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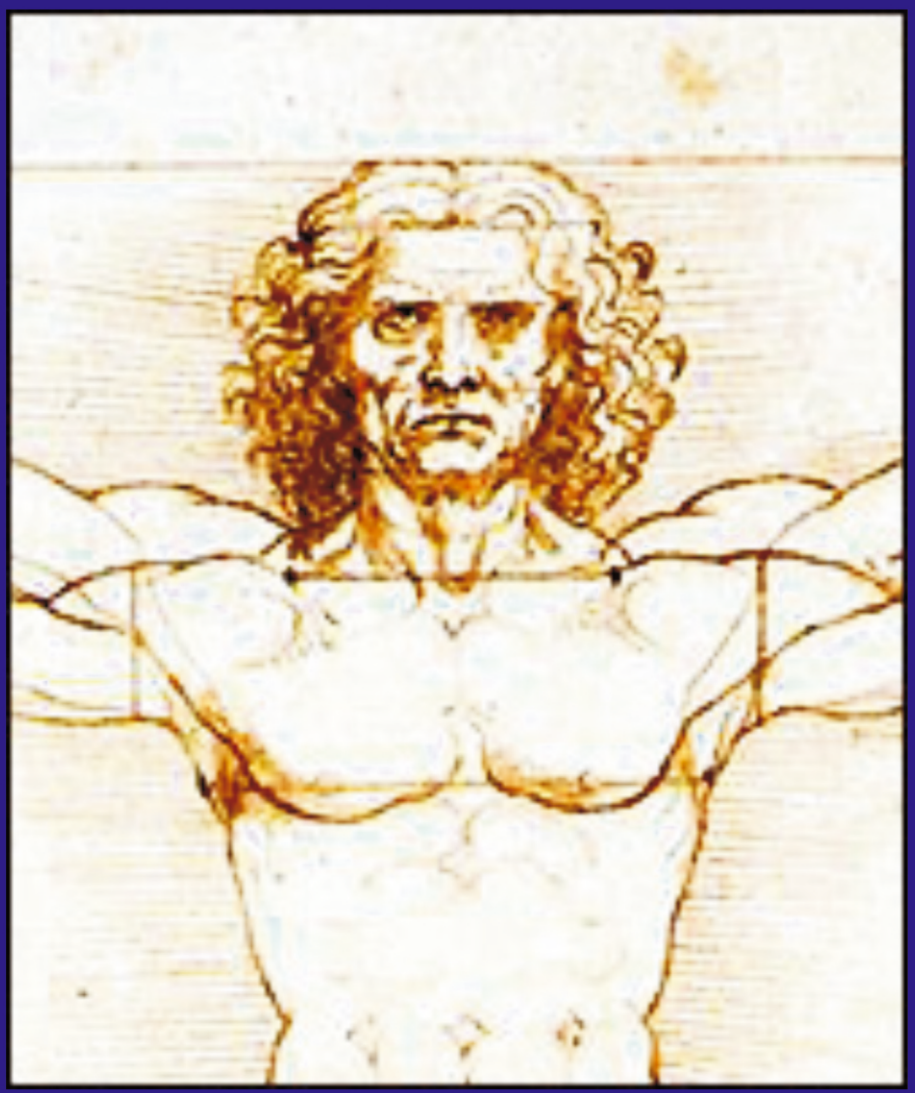

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Read to understand

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Work to be remembered

Avdo Ćeranić

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Editorial

NECROTIZING SOFT TISSUE INFECTIONS: AN UNPREDICTIBLE, LIFE-THREATENING INFECTIONS

Zogic Enes, Alihodzic Kemal, Tokovic Demir, Nicevic Aldin

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Necrotizing soft tissue infections (NSTIs) are serious and potentially fatal rapidly progressive and aggressive infections of subcutaneous tissue, fascia, and sometimes muscles (manifesting as necrotizing pyomyositis). They are characterized by rapid spread and are associated with significant morbidity and mortality (1, 2). Published studies report various incidence data for NSTIs. Chen LL reported an incidence of NSTIs of 0.3 to 15 cases per 100,000 population (3), and several other studies reported an annual incidence rate ranging from 0.72 to 9.2 per 100,000 person-years (4). NSTIs occur less frequently in children than in adults, with an incidence of 0.08 to 0.13 per 100,000 per year (5). Based on previous research and data available in the literature, they occur more often in men, accounting for up to 2/3 of all cases (6).

Regarding treatment outcomes, an important predictive factor is the patient's age, even though there is no age predilection for NSTIs. Those over 50 years of age are mostly affected and have a worse prognosis (2, 7, 8, 9). The frequency of these infections has increased in recent years, so healthcare personnel are increasingly encountering this dangerous disease.

According to earlier data from the literature, this infection is caused by polymicrobial agents, both anaerobic and aerobic bacteria. However, some studies report the prevalence of monomicrobial NSTIs to be up to 60-80%, with the causative agents most often originating from the genitourinary and digestive tracts and the skin (2).

Streptococcus pyogenes, a Gram-positive beta-hemolytic streptococcus of serological group A, is one of the most common organisms isolated in cases of NSTIs (1). If the infection is caused by Gram-negative microorganisms, the infections can take on more rapid and fulminant forms (7). According to literature data, Staphylococcus aureus plays a significant role in the development of these infections in the USA, and methicillin-resistant Staphylococcus aureus (MRSA) was isolated in 14.6% of complicated soft tissue and skin infections in a substantial number of European countries (8). An increase in Gram-negative species, predominantly Klebsiella pneumoniae and E. coli as the causes of these infections, is recorded in England (8). In the study by Jabbouru et al, among those who did not survive, the most frequently isolated microorganisms as contributors to this infection were Pseudomonas and Proteus (9). Fungal infections are rare and mostly published as case reports (1).

The most common sites of infection are the perineal region, scrotum, and anterior abdominal wall, but it can also occur on any part of the body. The usual symptoms related to this infection are local pain, general weakness, fever, and hypotension. Additionally, tissue swelling, odor, skin necrosis, erythema, crepitations, and bullous changes can occur. Visible changes on the skin are smaller than an infection of the tissues beneath the skin, so it is vital to recognize NSTIs before the present changes on the skin affect a larger area (2, 8, 9, 10). The presence of comorbidities can significantly complicate the clinical picture and make treatment more difficult. The most common comorbidity in NSTIs is diabetes mellitus, and alongside it, there are also alcoholism, arterial hypertension, chronic renal and liver failure, cirrhosis, obesity, and immunosuppression. Immunosuppressed patients are more susceptible to NSTIs, and clinical findings on physical examination may be less pronounced, with nonspecific laboratory findings, making diagnosis even more challenging (1).

For the successful treatment of this infection, one of the most important factors is early recognition or suspicion of the disease. Additionally, aggressive resuscitation of the patient, the use of broad-spectrum antibiotics until the causative agent is isolated, and subsequently administering antibiotics according to

the antibiogram, as well as early and extensive surgical intervention, are necessary. Diagnosis of NSTI is typically based on clinical presentation. Radiological imaging and laboratory tests play a crucial role in predicting infection severity and treatment outcomes. This led to the development of the LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) scoring system. The increasing misuse of antibiotics contributes to greater resistance of microorganisms, which will likely become an even more significant problem in the future (2, 11, 12). Urgent surgical treatment involving the radical removal of necrotic and devitalized tissue stands as a major determinant of favorable treatment outcomes. If the initial surgical intervention is not performed within the first 24 hours of symptom onset, the mortality rate increases significantly. Literature data indicate that up to 10 surgical debridements are conducted during treatment, with an average of 2.5. The necessity of Hyperbaric Oxygen Therapy (HBOT) in the treatment of these infections has not been definitively proven (1-10).

Authors' contributions

ZE: Writing – original draft, Conceptualization, Supervision, Validation, editing; **AK**: Investigation, Writing, Validation; **TD**: data collection, writing; **NA**: Investigation, Validation, Visualization, writing

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Original article

THE RELATIONSHIP BETWEEN GYNECOLOGIC CANCER AND REPRODUCTIVE HEALTH AWARENESS AND OBESITY IN WOMEN: A CROSS-SECTION STUDY

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Abstract: **Purpose:** This study was conducted to determine the effect of obesity awareness on gynecological cancer and reproductive health awareness in women.

Materials and Methods: This study is a cross-sectional study. The sample of the study consisted of overweight and obese women. Data were collected using the introductory information form, obesity awareness scale, and gynecological cancers awareness scale via a Google form.

Results: Obesity was found to have a statistically significant association with reproductive health, including the risk for pregnancy and baby, uterus, ovary and breast cancer, menstrual irregularity, age of first menstruation, polycystic ovary syndrome, cesarean section risk, preeclampsia, gestational diabetes, stillbirth risk, birth defects, the chance of conception, the success of fertility treatment, early menopause, osteoporosis, baby weight, and iron deficiency anemia. The total mean score Obesity Awareness Scale and Gynecologic Cancer Awareness Scale was significantly higher among those who believed in this association. A highly significant positive correlation was observed between total and sub-dimension mean scores of women's Obesity Awareness Scale and Gynecologic Awareness Scale.

Conclusion: It has been determined that obesity awareness in women is related to reproductive health and gynecological cancer awareness.

Keywords: Obesity, Gynecologic cancer, Reproductive health, Awareness.

INTRODUCTION

Obesity is characterized by the abnormal or excessive accumulation of fat in the body, posing a significant health risk. It is a substantial global public health issue that is on the rise (1). According to the World Health Organization (WHO), people with a body mass index of 25 kg/m^2 and above are overweight, while those with a body mass index of 30 kg/m^2 and above are obese.

In 2016, 13% of the world's adult population (15% for women; 11% for men) were obese (2). According to the Turkish Statistical Institute (TSI, 2019), one in five people (21.1%) in Turkey is obese (24.8% for women; 17.3% for men) (3). Obesity is more common in women than in men because of increased fat tissue, metabolic rate, mood swings, and sedentary life resulting from hormonal fluctuations (such as pregnancy, childbirth, and menopause) (4, 5, 6). Obesity in women causes cycle irregularities, polycystic ovary syndrome, infertility, risky pregnancy, and problems related to the birth process, adversely affecting reproductive health (7-10). Furthermore, obesity is associated with an increased risk of gynecologic cancers. Research shows that obesity is positively correlated with breast, endometrial, and ovarian cancer (11-14). We need to raise women's awareness of obesity to prevent gynecologic cancers and reduce its adverse effects on reproductive health (15). Women who are aware of the impact of obesity on gynecologic cancers and reproductive health may be more likely to reach and maintain a healthy weight. Research suggests that people with high awareness of obesity are better at managing body weight and improving their quality of life (16, 17). However, most women are unaware of the impact of obesity on reproductive health (18, 19). Therefore, all health professionals should counsel women regarding the consequences of obesity on reproductive health (18). While there has been a growing body of

awareness-based research in recent years, there is no research focusing on the effect of obesity awareness on gynecologic cancer and reproductive health awareness. Hence, this study aims to determine the effect of obesity awareness on gynecologic cancer and reproductive health awareness. This study will fill a gap in the literature, help us make a societal assessment, and guide health professionals in planning training and consultancy programs.

MATERIAL AND METHODS

Study Design and Participants

This cross-sectional and descriptive study aimed to evaluate the effect of obesity awareness on gynecologic cancer and reproductive health awareness in women.

The study sample comprised women residing in a southern province of Turkey diagnosed with obesity. Data collection took place in the province of Osmaniye from July to March 2021. Simple, random sampling was employed to recruit participants, ensuring an equal opportunity for all individuals in the population to be selected. A power analysis was conducted to determine the appropriate sample size, revealing that a sample of 420 participants would be sufficient to detect significant differences.

