group included 36 males (48%) and 39 females (52%). Of these, 31 (41.3%) had left side involvement, 44 (58.7%) had right side involvement, and no bilateral cases. The fetal factors in the fracture and control groups are summarized in Table 1.

The factors that were not statistically significant (p>0.05) were gender, height, head circumference, and Apgar scores at 1 and 5 minutes.

A statistically significant intergroup difference was observed regarding the mean birth weight. Mean birth weight was higher in the fracture group than in the control group (p=0.001; p<0.01). Furthermore, statistical risk analysis showed that a 500-g increase in infant weight increased the risk of clavicular fracture by 1,924- fold [%95 confidence interval (CI): 1,269-2,918]. Another significant fetal factor was fetal distress (p=0,003; p<0,01). The presence of fetal distress complication was associated with an increased risk of fracture of the clavicle 7,653 times (95% CI: 1,663-35,227).

**Maternal factor analysis:** The maternal factors for the fracture and control groups are showed in Table 2.

The maternal characteristics that were not statistically significant (p>0.05) were age, weight, weight gain during pregnancy, parity, and gravidity.

Smoking was found to be a statistically significant risk factor for newborn clavicle fracture (p=0,003; p<0,01). Statistical risk analysis showed that smoking during pregnancy increased the risk of clavicular fracture by 4.421-fold (%95 CI: 1,546-12,643).

Considering the comorbidities of mothers; there was a statistically significant difference between two groups (p=0,026; p<0,05). The presence of comorbidities increased the risk of clavicle fracture by 2,847- fold (%95 CI: 1,104-7,343). In the additional disease group, statistical analysis showed that hypothyroidism increases the risk considerably by 4.571 times (p=0,014; p<0,05, %95 CI: 1,234-16,935).

The statistical analysis of the two groups showed that having complications during pregnancy was also a risk factor for fracture (p=0.003; p<0.01). Pregnancy complications increase the risk by 2,977-fold (%95 CI: 1,438-6,163).

**Delivery factor analysis:** Delivery factors for neonatal clavicle fracture and control groups are showed in Table 3.

The delivery factors that were not statistically significant (p> 0.05) were gestational age, oxytocic induction, episiotomy, and presentation.

**Table 1.** Assessment of newborn cruciate fractures according to fetal characteristics

| Fetal factors | | Fracture group (n=75) | Control group (n=75) | p-value | OR (%95 CI) |
|---|---|---|---|---|---|
| **Sex** | **Female** | 39 (52%) | 39 (52%) | [b]**1,000** | 1,000 |
| | **Male** | 36 (48%) | 36 (52%) | | 0.527-1,898 |
| **Weight (gr)** | Min-max (median) | 2300-4600 (3600) | 2370-4230 (3350) | [c]**0,001**** | 1,924 |
| | Mean±SD | 3543,73±450,67 | 3321,53±375,90 | | 1,269-2,918 |
| **Height (cm)** | Min-max (median) | 45-57 (52) | 45-56 (51) | [c]**0,166** | 1,101 |
| | Mean±SD | 51.17±2.53 | 50.63±2.27 | | 0.961-1,261 |
| **Head circumference (cm)** | Min-max (median) | 31-38 (34) | 32-38 (34) | [c]**0,477** | 1,090 |
| | Mean±SD | 34.48±1.42 | 34.32±1.33 | | 0.861-1,379 |
| **APGAR= 1 min** | Min-max (median) | 4-9 (8) | 7-9 (8) | [a]**0,427** | 1,000 |
| | Mean±SD | 8.03±0.68 | 8.03±0.37 | | 0.553-1,807 |
| **APGAR= 5 min** | Min-max (median) | 7-10 (9) | 8-10 (9) | [a]**0,529** | 1,158 |
| | Mean ±SD | 9.08±0.49 | 9.05±0.36 | | 0.546-2,458 |
| **Fetal distress/complication** | **Yes** | 62 (45.9) | 73 (54.1) | [b]**0,003**** | 7,653 |
| | **No** | 13 (86.7) | 2 (13.3) | | 1,663-35,227 |

[a]Mann-Whitney U Test, [b]Pearson chi-square test, [c]Student t-test, **p<0.01, SD: Standard deviation, OR: Odds ratio