Inclusion criteria:

1. Being 18-65 years of age
2. Having no learning difficulties,
3. Having no hearing-speech problems,
4. Having no mental disorders
5. Being overweight or obese.

Exclusion criteria:

1. Having gynecologic cancer,
2. Having a hysterectomy,
3. Declining to participate,
4. Having a mental disorder
5. Having communication problems due to language differences

Data were collected using a demographic characteristics questionnaire, a Reproductive Health Awareness Form, the Gynecologic Cancer Awareness Scale (GCAS), and the Obesity Awareness Scale (OAS).

Demographic Characteristics Questionnaire; The demographic characteristics questionnaire was constructed following an extensive review of the literature by the researchers (18, 19). It comprised a total of 35 items, with 13 items assessing sociodemographic characteristics and 22 items focusing on knowledge pertaining to the impacts of obesity on reproductive health.

Obesity Awareness Scale (OAS); The Obesity Awareness Scale (OAS) was developed by Allen and adapted to Turkish by Kafkas and Özen (20, 21). The scale consists of 21 items and three subscales: obesity awareness (8 items), nutrition (7 items), and physical activity (8 items). The scale has a Cronbach's alpha of 0.872, which was 0.863 in this study.

Gynecologic Cancer Awareness Scale (GCAS); The Gynecologic Cancer Awareness Scale (GCAS) was developed by Dal and Ertem (22). The scale consists of 41 items and four subscales: (1) routine control of gynecologic cancers and awareness of serious illness perception, (2) awareness of gynecologic cancer risks, (3) awareness of prevention of gynecologic cancers, and (4) early diagnosis and information awareness in gynecologic cancers. The total score ranges from 41 to 205, with higher scores indicating higher awareness of gynecologic cancers. The scale demonstrated high internal consistency, with a Cronbach's alpha coefficient of 0.944 (22), which was found to be 0.936 in the present study.

Reproductive Health Awareness Form; The Reproductive Health Awareness Form was developed by the researchers through an extensive review of the relevant literature. The form encompassed 22 items, focusing on women's knowledge, attitudes, and perceptions regarding reproductive health.

The data were collected online (Google Docs) by the researchers between April 2021 and September 2021. Women who met the inclusion criteria were reached through social media platforms. Prior to data collection, participants were provided with detailed information regarding the research objectives and procedures. Each participant was given approximately 20-25 minutes to complete the data collection forms.

Statistical Analyses

Statistical Package for Social Sciences (SPSS) 25 program was used in the analysis of the data. Normality was tested using skewness and kurtosis values. Number, percentage, mean, standard deviation, median, and minimum-maximum values were used for descriptive data. The data were analyzed using the Mann-Whitney U test, independent samples t-test, One Way ANOVA test, Welch test, Kruskal-Wallis test, Chi-Square test, and Pearson Correlation. Cronbach's alpha analysis was also used.

RESULTS

Table 1 shows the participants' sociodemographic characteristics.

There was a significant difference in sociodemographic characteristics (marital status, education, pap smear test, age, body mass index, number of pregnancies, and number of children) between overweight and obese participants ($p < 0.05$). Obese participants were older than overweight participants. More obese

Table 1. *Socio-demographic characteristics of overweight and obese women (n : 420)*

	Overweight	**Obese**	**Total**	
	Median (Min-Max)	**Median (Min-Max)**	**Median (Min-Max)**	**p**
Age	29 (18-60)	40 (19-68)	34 (18-68)	**P^a=.000**
Marital Status	**n (%)**	**n (%)**	**n (%)**	
Single	107 (44.2)	55 (30.9)	162 (38.6)	
Married	135 (55.8)	123 (69.1)	258 (61.4)	**P^b=0.006**
Level Of İncome				
İncome < Expense	84 (34.7)	61 (34.3)	145 (34.5)	
İncome = Expense	123 (50.8)	93 (52.2)	216 (51.4)	
İncome > Expense	35 (14.5)	24 (13.5)	59 (14)	P^b=0.944
Educational Status				
Literate	15 (6.2)	12 (6.7)	27 (6.4)	
Primary School Graduate	17 (7)	48 (27)	65 (15.5)	
Secondary School Graduate	19 (7.9)	17 (9.6)	36 (8.6)	
High School Graduate	69 (28.5)	45 (25.3)	114 (27.1)	
Graduated From a University	122 (50.4)	56 (31.5)	178 (42.4)	**p^b=.000**
Working Status				
Employed	97 (40.1)	59 (33.1)	156 (37.1)	
Nonemployed	145 (59.9)	119 (66.9)	264 (62.9)	p^b=0.146
Family Type				
Nuclear Family	210 (86.8)	154 (86.5)	364 (86.7)	
Extended family	32 (13.2)	24 (13.5)	56 (13.3)	p^b=0.938
Living Place				
City	208 (86)	146 (82)	354 (84.3)	
Town	8 (3.3)	10 (5.6)	18 (4.3)	
Village	26 (10.7)	22 (12.4)	48 (11.4)	p^b=0.427
Pap Smear Test Make Status				
Yes	54 (22.3)	62 (34.8)	116 (27.6)	
No	188 (77.7)	116 (65.2)	304 (72.4)	**P^b=0.005**
Obesity Education Taking Status				
Yes	41 (16.9)	38 (21.3)	79 (18.8)	
No	201 (83.1)	140 (78.7)	341 (81.2)	P^b=0.254
	Median (Min-Max)	**Median (Min-Max)**	**Median (Min-Max)**	
BMI	27.8 (25–29.8)	33.7 (30–77.8)	29.3 (25–77.8)	**P^a=.000**
Number of Pregnancies	1 (0-8)	2 (0-11)	2 (0-11)	**P^a=.000**
Number of Children	1 (0-6)	2 (0-10)	1 (0-10)	**P^a=.000**

p^a: Mann Whitney U test p^b: Chi-Square test

participants had pap smear tests than overweight participants. More obese participants were married than overweight participants. Obese participants were less educated than overweight participants. The statistical difference between the two groups was due to the difference between the groups with primary school and bachelor's degrees. The two groups did not significantly differ by income, employment, family type, place of residence, and training in obesity ($p > 0.05$).

Participants had a mean OAS and GCAS score of 60.94 ± 6.23 and 155.39 ± 18.63, respectively ($p > 0.05$). Overweight participants had a significantly higher OAS "nutrition" subscale score than obese participants ($p < 0.05$). Overweight participants had significantly higher GCAS "awareness of prevention of gynecologic cancers" and "early diagnosis and information awareness in gynecologic cancers" subscale scores than obese participants ($p < 0.05$) (Table 2).

Table 2. *Distribution of scale means of overweight and obese women (n : 420)*

	Overweight	Obese	Total		Cronbach'sAlpfa
	Ort ± SS	**Ort ± SS**	**Ort ± SS**	**p; t**	
OAS	61.35 ± 6.25	60.39 ± 6.17	60.94 ± 6.23	p:0.121; t:1.554	0.863
	Median (Min-Max)	**Median (Min-Max)**	**Median (Min-Max)**	**P; U**	
Obesity Awareness	27 (17-36)	28 (17-35)	27 (17-36)	p:0.802; U:21231.500	
	Ort ± SS	**Ort ± SS**	**Ort ± SS**	**p; t**	
Nutrition	18.92 ± 2.42	18.38 ± 2.46	19 ± 2.45	**p:0.025**; t:2.245	
Physical Activity	14.92 ± 1.74	14.77 ± 1.84	14.86 ± 1.78	p:0.389; t:0.862	
GCAS	156.49 ± 19.05	153.9 ± 17.99	155.39 ± 18.63	p:0.159; t:0.257	0.936
Routine Control in Gynecological Cancers and Awareness of Perception of Serious Disease	86.74 ± 12.6	85.35 ±12.31	86.15 ± 12.48	p: 0.261; t: 1.126	
	Median (Min-Max)	**Median (Min-Max)**	**Median (Min-Max)**	**P; U**	
Awareness of Gynecological Cancer Risks	29 (18-45)	29 (17-45)	29 (17-45)	p: 0.742; U: 21134.000	
Awareness of Prevention from Gynecological Cancers	23 (8-30)	22 (6-30)	22 (6-30)	**p: 0.043;** U: 19060.000	
Early Diagnosis and Information Awareness in Gynecological Cancers	18 (8-20)	17 (10-20)	17 (8-20)	**p: 0.026** ; U: 18840.000	

t: Independent Samples t Test, U: Mann Whitney U test

Table 3. *Distribution of scale averages by women's socio-demographic characteristics (n : 420)*

	OAS	Testing and Materiality	GCAS	Testing and Materiality
	Ort ± SS		**Ort ± SS**	
Age				
18-34	61.06 ± 6.32		156.19 ± 18.42	
35-51	61.19 ± 6.13	F:1.559	155.91 ± 18.85	F: 2,751
52-68	59.26 ± 5.97	p:0.203	148.77 ± 17.99	p: 0.065
Marital Status				
Single	61.39 ± 6.26	t:1.164	155.05 ± 18.86	t: - 0.299
Married	60.66 ± 6.2	p:0.245	155.61 ± 18.52	p: 0.765
Level Of İncome				
İncome < Expense	60.84 ± 6.14	3>1	153.48 ± 18.46	3>1, 3>2
İncome = Expense	60.49 ± 6.36	F:3.450	154.61 ± 17.97	F: 5.997
İncome > Expense	62.86 ± 5.64	**p:0.033**	162.98 ± 19.85	**p:0.003**
Educational Status				
Literate	61.48 ± 6.25		150.22 ± 20.64	
Primary School Graduate	60.35 ± 5.93		149.57 ± 17.95	
Secondary School Graduate	58.31 ± 5.76	5 > 3	153.11 ± 17.3	5 > 2
High School Graduate	60.42 ± 6.37	F:3.228	154.18 ± 18.22	F: 4.739
Graduated From a University	61.94 ± 6.17	**p:0.013**	159.54 ± 18.32	**p: 0.001**
Working Status				
Employed	61.34 ± 6.83	t:0.965	160.35 ± 19.57	t: 4.149
Nonemployed	60.71 ± 5.84	p:0.335	152.47 ± 17.43	**p: 0.000**

Family Type				
Nuclear Family Extended family	61.19 ± 5.97 59.34 ± 7.54	t:1.754 p:0.084	156.64 ± 18.27 147.29 ± 19.07	t: 3.546 **p:0.000**
Living Place				
City Town Village	60.84 ± 6.19 62.11 ± 6.41 61.25 ± 6.53	F:0.421 p:0.657	155.99 ± 18.27 156.33 ± 17.69 150.65 ± 21.15	F: 1.769 p: 0.172
Pap Smear Test Make Status				
Yes No	61.11 ± 5.94 60.88 ± 6.34	t:0.344 p:0.731	159.43 ± 19.33 153.85 ± 18.15	t: 2.766 **p: 0.006**
Obesity Education Taking Status				
Yes No	63.04 ± 6.7 60.46 ± 6.02	t:3.360 **p:0.001**	165.49 ± 19.22 153.05 ± 17.71	t: 5.534 **p: 0.000**
BMI				
25-29,9 30 and over	61.35 ± 6.25 60.39 ± 6.17	t:1.554 p:0.121	156.49 ± 19.05 153.9 ± 17.99	t:1.411 p: 0.159
Number of Pregnancies				
0-1 1 and 3 4 and over	61.31 ± 6.24 61.15 ± 6.18 59.8 ± 6.26	F:1.762 p:0.168	154.79 ± 19.06 157.35 ± 17.83 152.33 ± 19.22	F: 2.204 p: 0.112
Number of Children				
0-1 1 and 3 4 and over	61.43 ± 6.35 60.71 ± 6.07 60.41 ± 6.37	F:0.870 p:0.420	155.05 ± 19.03 157.77 ± 18.06 149.11 ± 18.05	2 > 3 F: 5.344 **p: 0.005**

t: Independent Samples t Test, F: One Way ANOVA test

Table 4. *Mean OAS and GCAS scores according to reproductive health awareness (n : 420)*

	OAS	**Testing and materiality**	**GCAS**	**Testing and materiality**
Reproductive Health Awareness Questions	**Ort ± SS**		**Ort ± SS**	
Does obesity affect women's reproductive health?				
Yes No I don't know	61.7 ± 5.79 54.22 ± 6.91 58 ± 6.9	F = 16.534 **p = 0.000**	157.81 ± 17.51 134.33 ± 21.48 145.97 ± 19.26	F = 18.819 **p= 0.000**
Does being obese pose a risk to the pregnancy period?				
Yes No I don't know	61.43 ± 6.07 54.33 ± 7.11 56.77 ± 5.36	F=13.766 **p = 0.000**	156.67 ± 18.29 138.44 ± 19.65 144.23 ± 16.9	F= 10.457 **p = 0.000**
Is the presence of obesity in the mother risky for the baby?				
Yes No I don't know	61.53 ± 6.04 54.5 ± 7.34 58 ± 5.66	F = 13.992 **p = 0.000**	157.42 ± 18.05 137 ± 17.84 144.22 ± 16.99	F = 17.561 **p = 0.000**
Does obesity affect the risk of uterine cancer in women?				
Yes No I don't know	62.6 ± 6.7 58.86 ± 7.44 59.64 ± 5.33	W = 12.094 **p = 0.000**	161.59 ± 18.25 147.5 ± 22.65 150.51 ± 17.05	F = 20.998 **p = 0.000**

Does obesity affect the risk of ovarian cancer in women?				
Yes	62.68 ± 6.01		162 ± 17.23	
No	57.61 ± 6.55	F = 17.000	152 ± 19.25	F = 27.591
I don't know	59.5 ± 5.94	**p = 0.000**	149.08 ± 17.71	**p = 0.000**
Does obesity affect the risk of breast cancer in women?				
Yes	62.77 ± 6.02		161,09 ± 18,25	
No	59.09 ± 7.39	F = 12.446	150.71 ± 19.94	F = 13.398
I don't know	59.88 ± 5.87	**p = 0.000**	151.9 ± 17.7	**p = 0.000**
Does obesity cause menstrual irregularity in women?				
Yes	61.9 ± 6.01		157.75 ± 18.36	
No	57.07 ± 6.05	F = 16.720	144.8 ± 18.59	F = 11.451
I don't know	58.43 ± 5.98	**p = 0.000**	149.64 ± 17.21	**p = 0.000**
Does being obese affect the risk of polycystic ovary syndrome?				
Yes	62.36 ± 5.96		159.58 ± 18.17	
No	57.79 ± 8.46	F = 15.283	141.79 ± 23.44	F = 16.215
I don't know	59.24 ± 5.88	**p = 0.000**	150.69 ± 17.24	**p = 0.000**
Does obesity affect the risk of cesarean delivery in women?				
Yes	62.08 ± 5.77		158.38 ± 18.62	
No	55.69 ± 7.47	F = 19.085	141.44 ± 17.26	F = 14.402
I don't know	58.75 ± 6.27	**p = 0.000**	149.68 ± 16.65	**p = 0.000**
Does obesity affect the risk of miscarriage during pregnancy?				
Yes	61.76 ± 5.93		157.78 ± 18.55	
No	59 ± 8.19	F = 6.429	148.87 ± 20.31	F = 6.287
I don't know	59.64 ± 6.18	**p = 0.002**	151.73 ± 17.75	**p = 0.000**
Does obesity affect the age of first menstruation in women?				
Yes	61.64 ± 5.95		158.34 ± 17.88	
No	58.95 ± 6.38	F = 4.358	141.36 ± 22.48	F = 12.398
I don't know	59.94 ± 6.55	**p = 0.017**	152.02 ± 17.9	**p = 0.000**
Does obesity affect the risk of preeclampsia during pregnancy?				
Yes	62.34 ± 6		161.46 ± 18.76	
No	56.6 ± 8.91	F = 11.063	141.6 ± 20.82	F = 19.985
I don't know	60.27 ± 5.85	**p = 0.000**	152.03 ± 16.83	**p = 0.000**
Does obesity affect the risk of gestational diabetes?				
Yes	61.92 ± 6.04		158.32 ± 18.67	
No	55.67 ± 6.33	F = 15.816	139.08 ± 17.33	F = 16.133
I don't know	58.7 ± 5.9	**p = 0.000**	148.71 ± 15.92	**p = 0.000**
Does obese pregnancy affect the baby's risk of stillbirth?				
Yes	62.14 ± 5.96		159.81 ± 19.04	
No	58.74 ± 8.2	W = 7.172	146.9 ± 20.13	F = 12.242
I don't know	60.06 ± 5.92	**p = 0.001**	152.19 ± 16.82	**p = 0.000**
Does being obese in pregnant women affect the baby's weight?				
Yes	62.1 ± 5.91		160.47 ± 17.19	
No	60.03 ± 6.05	F = 6.948	152.82 ± 18.82	F = 16.337
I don't know	59.77 ± 6.54	**p = 0.001**	149.34 ± 18.59	**p = 0.000**
Does obesity affect the protectiveness of hormonal birth control methods?				
Yes	61.8 ± 6.31		159.18 ± 18.34	
No	59.24 ± 7.53	F = 3.351	153.71 ± 22.65	F = 5.711
I don't know	60.6 ± 5.84	p = 0.05	152.84 ± 17.67	**p = 0.000**

Does maternal obesity affect newborn birth defects?				
Yes	62.49 ± 6.05		161.8 ± 17.48	
No	60.05 ± 6.94	F = 11.652	152.5 ± 20.1	F = 23.887
I don't know	59.54 ± 5.92	**p = 0.000**	149.43 ± 17.39	**p = 0.000**
Does being obese affect the chances of conceiving?				
Yes	61.58 ± 6.09		157.75 ± 18.89	
No	59.5 ± 7.23	F = 5.702	146.7 ± 17.36	F = 9.410
I don't know	59.26 ± 5.98	**p = 0.004**	150.25 ± 16.27	**p = 0.000**
Does being obese affect the success of fertility treatment?				
Yes	61.58 ± 5.98		157.99 ± 18.66	
No	59.73 ± 6.23	F = 4.816	149.95 ± 18.41	KW = 18.86
I don't know	59.54 ± 6.64	**p = 0.009**	149.76 ± 17.22	**p = 0.000**
Does obesity affect early menopause?				
Yes	62.4 ± 5.94		161.38 ± 17.96	
No	60.49 ± 6.48	F = 13.148	148.36 ± 15.94	F = 24.473
I don't know	59.19 ± 6.08	**p = 0.000**	149.62 ± 17.73	**p = 0.000**
Does obesity cause osteoporosis in women?				
Yes	62.24 ± 5.52		160.76 ± 17.02	
No	60.69 ± 8.08	W = 7.395	152.85 ± 20.88	F = 12.616
I don't know	59.92 ± 6.12	**p = 0.001**	151.48 ± 18.35	**p = 0.000**
Does obesity cause iron deficiency anemia in women?				
Yes	62.59 ± 5.72		160.99 ± 18.16	
No	58.86 ± 6.54	F = 10.945	149.8 ± 21.5	F = 13.592
I don't know	60.1 ± 6.26	**p = 0.000**	152.16 ± 17.14	**p = 0.000**

F: One Way Anova test, W: Welch test, KW: Kruskal-Wallis test

Table 5. *The relationship between the mean scores of OAS and GCAS (n : 420)*

		OAS	Obesity Awareness	Nutrition	Physical Activity
GCAS	**r***	.500	.436	.442	.359
	p	**0.000**	**0,000**	**0.000**	**0.000**
Routine Control in Gynecological Cancers and Awareness of Perception of Serious Disease	**r***	.423	.364	.405	.270
	p	**0.000**	**0.000**	**0.000**	**0.000**
Awareness of Gynecological Cancer Risks	**r***	.322	.321	.214	.256
	p	**0.000**	**0.000**	**0.000**	**0.000**
Awareness of Prevention from Gynecological Cancers	**r***	.354	.288	.327	.274
	p	**0.000**	**0.000**	**0.000**	**0.000**
Early Diagnosis and Information Awareness in Gynecological Cancers	**r***	.470	.383	.379	.437
	p	**0.000**	**0.000**	**0.000**	**0.000**

**Pearson Correlation*

Table 3 shows the distribution of scale scores by sociodemographic characteristics. Income, education, and training in obesity significantly affected participants' OAS scores ($p < 0.05$). Participants with a positive income (income > expense), those with bachelor's degrees, and those who had received training in obesity before had significantly higher OAS scores. Participants' GCAS scores significantly differed by income, education, employment, family type, pap smear test, training in obesity, and the number of children ($p < 0.05$). Participants with a positive income, those with bachelor's degrees, those with jobs, those with nuclear families, those who had a pap smear test, those who had received training in obesity, and those with 1-3 children had higher GCAS scores.

Table 4 shows the participants' OAS and GCAS scores by their answers to questions about reproductive health awareness. The two groups had similar lev-

els of awareness of reproductive health. The groups significantly differed in their answers to the question, "Does obesity affect the risk of gestational diabetes during pregnancy?" More overweight participants responded "yes" to the question than obese participants ($p < 0.05$). Participants who believed that obesity was associated with reproductive health, risky birth, uterine, ovarian, and breast cancer, menstrual irregularity, polycystic ovary syndrome, cesarean delivery, preeclampsia, gestational diabetes, stillbirth, congenital disabilities, fertility treatment success, early menopause, osteoporosis, baby weight, and iron deficiency anemia had higher OAS and GCAS scores ($p < 0.05$). Participants who thought that obesity affected the protectiveness of hormonal birth control methods had a statistically higher GCAS score ($p < 0.05$).

Table 5 shows the mean scale scores. A statistically significant positive correlation was observed between the total scores and subscale scores of OAS and GCAS ($p < 0.05$).

DISCUSSION

Obesity is associated with many obstetric and gynecological problems in terms of reproductive health. Participants were highly aware of the effects of obesity on reproductive health. More overweight participants responded "yes" to the question "Does obesity affect the risk of gestational diabetes during pregnancy?" than obese participants.

It was found that Polish women with high BMI knew more about gestational diabetes (23). Ersoy et al. conducted a study on women with obesity and reported two results (24). First, women were adequately aware of the effects of obesity on pregnancy. Second, women who regarded obesity as a high-risk factor for gestational diabetes had significantly higher BMI values than those who did not. Our results are consistent with the literature.

Participants had a mean OAS score of 60.94 ± 6.23, indicating sufficient awareness. Terzi et al., Özkan et al., and Sözen et al. found that women had a mean OAS score of 60.6 ± 7.0, 60.64 ± 9.86, and 61.73 ± 6.01, respectively (25, 26, 27). Our results are consistent with the literature.

Participants had a mean GCAS score of 155.39 ± 18.63, suggesting above-average awareness of gynecologic cancer. Özcan et al., Alp Dal et al., and Kaya Şenol et al. reported that women had a mean GCAS score of 150.53 ± 18.26, 161.19 ± 19.27, and 150.7 ± 20.6, respectively (28, 29, 30). Gözüyeşil et al. determined that women had a median GCAS score of 153 (57-201). Our results are consistent with the literature (31).

Overweight participants had higher GCAS "awareness of prevention of gynecologic cancers" and "early diagnosis and information awareness in gynecologic cancers" subscale scores than obese participants. Research also shows that women with higher BMI are less aware of gynecologic cancers (28).