**Table 2.** Assessment of newborn cruciate fracture according to maternal characteristics

| Maternal factors | | Fracture group (n=75) | Control group (n=75) | p-value | OR (%95 CI) |
|---|---|---|---|---|---|
| **Age (year)** | Min-max (median) | 20-44 (29) | 18-40 (27) | [c]**0.181** | 1,043 |
| | Mean±SD | 28.92±5.12 | 27.77±5.33 | | 0.980-1,110 |
| **Weight (kg)** | Min-max (median) | 55-113 (77) | 62-109 (76) | [c]**0.285** | 1,017 |
| | Mean ±SD | 78.73±10.96 | 76.92±9.69 | | 0.986-1,050 |
| **Weight gain (kg)** | Min-max (median) | 8-33 (16) | 8-31 (14) | [c]**0.177** | 1,041 |
| | Mean ±SD | 16.71±5.99 | 15.48±5.05 | | 0.982-1,105 |
| **Gravidity** | Min-max (median) | 1-6 (2) | 1-6 (2) | [a]**0.496** | 1,078 |
| | Mean ±SD | 2.08±1.11 | 1.99±1.13 | | 0.808-1,437 |
| | **1** | 28 (46.7) | 32 (53.3) | | |
| | **2** | 24 (50.0) | 24 (50.0) | | |
| | **≥3** | 23 (54.8) | 19 (45.2) | | |
| **Parity** | Min-max (median) | 1-5 (2) | 1-4 (1) | [a]**0.387** | 1,075 |
| | Mean±SD | 1.91±0.90 | 1.84±1.03 | | 0.770-1,501 |
| | **1** | 29 (43.3) | 38 (56.7) | | |
| | **2** | 28 (59.6) | 19 (40.4) | | |
| | ≥3 | 18 (50.0) | 18 (50.0) | | |
| **Additional medical diseases** | **No** | 58 (46.0) | 68 (54.0) | [b]**0,026*** | 2,847 |
| | **Yes** | 17 (70.8) | 7 (29.2) | | 1,104-7,343 |
| **Hypothyroidism** | **No** | 63 (84.06) | 72 (96.0) | [b]**0,014*** | 4,571 |
| | **Yes** | 12 (16.0) | 3 (4.0) | | 1,234-16,935 |
| **Smoking** | **No** | 57 (44.9) | 70 (55.1) | [b]**0,003**** | 4,421 |
| | **Yes** | 18 (78.3) | 5 (21.7) | | 1,546-12,643 |
| **Pregnancy complications** | **No** | 43 (41.7) | 60 (58.3) | [b]**0,003**** | 2,977 |
| | **Yes** | 32 (68.1) | 15 (31.9) | | 1,438-6,163 |

[a]Mann-Whitney U test, [b]Pearson chi-square test, [c]Student t-test, [d]Fisher's exact test, *p<0.05, **p<0.01, SD: Standard deviation, OR: Odds ratio, kg: Kilogram

**Table 3.** Assessment of newborn cruciate fracture according to delivery factors

| | | Fracture group (n=75) | Control group (n=75) | [b]p-value | OR (%95 CI) |
|---|---|---|---|---|---|
| **Epidural anesthesia** | **No** | 39 (39.8) | 59 (60.2) | **0.001**** | 3,404 |
| | **Yes** | 36 (69.2) | 16 (30.8) | | 1,666-6,954 |
| **Oxytocic induction** | **No** | 29 (60.4) | 19 (39.6) | **0.080** | 1,858 |
| | **Yes** | 46 (45.1) | 56 (54.9) | | 0.925-3,733 |
| **Episiotomy** | **No** | 8 (47.1) | 9 (52.9) | **0.797** | 1,142 |
| | **Yes** | 67 (50.4) | 66 (49.6) | | 0.415-3,139 |
| **Instrumental delivery** | **No** | 67 (47.9) | 73 (52.1) | **0.048*** | 4,358 |
| | **Yes** | 8 (80.0) | 2 (20.0) | | 0.894-21,256 |
| **Presentation** | **Vertex** | 63 (48.1) | 68 (51.9) | **0.220** | 1,850 |
| | **Breech** | 12 (63.2) | 7 (36.8) | | 0.685-4,995 |
| **Gestational week** | Min-max (median) | 35-41 (39) | 36-41 (39) | [c]**0,718** | 1,055 |
| | Mean±SD | 38,93±1.22 | 39.00±1.03 | | 0,792-1,402 |