Obese women are less likely to participate in cervical cancer screening (32, 33). However, some studies show that obese women attend screenings more often (34). Participants with a positive income, those with bachelor's degrees, and those who had received training in obesity had higher awareness of obesity. Evaluated the awareness of women of reproductive age about the risks of obesity and found that low-income women knew less about the risks of obesity evaluated overweight and obese people's attitudes towards obesity and found that those with higher education levels were more aware of the effects of obesity on health (35, 36). İnvestigated how much pregnant women knew about obesity and determined that women with higher levels of education knew more about the risks of obesity looked into the impact of a public education campaign for obesity and reported that education was associated with obesity awareness (37, 38).

Employed participants with a positive income, bachelor's degrees, and nuclear families were more aware of gynecologic cancers. Found that self-employed and highly educated low-income women had lower awareness of gynecologic cancers than other groups (29). Gözüyeşil et al. determined that high-income women had higher awareness of gynecologic cancers (31). Reported no significant relationship between income, employment status, and gynecologic cancer awareness (28, 30). Stated that women with primary school degrees were less aware of gynecologic cancers than others (29). Although earlier studies have reported different results, high-income working women are likely to be more aware of cancer because they are likely to have higher education and more access to information. Most working women in Turkey live in nuclear families and have higher education and more access to information, which may explain why they are more aware of gynecologic cancers.

The pap smear test is the most effective method for the early diagnosis of cervical cancer (39). Our participants who took pap smear tests were more aware of gynecologic cancers than those who did not. Also found that women who took pap smear tests were more aware of gynecologic cancers than those who did not (40).

Participants with 1-3 children were more aware of gynecologic cancers than those with more than three children. Evaluated the awareness of women of reproductive age and postmenopausal period about gynecological cancers and determined that women with 1-3 children were more aware of gynecologic cancers than those with more than three children (30).

Participants who were aware of the effects of obesity on reproductive health were also more aware of obesity than those who were not. Reported that women knew enough about obesity and its effects on health (41). Investigated how much women of reproductive age knew about the effects of obesity on reproductive health and found that most women had a positive tendency towards obesity and did not know enough about its effects on reproductive health (42).

Screening and early detection are critical to reducing cancer-related death rates (43). However, women apply to healthcare institutions too late because they do not know enough about health risks and ignore their health problems (28).

We must raise women's awareness to protect them from cancer and cancer-related deaths. Our results showed that women who were aware of the effects of obesity on reproductive health were more aware of gynecological cancers than those who were not.

CONCLUSION

Our results indicate that overweight and obese women who are more aware of obesity are also more aware of reproductive health and gynecological cancers. Income, education, and training in obesity affect women's awareness of obesity. Income, education, employment status, family type, pap smear test, training in obesity, and the number of children affect women's awareness of gynecologic cancers. Healthcare professionals should consider the sociodemographic characteristics of women to solve the problem of obesity. They should provide women with training to raise their awareness of obesity and its adverse effects on reproductive health. Therefore, authorities should provide healthcare professionals with in-service training programs to raise their awareness of the effects of obesity on women's health. In addition, researchers should focus on obesity awareness in large samples.

Ethical Approval

The study received approval from the Scientific Research and Publication Ethics Committee of a state university. The initial page of the online questionnaire served as the electronic informed consent form. All participants were provided with comprehensive information about the study's purpose and procedure, and they were explicitly informed that their participation was entirely voluntary, with the freedom to withdraw from the study at any point. Each stage of the research adhered to the ethical principles outlined in the Declaration of Helsinki by the World Medical Association.

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Licensing

Sažetak

VEZA IZMEĐU GINEKOLOŠKOG KARCINOMA, SVESTI O REPRODUKTIVNOM ZDRAVLJU I SVESTI O GOJAZNOSTI KOD ŽENA: STUDIJA PRESEKA

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Cilj: Ovo istraživanje je sprovedeno kako bi se utvrdio uticaj svesti o gojaznosti na svest o ginekološkom karcinomu i reproduktivnom zdravlju kod žena.

Materijali i metode: Ovo je studija preseka. Uzorak studije činile su žene sa prekomernom težinom i gojaznošću. Podaci studije prikupljeni su korišćenjem obrasca sa osnovnim informacijama, skale svesti o gojaznosti i skale svesti o ginekološkim karcinomima putem Google obrasca.

Rezultati: Utvrđeno je da gojaznost ima statistički značajnu povezanost sa reproduktivnim zdravljem, uključujući rizik za trudnoću i bebu, karcinom materice, jajnika i dojke, menstrualne nepravilnosti, uzrast kod prve menstruacije, sindrom policističnih jajnika, rizik od preeklampsije, gestacijski dijabetes, rizik od mrtvorođenosti, poremećaje pri rođenju, šansu za začeće, uspeh lečenja neplodnosti, rana menopauza, osteoporoza, težina bebe i nedostatak gvožđa - ukupni prosečni rezultati skale svesnosti o gojaznosti i skale svesnosti o ginekološkim karci-

nomima kod onih koji smatraju da su ove stavke povezane su statistički značajno viši. Utvrđena je visoko značajna pozitivna korelacija između ukupnih i poddimenzionalnih prosečnih vrednosti skale svesnosti o gojaznosti i skale svesnosti o ginekološkim karcinomima kod žena.

Zaključak: Utvrđeno je da je svest o gojaznosti kod žena povezana sa svešću o reproduktivnom zdravlju i ginekološkom karcinomu.

Ključne reči: Gojaznost, Ginekološki karcinom, Reproduktivno zdravlje, Svest.

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RETROGRADE TALON INTRAMEDULLARY NAILS VERSUS DISTAL LOCKING PLATES IN THE MANAGEMENT OF EXTRA-ARTICULAR DISTAL FEMORAL SHAFT FRACTURES

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Abstract: **Introduction:** Distal femoral shaft fractures are characterized by their increasing incidence and complexity, presenting a significant challenge in management. The objective of this retrospective study was to compare the clinical and radiological results of patients with extra-articular distal third femoral shaft fractures treated using either retrograde Talon Distal Fix nail or a distal femur locking plate.

Material and Method: The study comprised 40 patients aged > 18 years who presented at our hospital with a distal third femoral shaft fracture between January 2017 and January 2023. The patients were divided into two groups: Group TDN, treated with retrograde Talon Distal Fix nailing (n = 18), and Group DLP, treated with a distal locking plate (n = 22). Demographic data, follow-up period, operating time, time to union, range of motion (ROM), mechanism of injury (traffic accident, fall from height, workplace accident, gunshot injury), fracture type, complications, and surgical method were retrospectively recorded. Clinical evaluation included deformity, knee ROM, pain, and the knee total score (KSS) for walking and knee stability.

Results: The mean age of the patients was 48.03 ± 12.31 (min-max: 23-69) years, and the mean follow-up time for all patients was 15.88 ± 2.32 (12-21) months. The mean time to union was 25.55 ± 1.86 (22-30) weeks. Delayed union and non-union rates were similar between the research groups ($P = 1.000$, $P = 0.673$, respectively). Union time (weeks) and mean ROM were not significantly different between the groups ($P = 0.881$, $P = 0.892$, respectively). The mean operation time of the TDF group (48.78 ± 3.94 minutes) was significantly lower than that of the DLP group (62.45 ± 3.33 minutes) ($P < 0.001$). The mean blood loss values of the TDF group (267.5 ± 32.4) were significantly lower than those of the DLP group (324.1 ± 20.2) ($P < 0.001$).

Conclusion: This study demonstrated that both retrograde talon nails and locking plates provided satisfactory clinical and radiological results in the management of distal third femoral shaft fractures. Moreover, the retrograde talon nail offered the advantages of a shorter operating time and less intraoperative blood loss.

Keywords: Talon Distal Fix, locking plate, distal third femur, union, distal locking.

INTRODUCTION

Distal third femoral shaft fractures account for approximately 4-6% of all femur fractures (1). These fractures are associated with a high risk of complications, including non-union and delayed union. They commonly occur in young patients due to high-energy trauma, while in elderly patients, low-energy trauma may be the cause. The primary goal of treatment is to achieve problem-free union and enable patients to resume their previous daily activities. Despite advancements in surgical techniques and implant technology, there is an ongoing debate among surgeons regarding the optimal choice of implants for treating distal femoral fractures, leading to variations in surgical procedures.

Several treatment options exist for extra-articular distal femoral fractures, such as open reduction and internal fixation using anatomic plating, less invasive stabilization systems (LISS), antegrade and retrograde intramedullary nailing, and distal femur replacement. However, there is currently no consensus on the in-

dications for each of these treatment strategies, and the debate among surgeons continues (2, 3). The use of locking plates in minimally invasive fixation techniques involves a biological osteosynthesis method, which minimizes damage to soft tissues and preserves the fracture hematoma. Intramedullary fixation techniques offer greater biomechanical stability compared to plate fixation and require less surgical dissection (4).

A newly introduced femoral intramedullary nailing system, the deployable Talon Distal Fix, can be used both antegrade and retrograde in femoral fractures. The Talon Distal Fix Femoral Nail (Orthopedic Designs North America Inc., FL, USA) features a distal locking mechanism provided by expandable talons, eliminating the need for traditional distal locking techniques. This unique locking system shortens operating time, reduces blood loss, and minimizes radiation exposure. To the best of our knowledge, there are no reports in the literature regarding the use of retrograde Talon Distal Fix in the treatment of distal femur fractures.

The objective of this retrospective study was to compare the clinical and radiological outcomes of patients with extra-articular distal third femoral shaft fractures treated with retrograde Talon Distal Fix and distal femur locking plate.

MATERIAL AND METHODS

This retrospective study was conducted at the Orthopaedics and Traumatology Department of a tertiary-level training and research hospital. Approval for the study was obtained from the Ethics Committee of Hitit University, and informed consent was obtained from all participants in accordance with the Declaration of Helsinki. The study included 40 patients aged > 18 years who presented at the hospital with a distal third femoral shaft fracture between January 2017 and January 2023, and met the study inclusion criteria. The patients were divided into two groups: Group TDF (retrograde Talon Distal Fix nailing, n = 18) and Group DLP (distal locking plate, n = 22).

The study inclusion criteria were as follows: age ≥ 18 years, fracture classified as AO/OTA 33 A1, A2, or A3, and a postoperative follow-up period of at least 12 months. Patients were excluded from the study if they were aged < 18 years, if more than 3 weeks had passed since the trauma, if they had multi-trauma, a neuropathic diagnosis, rheumatoid arthritis, a fracture extending to the joint, pathological fracture, active or chronic infection, or a history of surgery on the same side leg. Fractures were classified according to the AO classification system. Radiographic and clinical evaluations were performed on first preoperative presentation, at 2 weeks, 2 months, 4 months postoperatively, and then at 3-month intervals until the end of 1 year.

Demographic data, follow-up period, operating time, time to union, range of joint motion (ROM), mechanism of injury (traffic accident, fall from height, workplace accident, firearms injury), fracture type, complications, and surgical method (Talon nail or locking plate) were recorded retrospectively. Clinical evaluations included assessment of deformity, knee ROM, pain, and the knee total score (KSS) (5) for walking and knee stability, which were categorized as excellent, good, fair, or poor.

Femur alignment was evaluated with respect to varus-valgus, shortening, and antecurvatum-recurvatum using radiological evaluation scores on anteroposterior (AP) and lateral radiographs (6). Osseous healing was defined as the presence of callus in at least 3 of 4 cortices on AP and lateral radiographs, while clinical healing was defined as the absence of pain and sensitivity in the fracture region.

Surgical Technique for Group TDF

The operations were performed on a radiolucent operating table under general or spinal anesthesia. With the patient in a supine position, the knee was flexed to 30° to relieve the deforming forces of the gastrocnemius and facilitate nail placement. A 3 cm infrapatellar skin incision was made, and the patellar tendon was longitudinally separated from the midline. The placement point was defined under fluoroscopy guidance to be on the intercondylar notch on the anterior side of the Blumensaats line and parallel to the mid-axis of the femoral shaft, as confirmed on both AP and lateral radiographs.

Following closed reduction, the reduction status was confirmed on imaging. A guidewire was advanced intramedullary to the proximal femoral fragment, and reaming was initiated. Nail length was measured, and a talon nail one size smaller than the last reamer used was placed intramedullarly over the guidewire. The retractable talon anchors providing axial and rotational stability for distal locking were fully expanded, followed by the placement of 2 or 3 screws for proximal locking (Figure 1).

Surgical Technique for Group DLP

Under general or spinal anesthesia, the patient was positioned supine with the knee flexed at 40°. An incision was made at the joint level, extending proximally from the lateral side. The distal locking plate (DLP) was inserted submuscularly below the vastus lateralis toward the proximal part and was fixed with a temporary Kirschner wire under fluoroscopy guidance. Closed reduction was performed, and distal and proximal locking screws were placed percutaneously

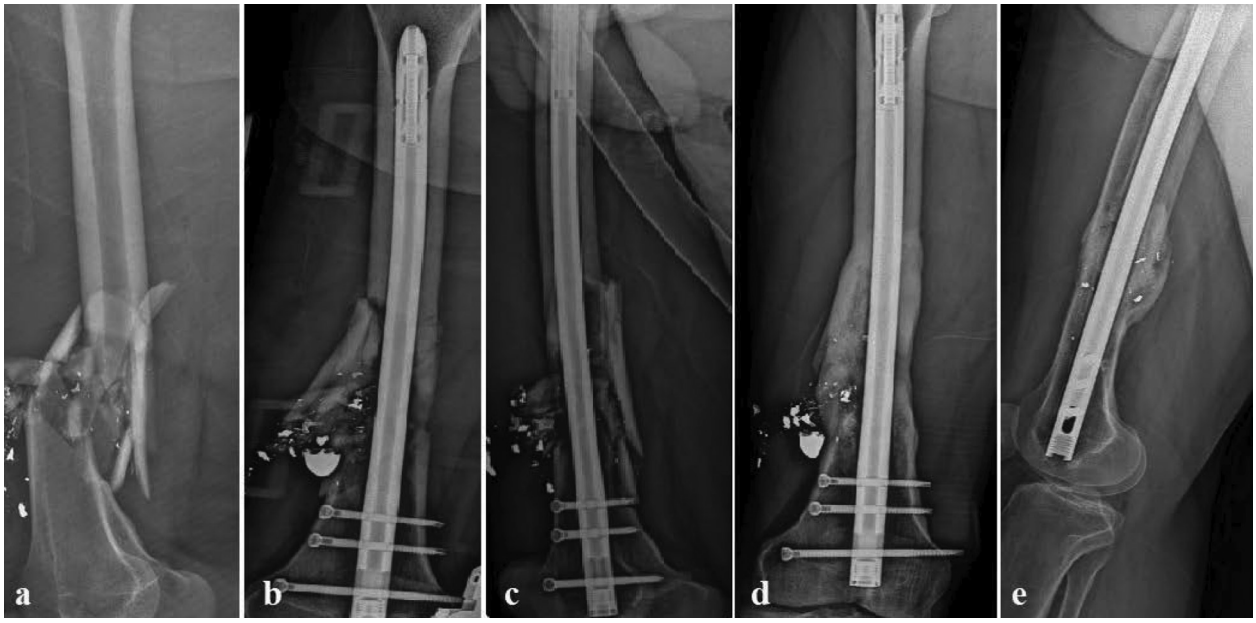

Figure 1. *(a), Preoperative radiographof a 38-year-old man with type A3 open distal third femoral fracture; (b and c) early postoperative radiograph of distal third femoral fracture managed by Talon distal fix nail; (d and e) Follow up radiograph at 18 weeks showing fracture consolidation*

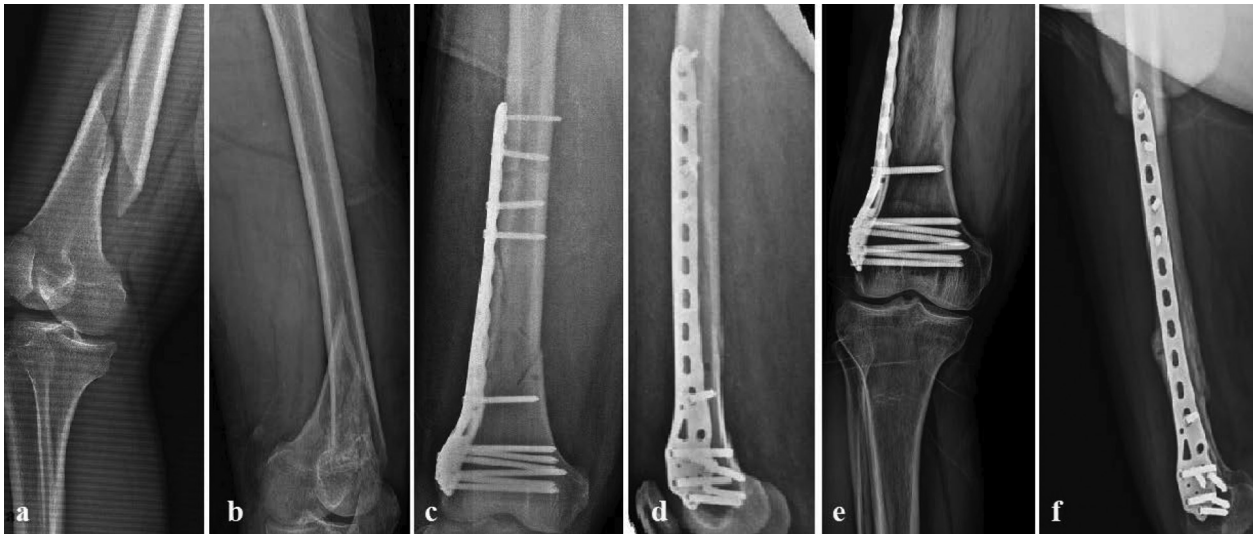

Figure 2. *(a and b), Preoperative anteroposterior and lateral radiographs of a 52-year-old women with type A2 distal third femoral fracture; (c and d) early postoperative radiograph of distal third femoral fracture managed by locking plate; (d and f) Follow up radiograph at 18 weeks showing fracture consolidation*

over the plate. A compression screw was used when compression of the proximal part was required. The reduction and implant status were confirmed under fluoroscopy (Figure 2).

Postoperative Protocol

Under the supervision of a physiotherapist, isometric quadriceps exercises were initiated as tolerated, along with early passive and graduated active knee and hip joint movements on the first postoperative day for both groups. Non-weight-bearing mobilization with a walker was allowed from the first postoperative day. Partial weight-bearing was permitted in the 3rd week for AO A1 fractures and in the 5th week for AO A2 and AO A3 fractures in Group TDF, and in the 6th week for Group DLP. Full weight-bearing was allowed as tolerated after confirming bone union on AP and lateral radiographs in both groups.

Statistical Methods

Data analysis was performed using SPSS (Version 22, SPSS Inc., Chicago, IL, USA) software. Descriptive statistics for categorical data were reported as frequency and percentage. The Pearson Chi-square test or

Fisher's exact test were used for comparing categorical variables between research groups based on sample sizes in the crosstab. Descriptive statistics for continuous data were reported as mean ± standard deviation (SD) since the assumption of normal distribution was met. Shapiro-Wilk test, Histogram, and Q-Q graphs were used to examine the assumption of normal distribution for numerical data. Levene's test was used to examine the assumption of homogeneity of variances. Since the parametric test assumptions were met, Student's t-test was used to compare continuous data between the two independent groups. The level of statistical significance was set at $P < 0.05$ for all comparisons.

RESULTS

The study analyzed data from 40 patients, with 18 (45%) in the TDF (Talon Distal Fix Nail) group and 22 (55%) in the DLP (Distal Locking Plate) group. Among the patients, 55% (n = 22) were male and 45% (n = 18) were female. The mean age of the patients was 48.03 ± 12.31 years (min-max: 23-69). The average follow-up time for all patients was 15.88 ± 2.32 months (range: 12-21 months), and the mean time to union was 25.55 ± 1.86 weeks (range: 22-30 weeks).

The comparison of demographic and clinical characteristics between the research groups is presented in Table 1. The distribution of gender ratios was statistically similar between the study groups ($P = 0.482$). The mean age did not show a significant difference between the groups ($P = 0.302$). Specifically, the mean age was 45.78 ± 13.22 years in the TDF group and 49.86 ± 11.49 years in the DLP group. Additionally, the rates of delayed union and non-union were similar among the research groups ($P = 1.000$, $P = 0.673$, respectively). The distribution of AO 33 classification rates was also similar between the groups ($P = 0.894$).

Table 1. *Statistical findings for the comparison of socio-demographic and clinical characteristics of the patients*

		Groups		*P* values
		TDF (n = 18)	**DLP (n = 22)**	
Gender	Male Female	11 (61.1%) 7 (38.9%)	11 (50%) 11 (50%)	0.482[a]
Delayed union	No Yes	15 (83.3%) 3 (16.7%)	19 (86.4%) 3 (13.6%)	1.000[b]
Non-union	No Yes	16 (88.9%) 2 (11.1%)	18 (81.8%) 4 (18.2%)	0.673[b]
AO 33 classification	A1 A2 A3	8 (44.4%) 6 (33.3%) 4 (22.2%)	10 (45.5%) 6 (27.3%) 6 (27.3%)	0.894[a]
KSS score	Poor Fair Good Excellent	1 (5.6%) 2 (11.1%) 3 (16.7%) 12 (66.7%)	1 (4.5%) 4 (18.2%) 7 (31.8%) 10 (45.5%)	0.617[b]
Radiological score	Poor Fair Good Excellent	0 (0%) 2 (11.1%) 5 (27.8%) 11 (61.1%)	2 (9.1%) 3 (13.6%) 7 (31.8%) 10 (45.5%)	0.681[b]
Age		45.78 ± 13.22	49.86 ± 11.49	0.302[c]
Follow-up time (month)		15 ± 2.14	16.59 ± 2.26	**0.029[c]**
Union time (week)		25.5 ± 1.91	25.59 ± 1.86	0.881[c]
ROM		109.1 ± 6.26	108.8 ± 5.17	0.892[c]
Operation time (minute)		48.78 ± 3.94	62.45 ± 3.33	**< 0.001[c]**
Blood loss		267.5 ± 32.4	324.1 ± 20.2	**< 0.001[c]**

[a]Chi-square test with n (%)
[b]Fisher exact test with n (%)
[c]Student's t-test with mean ± standard deviation (SD)
TDF: Talon DistalFix Nail, DLP: Distal Locking Plate