[b]Pearson Chi-Square Test, [c]Student t Test, *p<0.05, **p<0.01, SD: Standard deviation, OR: Odds ratio

Epidural anesthesia was found to be a statistically significant risk factor for clavicle fracture (p=0.001; p<0.01). Statistical risk analysis showed that epidural anesthesia during delivery has an increased risk of clavicular fracture by 3,404- fold (%95 CI: 1,666-6,954).

Among the delivery factors, instrumental delivery was another significant factor was instrumental delivery (p=0.048; p<0.05). Our data showed that instrumental delivery significantly increased fracture risk by 4,358- fold (%95 CI: 0.894-21,256).

## DISCUSSION

Clavicular fractures are the most frequently encountered neonatal bone fractures (10, 11). The long-term prognosis of a fractured clavicle is very good and heals without any complications, so it is not considered a significant birth injury (2). However, in addition to increasing physician and parental anxiety, it can also create a potential risk of medicolegal issues. Therefore, it is important to identify potential preventive factors.

The mechanism underlying clavicle fracture during delivery remains unclear. It was previously suggested that fetal shoulder compression on the maternal symphysis pubis could be the reason or it may be fractured while attempting to relieve shoulder dystocia (12). However, in most cases, the fracture occurs spontaneously during vaginal delivery.

Most of the studies reported previously supported that most of the risk factors were either related to fetal physical characteristics or difficult prolonged delivery, so it was acknowledged as an inevitable complication of labor (13, 14). However, some studies have claimed that the majority of affected infants did not undergo difficult labor or delivery processes (13, 15). The current consensus is that most neonatal clavicle fractures are unavoidable complications of labor (3, 9, 10, 13, 14).

The reported incidences of neonatal clavicle fracture range between 0.2 and 4.4% (8, 11, 13-16). In our institution, we found the incidence as 2.8% and it is within the acceptable range reported previously.

In the past, many reports have investigated the potential risk factors for fetal, maternal, and delivery in neonatal clavicle fractures. The most frequently cited risk factors are birth weight, shoulder dystocia, instrumental delivery, maternal age, maternal height, maternal diabetes, prolonged labor, and low Apgar score (3, 4, 8, 9, 10, 13, 14, 15, 17). However, some of the suggested risk factors and some potential risk factors that have not been investigated have still remained controversial. This study was developed to analyze the risk factors for neonatal clavicular fractures and to compare the data with those of previous studies to clarify specific risk factors and the precautions to avoid them.

In this study, we divided possible risk factors into three groups; fetal factors, maternal factors, and delivery factors.

In the analysis of fetal factor, sex, height, head circumference, and Apgar scores at 1 and 5 min were not identified as risk factors. Although some studies suggested that lower Apgar scores at 1 st minute is associated with higher fracture risk (4, 10), most of the reports could not find any statistical significance between Apgar scores and fracture, similar to our study (3, 8, 13, 14, 16). The two fetal risk factors that we found to be significant were birth weight and fetal distress after birth. In the literature, almost all reports have shown that increased fetal weight is a risk factor for neonatal clavicle fracture (3, 4, 8, 14, 15, 17). Our statistical risk analysis showed that a 500- g increase in infant's weight increased the risk of clavicular fracture by 1,924- fold. Fetal distress was another significant fetal risk factor that reached significance in the present study. In the fracture fetal distress group, 10 patients were diagnosed with dyspnea and interned to the NICU, and 4 patients were diagnosed with sepsis and interned to the NICU. Beall et al. (17) claimed that meconium aspiration was significantly related to clavicle fractures, but we did not have any patient diagnosed with meconium aspiration in the fetal distress group.