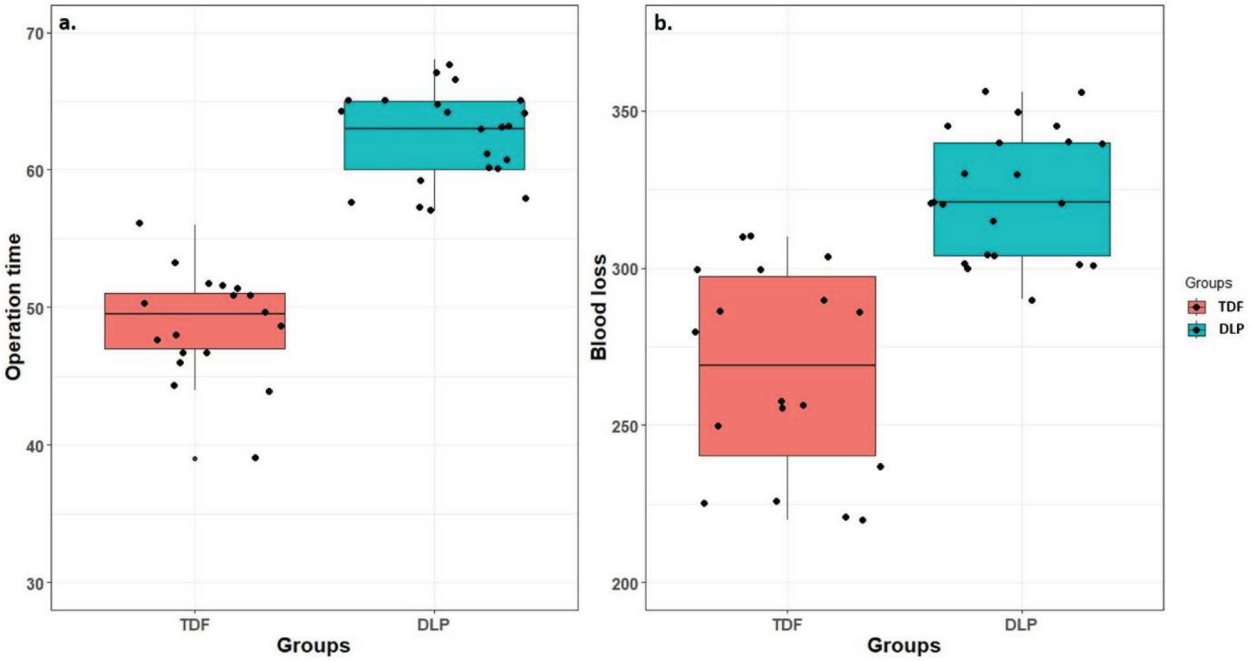

Figure 3. *Boxplot with jitters showing operative times (minutes)* **(a.)** *and blood loss* **(b.)** *values between groups TDF: Talon DistalFix Nail, DLP: Distal Locking Plate*

Table 2. *Statistical findings for the comparison of the reasons for the operation between the groups*

		Groups		*P* values
		TDF (n = 18)	**DLP (n = 22)**	
Traffic accident	No Yes	14 (77.8%) 4 (22.2%)	17 (77.3%) 5 (22.7%)	1.000[b]
Fall from height	No Yes	10 (55.6%) 8 (44.4%)	10 (45.5%) 12 (54.5%)	0.525[a]
Work accident	No Yes	15 (83.3%) 3 (16.7%)	18 (81.8%) 4 (18.2%)	1.000[b]
Shooting	No Yes	15 (83.3%) 3 (16.7%)	20 (90.9%) 2 (9.1%)	0.642[b]

[a]Chi-square test with n (%)
[b]Fisher exact test with n (%)
TDF: Talon DistalFix Nail, DLP: Distal Locking Plate

Furthermore, the distributions of KSS and radiological scores did not show significant differences among the study groups ($P = 0.617$, $P = 0.681$, respectively).

The mean follow-up time in the TDF group (15 ± 2.14 months) was significantly lower than the mean follow-up time in the DLP group (16.59 ± 2.26 months) ($P = 0.029$). However, the union time (weeks) and mean ROM were not significantly different between the two groups ($P = 0.881$, $P = 0.892$, respectively). The mean operation time in the TDF group (48.78 ± 3.94 minutes) was significantly lower than the mean operation time in the DLP group (62.45 ± 3.33 minutes) ($P < 0.001$). Additionally, the mean blood loss in the TDF group (267.5 ± 32.4) was significantly lower than the mean blood loss in the DLP group (324.1 ±

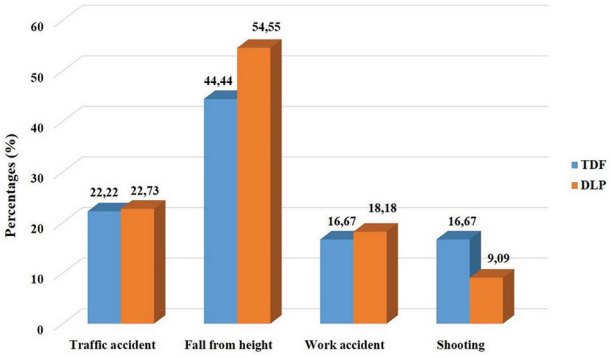

Figure 4. *Bar graph showing percentages of operation reasons among groups, TDF: Talon DistalFix Nail, DLP: Distal Locking Plate*

20.2) ($P < 0.001$). Box plots displaying the distribution of operation times and blood loss values among the groups are shown in Figure 3.

The statistical findings for the comparison of the reasons for the operation between the research groups are presented in Table 2. The distributions of traffic accidents, falls from height, workplace accidents, and gunshot injuries were statistically similar between the groups ($P = 1.000$, $P = 0.525$, $P = 1.000$, $P = 0.642$, respectively). Bar graphs illustrating the distribution of the reasons for the operation among the groups are shown in Figure 4.

DISCUSSION

The results of this retrospective study showed that both retrograde talon intramedullary nailing and locking plate can be safely used in the treatment of distal third femoral shaft fractures. There were no significant differences between the two groups in terms of bone union, delayed union, fracture healing, or complications.

Distal third femoral shaft fractures pose a challenge due to their complexity and high rates of complications. These fractures can result from high-energy trauma in young patients and low-energy trauma in older adults (7). Despite advancements in surgical techniques and implants, complications such as osteoarthritis, non-union, malunion, and residual stiffness are still common (8). Therefore, the optimal treatment for these fractures remains a topic of debate.

Both retrograde intramedullary nailing and locking plate fixation are common surgical methods for distal femoral fractures (9). Minimally invasive approaches with biological osteosynthesis principles are preferred to reduce complication rates. The aim of this study was to evaluate the efficacy of retrograde talon nailing in distal third femoral shaft fractures and compare the results with those of patients treated with locking plate.

The functional and radiological results of both groups were found to be similar, except for the mean operating time and intraoperative blood loss. Retrograde talon nailing showed advantages in terms of shorter operating time and less intraoperative blood loss compared to conventional femoral nails. The deployable talons at the distal end of the Talon Distal Fix nail facilitated distal locking, resulting in these advantages.

There is limited literature on Talon implants (10, 11), and the current study is the first to report the results of retrograde Talon Distal Fix in distal femur fractures.

Both intramedullary nailing and locking plate fixation have shown satisfactory results in previous studies, but the superiority of one technique over the other is not yet fully defined. Biomechanical studies have suggested that locking systems may be better than classic internal fixation systems. However, clinical studies have not consistently demonstrated significant differences in functional outcomes between the two techniques (12-20).

In the current study, both groups showed similar rates of non-union and delayed union, consistent with previous findings. The functional results at the end of the first year were also similar between the groups. The main advantages of the Talon Distal Fix were its ease of application and shorter operating time compared to conventional locking nails.

The limitations of this study include its retrospective design and relatively small sample size. Larger prospective, controlled studies are needed to further investigate the efficacy of retrograde talon nailing in distal femoral shaft fractures. Despite its limitations, this study is valuable as the first to assess the use of retrograde talon nails in these fractures (12-24).

In conclusion, both retrograde talon intramedullary nailing and locking plate fixation are effective and safe treatment options for distal third femoral shaft fractures. The choice of surgical technique should be based on fracture type, characteristics, comorbidities, and the risk of non-union. The retrograde talon nail offers advantages of shorter operating time and reduced intraoperative blood loss, making it a valuable option in the management of these fractures. Further research with larger patient populations is warranted to validate the findings of this study and provide more comprehensive insights into the use of retrograde talon nails in distal femoral fractures.

CONCLUSION

In conclusion, the study results demonstrated satisfactory clinical and radiological outcomes with both retrograde talon nails and locking plates in the management of distal third femoral shaft fractures. The retrograde talon nail showed additional advantages, including shorter operating time and reduced intraoperative blood loss, which contributed to decreased morbidity, infection, and anesthesia-related complications.

Author Contributions

Conceived and designed the analysis: AD, Dİ, ŞK; Collected the data: AD, Dİ; Contributed data or analysis tools: Dİ, ŞK; Performed the analysis: AD, Dİ, ŞK; Wrote the paper: AD, ŞK.

Abbreviations

TDN — Talon Distal Fix nailing
DLP — Distal locking plate
ROM — Range of motion

KSS — Knee total score
LISS — Less invasive stabilisation system

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Sažetak

RETROGRADNI INTRAMEDULARNI KLINOVI NASPRAM DISTALNIH PLOČA ZA ZAKLJUČAVANJE U LEČENJU EKSTRAARTIKULARNIH PRELOMA DISTALNE FEMORALNE OSOVINE

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Uvod: Prelomi distalnog dela butne kosti karakterišu se povećanom učestalošću i složenošću i predstavljaju značajan izazov u lečenju. Cilj ove retrospektivne studije bio je uporediti kliničke i radiološke rezultate lečenja pacijenata sa ekstraartikularnim prelomima distalnog dela butne kosti, lečenih retrogradnim intramedularnim klinom ili distalnom zaključavajućom pločom butne kosti.

Materijali i Metode: Studija je obuhvatila 40 pacijenata starijih od 18 godina koji su se javili u našu bolnicu sa prelomom distalnog trećeg dela butne kosti u periodu od januara 2017. do januara 2023. godine. Pacijenti su podeljeni u dve grupe: Grupa TDN, koja je lečena retrogradnim intramedularnim klinom (n = 18), i Grupa DLP, koja je lečena distalnom zaključavajućom pločom butne kosti (n = 22). Demografski podaci, period praćenja, vreme operacije, vreme spajanja preloma, opseg pokreta (ROM), mehanizam povrede (saobraćajna nesreća, pad sa visine, radna povreda, prostrelna rana), tip preloma, komplikacije i hirurška metoda su retrospektivno zabeleženi. Klinička procena uključila je deformitet, opseg pokreta u kolenu, bol i ukupni bodovi za koleno (KSS) za hodanje i stabilnost kolena.

Rezultati: Prosečna starost pacijenata bila je 48,03 ± 12,31 (min-max: 23-69) godina, a prosečno vreme praćenja svih pacijenata bilo je 15,88 ± 2,32 (12-21) meseci. Prosečno vreme spajanja preloma iznosilo je 25,55 ± 1,86 (22-30) nedelja. Stope kasnog spajanja i neujedinjenja bile su slične između istraživačkih grupa (P = 1.000, P = 0.673, redom). Vreme spajanja (u nedeljama) i prosečni opseg pokreta (ROM) nisu značajno različiti između grupa (P = 0.881, P = 0.892, redom). Prosečno vreme operacije u grupi sa retrogradnim intramedularnim klinom (48,78 ± 3,94 minuta) bilo je značajno kraće od prosečnog vremena operacije u grupi sa distalnom zaključavajućom pločom (62,45 ± 3,33 minuta) (P < 0,001). Prosečne vrednosti gubitka krvi u grupi sa retrogradnim intramedularnim klinom (267,5 ± 32,4) bile su značajno manje od prosečnih vrednosti gubitka krvi u grupi sa distalnom zaključavajućom pločom (324,1 ± 20,2) (P <0,001).

Zaključak: Ova studija je pokazala da su kako retrogradni intramedularni klinovi tako i distalne zaključavajuće ploče pružili zadovoljavajuće kliničke i radiološke rezultate u lečenju preloma distalnog trećeg dela femura. Osim toga, retrogradni intramedularni klin je pružio prednosti kraćeg vremena operacije i manjeg gubitka krvi tokom operacije.

Ključne reči: Distalni fiksator, distalna zaključavajuća ploča, distalni trećina femura, spajanje, distalno zaključavanje.

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Original article

SURVIVIN EXPRESSION IN ORAL SQUAMOUS CELL CARCINOMA

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Abstract: **Introduction**: Survivin functions as an apoptosis inhibitor and a regulator of cell division. This study aimed to determine the correlation between survivin expression and clinicopathologic parameters of oral squamous cell carcinoma (OSCC) and determine its potential role in the progression/prognosis of this type of tumor.