In the analysis of maternal factors, our results were consistent with those of most of the previously reported studies that there was not any significant relationship between clavicle fractures and age, weight, weight gain during pregnancy, parity, and gravidity (3, 8-10, 13, 15, 16). Contrary to our findings, Beall et al. (17) and Ahn et al. (4) argued that advanced maternal age is significantly associated with fracture. However , most studies showed similar results regarding maternal age (3,8,10,13,15,16).

In the present study, two new maternal risk factors were: Smoking during pregnancy and maternal hypothyroidism. Our statistical analysis showed that babies to mothers who smoke during pregnancy have an increased risk of clavicular fracture by 4.421- fold, and hypothyroidi maternal hypothyroidism increases the risk by 4.571- fold. To our knowledge, these two risk factors have not been shown to be related to neonatal clavicle fracture in the literature.

Maternal smoking during pregnancy is a known cause of low birth weight, perinatal mortality, and disturbances in neurodevelopment (18, 19). The chemical toxins in tabacco, particularly nicotine, reach the fetus through the placenta and are concentrated in fetal blood at levels 15% greater than those of the mother (20). Today, nicotine has numerous

effects on the musculoskelatal system, including stimulating the sympathetic nervous system, causing vascular disturbances, inducing cell death, and decreasing bone mineral density, causing fracture-healing complications (21-23). A systematic review showed that congenital birth defects (digit anomalies, limb reduction defects, clubfoot) are associated with maternal smoking during pregnancy (18).

Many studies have shown that subclinical maternal hypothyroidism is associated with adverse obstetric outcomes and pregnancy complications, such as increased prevalence of spontaneous abortion, anemia, pre-eclampsia, gestational hypertension, placental abruption, postpartum hemorrhage, and adverse neonatal outcomes, such as premature delivery, low birth weight, and neonatal respiratory distress (24-26). Thyroid hormone is required for normal neuronal migration and myelination of the brain during fetal and early postnatal life, and hypothyroxinemia during these critical periods causes irreversible brain damage, with mental retardation and neurological abnormalities (27). In this entity, we investigated mothers diagnosed with pre-pregnancy hypothyroidism but not gestational hypothyroidism. Statistical analysis showed that hypothyroidism considerably increases the risk of developing hypothyroidism. To our knowledge, this is the first study to report the relationship between neonatal clavicle fractures and maternal hypothyroidism. Even if we can deduce that maternal hypothyroidism can be related to neonatal clavicle fractures through fetal distress and other pregnancy complications, we believe that further investigation is required to enlighten this new finding.

Encountering complications during pregnancy was also found related to clavicle fractures and pregnancy complications, increasing the risk by 2,977- fold. This entity included Rh or ABO hemolytic disease, gestational DM, gestational HT, preeclampsia, infectional diseases, and gestational hypothyroidism. Most studies did not investigate this relationship. Beall et al. (17) showed that gestational DM increases the risk, whereas Roberts et al. (9) and Chez et al. (13) showed the opposite. With a more general point of view, Kaplan et al. (14) and Peleg et al. (15) did not find any relationship between maternal complications and neonatal clavicle fracture.

Results of delivery factor analysis showed that gestational age, oxytotic induction, episiotomy, and presentation did not have an effect on neonatal clavicle fracture($p>0.05$). Our results were comparable to others, but when we looked at the literature, we saw that, like us, some authors did not find any significant relationship for gestational age (8, 15, 17). However, contrary to our findings, Chez et al. (13) and Roberts et al. (9) found that advanced gestational age ($40^{th}$ week) was related to neonatal clavicle fracture.

Among the delivery factors, instrumental delivery (vacoum and forceps) significantly increased fracture risk by 4.358-fold. This factor has been studied previously many times, and many studies supported our result (4, 8, 10), whereas some have reported reversals (3, 9, 10, 14).

Epidural anesthesia has been evaluated as a risk factor in some previous studies, but it was not considered a risk factor (3, 4, 9). However; in our study, epidural anesthesia was found to be a statistically significant risk factor for clavicular fracture and increased the risk of clavicular fracture by 3.404- fold. Epidural analgesia is associated with prolonged labor, decreased rates of spontaneous vaginal delivery, increased instrumental delivery, and fetal malposition (28, 29). We accept the instrumental delivery as a risk factor. In addition, some studies showed that prolongation of labor was related to clavicle fracture (9, 14). However, it has not been identified as a risk factor in most studies (1, 3, 4, 9). In the literature, only one report showed epidural anesthesia as a risk factor for birth trauma, but not for clavicle fracture (30).

### Study Limitations

The major limitation of this study was its retrospective design. Although our study population can be considered adequate, to assess the newly identified risk factors in this paper, prospective studies with larger sample sizes are required.

## CONCLUSION

To our knowledge, smoking during pregnancy, maternal hypothyroidism, and epidural anesthesia have not been identified as risk factors for neonatal clavicle fracture. The risk factors that are previously mentioned mostly were uncontrollable or unpredictable. However, smoking and epidural anesthesia are risk factors that can be prevented. Therefore, these two risk factors should be examined in further studies. The elimination of these factors can decrease neonatal clavicle fracture incidence.

### ETHICS

**Ethics Committee Approval:** The study was approved by the medical İstanbul Atlas University Non-Interventional Scientific Research Ethics Committee of thehe affiliated university and was conducted in accordance with the principles of the Declaration of Helsinki (date: 03.05.2024, number: E-22686390-050.99-41975).

**Informed Consent:** Since this study was retrospective, error confirmation was not required.

### FOOTNOTES

#### Authorship Contributions

Surgical and Medical Practices: S.E.B., M.T.D., Concept: S.E.B., O.B., Design: S.E.B., M.T.D., O.B., Analysis or Interpretation: M.T.D., Literature Search: S.E.B., Writing: S.E.B., M.T.D., O.B.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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Case Report

# Cases of Multiple Tracheobronchial Diverticulosis Characterized by Recurrent Pneumonia Episodes

## Tekrarlayan Pnömoniler ile Karakterize Çoklu Trakeobronşiyal Divertikülozis Olguları

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## ABSTRACT

Tracheal diverticulosis is a rare tracheal pathology that occurs in approximately 1-2% of the population. In order to draw attention to this rare tracheal pathology, we would like to present two cases in which tracheal diverticula were accompanied by bronchial diverticula. Case 1: A 58-year-old male patient presented to our outpatient clinic with a weight loss of approximately 7 kg in 1 month. Computed tomography (CT) revealed multiple tracheal diverticula in the trachea and bilateral main bronchi. Case 2: A 52-year-old male patient was admitted with complaints of right-sided pain and fever. CT and fiberoptic bronchoscopy revealed multiple diverticula in the bilateral bronchial system. Tracheal diverticula are paratracheal air cysts protruding from the tracheal wall. They are usually detected incidentally on imaging because patients are usually asymptomatic. Approximately 97% of the lesions are located in the right posterolateral wall and are usually solitary. The association between multiple and bronchial diverticula is very remarkable.

**Keywords:** Multiple, tracheal, bronchial, diverticulosis

## ÖZ

Trakeal divertikülozis, toplumun yaklaşık %1-2'sinde görülen, konjenital veya edinsel nedenlere bağlı olabilen nadir bir trakeal patolojidir. Bu nadir trakeal patolojiye dikkat çekmek amacıyla, trakeal divertikküllere, bronşial divertiküllerinin de eşlik ettiği iki olguyu sunmak istiyoruz. Olgu 1: Elli sekiz yaşında erkek hasta 1 ay içinde yaklaşık 7-8 kg kilo kaybı ile polikliniğimize başvurdu. Hastanın, son 2 yıl içinde 2 pnömoni atağı öyküsü vardı. Toraks bilgisayarlı tomografi (BT)'sinde trakea ve bilateral ana bronşlarda multipl trakeal divertiküller görüldü. Olgu 2: Elli iki yaşında erkek hasta sağ tarafta ağrı ve ateş şikayetleriyle başvurdu. BT'sinde trakea ve bronşların, geniş ve divertiküler yapıda olduğu görüldü. Fiberoptik bronkoskopi'de bilateral bronşiyal sistemde çok sayıda divertikül ve divertiküllerin orifislerinden gelen sekresyonlar izlendi. Trakeal divertiküller, trakeal duvardan çıkıntı yapan paratrakeal hava kistleridir ve hastalar genellikle asemptomatik olduğu için genellikle görüntülemelerde tesadüfen tespit edilirler. Yaklaşık %97'si sağ posterolateral duvarda bulunur ve genellikle soliterdirler. Multipl ve bronşiyal divertikül ile birlikteliği çok dikkat çekicidir.