Materials and methods: Immunohistochemical analysis of survivin expression was performed on 45 surgically obtained paraffin-embedded tissue samples of OSCCs. Data on patients' gender, age, tumor grade, site and stage, disease recurrence, metastasis occurrence, and disease-free interval (DFI) were correlated to survivin expression.

Results: Survivin immunoreactivity was observed in 77.8% of samples. No significant correlation between survivin expression and age ($p = 0.087$), gender ($p = 0.334$), tumor site ($p = 0.175$), presence of lymph node metastases ($p = 0.201$), or disease recurrence ($p = 0.451$) was found. Survivin expression was observed in well and moderately differentiated tumors and in all clinical stages ($p = 0.139$). Patients with low survivin expression had better survival rates than the group with medium and high survivin expression, i.e., there was a tendency of a shorter DFI in patients with higher expression of survivin ($p = 0.065$).

Conclusion: There is a tendency for a shorter disease-free period in patients with higher survivin expression. These data suggest that survivin expression in OSCC may act as an additional prognostic parameter that indicates an increased proliferative tumor potential. To further validate survivin as a prognostic marker in OSCC, a study with a larger sample size along with clinical follow-up data is needed.

Keywords: survivin, oral squamous cell carcinoma, prognosis.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is a significant public health problem, ranking among the six most commonly diagnosed malignant tumors worldwide, with a higher prevalence in developing countries (1). Carcinogenesis is a multistage process that may involve not only increased cell proliferation but also decreased cell apoptosis. Survivin is an inhibitor of apoptosis (IAP), which directly inhibits caspase-3 and -7 activity and regulates the cell cycle in the G2/M phase (2).

Survivin is expressed in fetal liver, kidney, and lungs (3), indicating its important role in tissue development (4). However, survivin expression cannot be detected in normal adult tissue, except in thymus tissue, CD34+ stem cells, placenta, basal epithelial cells, hepatocytes, endothelial cells, colon epithelial cells, endometrium, and lymphocytes (5, 6, 7).

Survivin has been recently identified as a promising novel therapeutic target and prognostic marker in different types of cancer (8). Increased survivin expression observed in various precancerous lesions, such as colon epithelial dysplasia and leukoplakia of the oral mucosa, indicates its function in the early stages of carcinogenesis (9, 10).

Survivin expression in tumor cells is most likely independent of the cell cycle, indicating its antiapoptotic role compared to normal cells, where its function in mitosis regulation is dominant. Furthermore, the variable intracellular localization of survivin in tumors (cytoplasmic and nuclear) may serve as an indicator of survivin activity and could potentially act as a prognostic marker for nasopharyngeal carcinoma and astrocytoma (11, 12).

Different studies have found survivin overexpression in poorly differentiated oral squamous cell carcinomas and better survival rates in patients with low expression (13). Except in OSCCs, survivin expression has been found in normal odontogenic epithelium and benign odontogenic lesions. For example, survivin mRNA expression was significantly higher in ameloblastomas than in the epithelium of tooth germs

(14). Various studies have also shown that survivin is expressed in the epithelial cells of pericoronary follicles, follicular cysts, and the basal/suprabasal epithelial layer of keratocystic odontogenic tumors (15, 16). All of these data suggest that survivin participates in the tumorigenesis of the odontogenic epithelium.

The aim of our study was to determine the correlation between survivin expression and clinicopathologic parameters of OSCC and determine its potential role in the progression/prognosis of this type of tumor.

MATERIAL AND METHODS

This study was conducted at the Clinical Centre of Montenegro from 2012 to 2018 and included 45 patients who required surgical treatment for oral carcinoma localized on the lower lip, tongue, or floor of the mouth. The study was carried out following the principles of the Helsinki Declaration (2002 version) and was approved by the Ethics Committee of the Clinical Center of Montenegro. All patients were followed up for a three-year period, and the time from the beginning of treatment (date of primary surgery) until disease recurrence (disease-free interval, DFI) was used to measure survival rates.

Surgical specimens were formalin-fixed, paraffin-embedded, and stained with hematoxylin and eosin for histological analysis. Two independent pathologists, unaware of the participants' clinical status, performed the analysis. Immunohistochemical detection of survivin protein was performed using the DAKO system (Labeled streptavidin-biotin LSAB+ method, DAKO, Denmark) following the manufacturer's instructions. The mouse monoclonal antibody – clone 5B10 (AbD Serotec, Germany) was used for survivin detection.

Positive internal and external staining controls were used, consisting of small salivary glands (presented on several sections) and proximal and distal kidney tubules, respectively.

Survivin expression was assessed in approximately 1000 cells on 10 high-power fields with the highest expression (hot spots) in each specimen. The expression was evaluated semi-quantitatively and categorized based on the percentage of cancer cells stained positive: score 0 indicated no tumor cell reactivity, score 1 indicated ≤ 5% positivity, score 2 indicated 5-10% positivity, and score 3 indicated ≥ 10% tumor cell positivity.

Data on patients' gender, age, tumor grade, site, and stage, as well as disease recurrence, metastasis occurrence, and DFI were correlated with survivin expression using Pearson's chi-squared test. The level of significance was set at 0.05.

RESULTS

Survivin expression was observed in 77.8% of the cases, with a positive reaction observed in the cytoplasm of tumor cells in all instances. The most frequent category of survivin expression was in samples with less than 5% positive tumor cells (score 1). Low expression of survivin (score 0 and 1) was found in two-thirds of the tumor samples.

Statistical analysis did not reveal statistically significant differences in survivin expression among the groups ($p = 0.057$) (Table 1).

Furthermore, there was no significant correlation between survivin expression and age, gender, tumor site, the presence of lymph node metastases, and disease recurrence (Table 2). Survivin expression was observed in well and moderately differentiated tumors and in all clinical stages, but without statistically significant differences.

However, concerning prognostic significance, it appears that patients with low survivin expression (score 0 and 1) had better survival rates compared to the group with medium and high survivin expression (score 2 and 3). There was a tendency for a shorter disease-free period in patients with higher expression of survivin ($p = 0.065$) (Table 3).

DISCUSSION

Survivin is known to be predominantly expressed during embryonic development and in fetal tissue, while its expression is weak or absent in normal and differentiated cells (17). However, recent studies have shown significant expression of survivin in mature adult tissues, including basal epithelial cells of the colon, hepatocytes, endothelial cells, endometrium, and lymphocytes (5, 17).

Table 1. *Immunohistochemical expression of survivin*

Variable		N (%)	p value
Survivin expression	score 0	10 (22.2%)	p = 0.057
	score 1: ≤ 5%	19 (42.2%)	
	score 2: 5-10%	9 (20.0%)	
	score 3: ≥10%	7 (15.6%)	

Table 2. *Statistical analysis of survivin expression and associated clinicopathological findings in OSCC*

Variables	N	Survivin expression N (%)	Score 0 N (%)	Score 1 N (%)	Score 2 N (%)	Score 3 N (%)	p-value
Cases	45	35 (77.8)	10 (22.2)	19 (54.2)	9 (25.8)	7 (20.0)	
Age							
< 60	18	16 (88.8)	2 (11.2)	6 (37.5)	7 (43.8)	3 (18.7)	0.087
≥ 60	27	19 (70.3)	8 (29.7)	13 (68.4)	2 (10.5)	4 (21.1)	
Gender							
Male	36	30 (83.3)	6 (16.7)	16 (53.3)	9 (30.0)	5 (16.7)	0.334
Female	9	5 (55.5)	4 (44.5)	3 (60.0)	0 (0.0)	2 (40.0)	
Grading							
G1	24	20 (83.3)	4 (16.7)	9 (45.0)	7 (35.0)	4 (20.0)	
G2	21	16 (76.0)	5 (24.0)	10 (62.0)	3 (19.0)	3 (19.0)	0.139
Staging							
I	14	12 (86.0)	2 (14.0)	6 (50.0)	2 (17.0)	4 (33.0)	
II	10	8 (80.0)	2 (20.0)	4 (50.0)	2 (25.0)	2 (25.0)	
III	7	6 (86.0)	1 (14.0)	4 (67.0)	1 (16.5)	1 (16.5)	0.139
IV	14	10 (71.0)	4 (29.0)	4 (40.0)	4 (40.0)	2 (20.0)	
Tumor site							
Lip	19	11 (58.0)	8 (42.0)	5 (46.0)	3 (27.0)	3 (27.0)	0.175
Tongue/ floor of mouth and tongue	26	24 (92.0)	2 (8.0)	14 (58.0)	6 (25.0)	4 (17.0)	
Metastasis (node)							
Positive (N+)	18	12 (67.0)	6 (33.0)	6 (50.0)	5 (42.0)	1 (8.0)	0.201
Disease recurrence	5	4 (80.0)	1 (20.0)	2 (50.0)	0 (0.0)	2 (50.0)	0.451

Table 3. *Survivin expression and DFI (disease free interval)*

	Survivin expression (0 i 1)	Survivin expression (2 i 3)	p-value
DFI (mean value - months)	18	12	p = 0,065

The subcellular localization of survivin includes the nucleus, cytoplasm, and mitochondria (18). It has been suggested that cytoplasmic survivin plays a crucial role in the survival of tumor cells by acting as an inhibitor of apoptosis, while nuclear survivin contributes to cell proliferation and helps maintain the integrity of the mitotic spindle. Consequently, higher expression of nuclear survivin may indicate accelerated mitotic processes, which can have a negative prognostic value in certain types of tumors (19).

In our study, we observed that survivin expression was exclusively cytoplasmic in all examined cases. The majority of the samples (2/3) showed low survivin expression, with little or no reactivity of tumor cells (less than 5% positive tumor cells). This is consistent with the characteristic expression pattern observed in many normal, differentiated human cells (17), as per the DAKO protocol used in our investigation. Therefore, we set the cut-off value for survivin overexpression in our study group at > 5%. Increased cytoplasmic survivin expression was detected in only a third of our patients (35.6%). However, it is essential to consider that half of the sample consisted of patients with lip cancer, which is typically well-differentiated and has a favorable prognosis due to early diagnosis. This may explain the lower expression of survivin observed in our cohort.

In contrast, some other malignancies, such as non-small cell lung cancer, pancreatic and colon cancers, soft tissue sarcomas, melanomas, and neuroblastoma, have demonstrated increased cytoplasmic expression of survivin (4, 20-26). The expression of cytoplasmic survivin has been identified as a negative prognostic factor in malignant tumors of the salivary glands, colon, and squamous cell carcinomas of the oral cavity (13, 26, 27). Our study also indicated a tendency towards a shorter disease-free period in patients with higher survivin expression. However, the possibility of different results on a larger study sample cannot be excluded.

Engels et al. investigated the relationship between cytoplasmic and nuclear survivin and its impact on prognosis in patients with OSCC (11). They observed that a change in the ratio of nuclear to cytoplasmic

survivin expression was a positive prognostic factor concerning the duration from the end of treatment to disease recurrence (relapse-free survival). In vitro experiments revealed that the intracellular localization of survivin is regulated by active transport from the nucleus to the cytoplasm, mediated by the specific receptor Crm1 and the corresponding sequence of amino acids within the protein known as NES (nuclear export signal). This mechanism appears to play a crucial role in the cytoprotective function of survivin, as exposure of tumor cells to cisplatin or radiation leads to the transport of survivin from the nucleus to the cytoplasm, reducing the sensitivity of cells to chemotherapy and radiotherapy (11).

CONCLUSION

In conclusion, our study revealed a tendency towards a shorter disease-free period in patients with higher survivin expression in oral squamous cell carcinoma (OSCC). This suggests that survivin expression may serve as an additional prognostic parameter, indicating an increased proliferative tumor potential. However, to further validate survivin as a prognostic marker in OSCC, larger studies with a greater sample size and comprehensive clinical follow-up data are required. Such investigations would contribute to a better understanding of the role of survivin in OSCC progression and aid in developing targeted therapeutic strategies for improved patient outcomes.