**Keywords:** Multiple, trakeal, bronşial, divertikülosis

## Introduction

Tracheal diverticulosis is a rare tracheal pathology that occurs in approximately 1-2% of the population and may be due to congenital or acquired causes. Most cases are asymptomatic and are detected incidentally (1). In order to draw attention to this rare tracheal pathology, we would like to present two cases in which tracheal diverticula were accompanied by multiple bronchial diverticula.

## Case Reports

Case 1: A 58-year-old male patient was admitted to our outpatient clinic with a weight loss of approximately 7-8 kg within 1 month. He was admitted to an external center with left chest pain and cough 1 month ago, and he had received quinolone treatment for pneumonia. He also had a medical history of other 2 pneumonia episodes in the last 2 years. On physical examination, he had no active respiratory findings

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other than weight loss and a smoking history of 15 packs/year. Chest Computed tomography (CT) revealed multiple tracheal diverticula in the trachea and bilateral main bronchi (Figure1 A,B), in addition to findings compatible with airway disease in bilateral lungs. During follow-up, the acute phase reactants became negative, weight loss was stopped, and the patient was discharged with a follow-up plan.

Case 2: A 52-year-old male patient was admitted with right-sided pain and fever. Pleural fluid was detected in the right hemithorax, and thoracentesis was performed. Pleural fluid was determined to be an exudate, and microbiological cultures of the fluid were negative. CT revealed that the trachea and bronchi were wide and diverticular (Figure 1C,D). The patient had a history of tuberculosis for 40 years and pneumonia for 2 years. Subsequently, fiberoptic bronchoscopy (FOB) was performed. The FOB revealed multiple diverticula in the bilateral bronchial system and secretions coming from the orifices of the diverticula (Figure1 E,F) and Klebsiella pneumoniae was isolated in the bronchial lavage culture. After antibiotherapy, the patient's symptoms regressed, and he was discharged. Informed consent was obtained from both patients.

## Discussion

Tracheal diverticula are paratracheal air cysts protruding from the tracheal wall. They are usually detected incidentally on imaging because patients are usually asymptomatic (2). Although often confused with the tracheocele, the tracheocele is considered to be the presence of a single sac with a wide opening, whereas the tracheal diverticulum is defined as the presence of multiple sacs with narrow openings (3). Approximately 97.9% of the tracheal diverticula are located on the right posterolateral wall and are usually solitary (4). This finding is believed to be related to the position of the trachea, esophagus, or aorta. The supporting effect of the esophagus or aorta on the trachea is more pronounced on the left posterolateral side, whereas the right side remains partially unsupported (5).

There are two types of tracheal diverticula; congenital and acquired. In adults, tracheal diverticula are mucosal herniations that occur in weak areas of the tracheal wall due to increased intraluminal pressure and are generally thought to be caused by conditions such as chronic obstructive pulmonary disease and chronic cough. Congenital tracheal diverticula are narrower, small-necked air sacs resulting

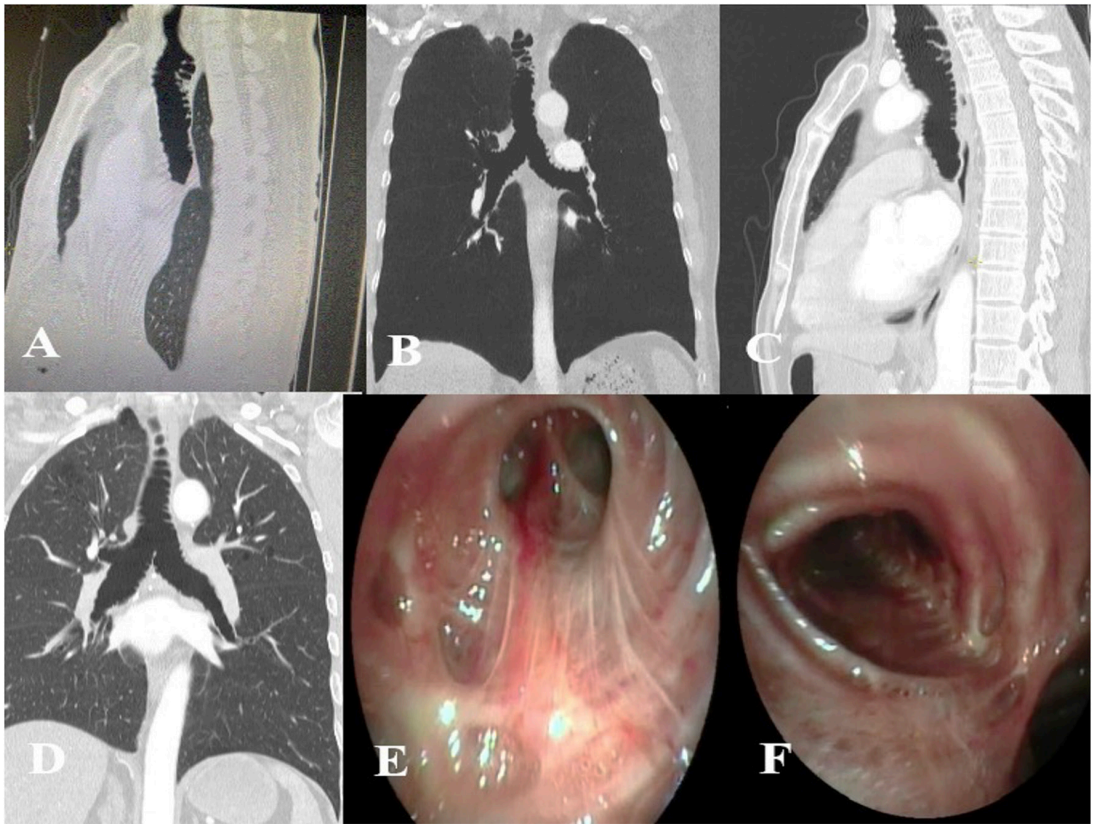


**Figure 1.** (A,B) Sagittal and coronal sections tomography of the first case. (C,D) Sagittal and coronal sections tomography of the second case. (E) Multiple infected diverticular orifices at the entrance to the right upper lobe. (F) Multiple diverticular orifices in the left main bronchus.

from defects in endodermal differentiation of the tracheal cartilage in six weeks of age. Congenital diverticula are typically filled with mucus, and they are also known as true diverticula because they involve all layers of the tracheal wall. (6). Diverticula may cause a number of complications, including recurrent infections, chronic cough, purulent sputum, hemoptysis, recurrent tracheobronchitis, and symptoms such as dysphagia, hoarseness, and odynophagia due to compression. In some cases, life-threatening abscesses may occur (7, 8).

Bronchial diverticula are less well known. In a study of thoracic CT scans of approximately 12512 patients, a total of 412 tracheal diverticula were identified in 299 patients, of which 84 (20.4%) were associated with bronchial DV (4).

CT scan and bronchoscopy are preferred for diverticulum diagnosis. CT can help determine whether the diverticulum is congenital or acquired based on the presence or absence of cartilage and the size of the diverticulum neck. Acquired diverticula tend to be larger and have more communication with the lumen. CT can also help the clinician identify various complications arising from the diverticulum and distinguish it from conditions that should be considered in the differential diagnosis, such as pharyngoesophageal (Zenker) diverticulum, blebs or bullae, or pneumomediastinum (9).

Most diverticula can be treated with mucolytic, antibiotics, or pulmonary rehabilitation. Rarely, depending on patient characteristics, symptoms, and complications, bronchoscopic laser or electrocoagulation and surgery may be required (10).

In conclusion, the tracheal diverticula were mostly single, and the association between multiple and bronchial diverticula was remarkable. During our literature search we found 2-3 studies reporting tracheobronchial diverticula (8, 9, 11). The fact that both of our patients had a history of recurrent pneumonia and originated from many different localisations as well as the right posterolateral wall may provide important information in the differential diagnosis of patients with similar clinical presentation and history.

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