Abbreviations

OSCC — oral squamous cell carcinoma
DFI — disease free interval

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Licensing

Sažetak

EKSPRESIJA SURVIVINA U ORALNOM SKVAMOCELULARNOM KARCINOMU

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Uvod: Survivin je inhibitor apoptoze i regulator ćelijske deobe. Cilj ovog istraživanja je bio da se utvrdi korelacija između ekspresije survivina i kliničko-patoloških parametara oralnog skvamocelularnog karcinoma (OSCC) kao i njegova potencijalna uloga u progresiji/prognozi ove vrste tumora. **Materijal i metode**: Imunohistohemijska analiza ekspresije survivina je sprovedena na 45 hirurški odstranjenih i parafinski ukalupljenih uzoraka oralnih skvamocelularnih karcinoma. Podaci o polu i starosti pacijenata, gradusu tumora, lokalizaciji i stadijumu, recidivu bolesti, pojavi metastaza i intervalu bez bolesti (DFI) su upoređeni sa ekspresijom survivina. **Rezultati:** Imunoreaktivnost na survivin je utvrđena u 77.8% uzoraka. Nije utvrđena značajna povezanost između ekspresije survivina i starosti ($p = 0.087$), pola ($p = 0.334$), lokalizacije tumora ($p = 0.175$) ili prisustva regionalnih metastaza ($p = 0.201$) i recidiva bolesti ($p = 0.451$). Ekspresija survivina je bila prisutna u dobro i umereno diferentovanim tumorima i u svim kliničkim stadijumima ($p = 0.139$). Pacijenti sa niskom ekspresijom survivina su imali bolje stope preživljavanja u odnosu na pacijente sa srednjom i visokom ekspresijom survivina tj. utvrđena je tendencija prisustva kraćeg DFI kod pacijenata sa višim nivoom ekspresije survivina ($p = 0.065$). **Zaključak**: Postoji tendencija kraćeg perioda bez bolesti kod pacijenata sa većom ekspresijom survivina. Ovi podaci upućuju da bi ekspresija survivina u oralnom skvamocelularnom karcinomu mogla biti dodatni prognostički parametar koji ukazuje na povećan proliferativni potencijal tumora. Da bi se survivin potvrdio kao prognostički parametar u oralnom skvamocelularnom karcinomu, potrebna je studija na većem uzorku pacijenata uz njihovo kliničko praćenje.

***Ključne reči**:* survivin, oralni skvamocelularni karcinom, prognoza.

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THE VALUE OF THE SYSTEMIC IMMUNE INFLAMMATION INDEX (SII) IN MIGRAINE PATIENTS TREATED WITH GREATER OCCIPITAL BLOCK TREATMENT

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Abstract: **Introduction:** Neuroinflammation plays a key role in various neurological conditions, including migraine. GON block has been used for both acute and preventive treatment in migraine sufferers. Exploring whether this localized nerve blocking therapy for migraines affects signs of systemic inflammation would be beneficial.

Materials and Methods: In this study, a total of 50 migraineurs (comprising high-frequency episodic and chronic migraine) and 60 healthy control volunteers of comparable ages and sexes were enrolled. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and SII levels in migraine patients, migraine sufferers, and healthy individuals are compared. This study examined hematological parameters and SII levels used as inflammatory markers in those diagnosed with migraine.

Results: It was determined that the mean platelet and PLR values of the case group's subjects were substantially lower than those of the patient group's subjects ($p < 0.05$). Biochemical characteristics of the cases were examined before and after treatment with greater occipital nerve (GON) block, revealing a statistically significant reduction in attack frequency, severity, and duration ($p < 0.001$). No significant differences were discovered when compared to post-treatment values ($p > 0.05$), even though the ratios were greater prior to GON block therapy in other measures.

Conclusion: These findings, in our opinion, are linked to the presence of a continuous inflammatory process even in the absence of episodes, supporting systemic inflammation in migraineurs. Thus, SII, an affordable and easily measurable marker in peripheral blood, may serve as a helpful predictive marker for migraine patients scheduled for GON block treatment. Further extensive research is needed to determine whether SII can be an independent prognostic factor in migraine patients.

Keywords: migraine, neuroinflammation, systemic immune inflammation index.

INTRODUCTION

The pathophysiology of migraine is believed to arise from a variety of causes. Neuroinflammation stands as a key mechanism in migraine, other neurological disorders, and their associated conditions. In fact, increasing research suggests that migraine, epilepsy, stroke, and COVID-19 infection might all be influenced by parenchymal neuroinflammation. The identification of neuroinflammation's crucial role in migraine has unveiled new insights into the disease's origins (1). Researchers reached the conclusion that the localized extracranial pathophysiology observed in chronic migraine sufferers (i.e., periosteal inflammation) should be considered as evidence that certain migraine attacks can initiate outside the head (2). Authors of a study similarly concluded that the localized extracranial pathophysiology seen in individuals with chronic migraines (i.e., periosteal inflammation) should be acknowledged as support for the notion that specific migraine attacks can commence beyond the skull.

Headache experts show a keen interest in migraine headache treatment. Both acute and preventative treatments encompass a wide array of medications with diverse mechanisms. While triptans, acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs)

are recommended by the American Headache Society and the American Academy of Neurology (2012) for managing acute attacks, acupuncture is suggested as a non-pharmacological approach alongside antiepileptics, antihypertensives, and antidepressants for prophylaxis (3, 4). The demand persists for a migraine treatment that is dependable, practical, affordable, and effective.

The dorsal rami of the C2 and C3 segments give rise to the greater occipital nerve (GON), which is composed solely of sensory fibers. It extends anteriorly to the vertex before becoming superficial on the inferolateral side of the occipital region. The convergence of sensory information from GON and the ophthalmic branch of the trigeminal nerve in the trigeminal nucleus caudalis is believed to contribute to the infrequent coexistence of occipital neuralgia and migraine headache symptoms (5). GON block is thought to alleviate pain and neuronal hyperexcitability by reducing afferent input to the trigeminal nucleus caudalis (6). Local anesthetic and corticosteroids are administered through a needle into the inferolateral aspect of the GON block in the occipital projection. Despite not being indicated in current guidelines for migraine headache management, the effectiveness of GON block treatment has been explored across varying degrees in studies (6, 7).

Central vestibular pathways and the inner ear are implicated in vascular and neurogenic inflammation, both as peripheral and central migraine triggers, as well as within central neural mechanisms. Peptide production from axon terminations of trigeminal ganglion cells triggers a sterile inflammatory response in the meningeal arteries (8, 9). According to specific findings, different pro-inflammatory components and cytokine levels are elevated in the peripheral blood of migraine patients. GON block has long been employed for treating and preventing migraines in patients. This study compares the hematological parameters of patients who received prophylactic GON block before and after treatment.

In clinical practice, the white blood cell count (WBC) is a common measure of inflammation. An increased "neutrophil-to-lymphocyte ratio" (NLR) may indicate inflammation and inflammation-related diseases even when WBC is within normal ranges (3). While it is widely recognized that hematologic disorders such as anemia and polycythemia are associated with headaches, there haven't been many studies examining the connections between headache features like frequency, severity, or duration and hematologic parameters.

Neutrophils play a key role in acute phase reactions that lead to inflammation, while lymphocytes are important participants in cellular and humoral processes. Due to its connection to inflammation, NLR, which is generated by neutrophils and lymphocytes in circulation, holds great significance. A complete blood count (CBC) can easily quantify the neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR), two straightforward, accessible, and cost-effective markers of inflammatory response. NLR, PLR, and the systemic immunological inflammation index (SII) have gained popularity as indicators of oxidative stress and systemic inflammation (10). Serum NLR, PLR, and SII levels might be associated with migraine, particularly during attacks. By identifying hematologic and biochemical biomarkers in different migraine subtypes, it could be possible to link increased inflammation to various clinical manifestations and the severity of the condition. In comparison to individuals with migraine or other headache syndromes, patients with subarachnoid hemorrhage (SAH) had higher NLR levels, according to research by Eryiit et al. (11). Despite earlier research that examined NLR and PLR rates in cases of acute and chronic migraine (12, 13), there hasn't been a comprehensive investigation of SII in the literature.

The systemic immune-inflammation index (SII) is calculated using the total peripheral platelet count (P) and the neutrophil-to-lymphocyte ratio (N/L) (SII = P N/L ratio) (13). This index may serve as a prognostic indicator in various malignant diseases, as high SII has been associated with poor outcomes in cancer patients (14, 15, 16). Our aim is to assess the predictive value of SII in migraineurs undergoing GON block treatment. Based on hematological data, this study analyzes the concentrations of NLR, PLR, and SII, which serve as indicators of inflammation, in patients with high-frequency episodic and chronic migraine (during interictal periods), as well as in healthy individuals.

MATERIAL AND METHODS

Between May 1, 2021, and May 1, 2022, our institution received applications from 114 patients in accordance with the cross-sectional study design. This investigation included a total of 50 migraine sufferers and 64 healthy control volunteers with matched ages and sexes. The age and sex of the control group were matched. Rheumatoid arthritis, diabetes mellitus, inflammatory bowel disease, asthma, dermatitis, hepatitis, AIDS, and other inflammatory disorders were also excluded from the control group. Patients were recruited from an outpatient headache clinic. Exclusion criteria encompassed conditions other than regulated hypertension, medication overuse headache, chronic inflammatory processes, hematologic disorders, recent history of infectious disease, renal failure, hypoparathyroidism, ischemic heart disease, history of

corticosteroid use, alcohol consumption, or smoking. Thorough examinations of neurological systems were conducted for both the patient and control groups.

Hematological parameters (neutrophil, lymphocyte, platelet, NLR, PLR, SII), demographic information, family history, chronic diseases, visual analog scale (VAS) scores, number of migraine attacks, attack duration, and hematological parameters were obtained from medical records before and after GON block treatment (15 days before and 15 days after the intervention). The ICHD-3 diagnostic criteria were employed for migraine diagnosis and categorization. All study calculations were based on patients' complete blood counts (CBCs). The initial CBC findings for each patient determined each value by dividing the total number of neutrophils by the total number of lymphocytes. For this purpose, regular electronic CBC equipment (XN-CBC, Sysmex, Bornbarch 1, 22848 Norderstedt, Germany) was used. Blood samples (2 cc) were collected in EDTA tubes and gently inverted 6-7 times for mixing. Samples were stored in the refrigerator (2-8 °C); delays in transferring blood to the tube could result in clotting and inaccurate results.

Diagnosis was made through clinical evaluation by a neurologist and blood tests were requested. A hematology specialist was consulted for hematological evaluation. Anamnesis and medications were used to exclude potential causes of systemic inflammation. While CRP was not examined to exclude participants with underlying inflammatory conditions that could affect study results, healthy subjects were included in the screening for exclusion criteria. No research in the literature exploring the relationship between migraine and SII was located. Therefore, the purpose of this study was to uncover any potential diagnostic correlations between migraine and a novel index called SII. The study focused on the hematological parameters and SII levels used as inflammatory markers in diagnosed migraine patients.

Statistics

Parametric tests were applied without conducting the normality test, as they are compatible with the Central Limit Theorem**.** The data's conformity to the normal distribution was assessed using the Shapiro-Wilk test. Student's t-test was utilized to compare normally distributed features between the patient and control groups, and the comparison of pre-and post-treatment measurements was conducted using the Paired t-test. Chi-square test statistics were employed to assess relationships between categorical variables. The relationships between quantitative variables were examined using the Pearson correlation coefficient. Descriptive statistics provide mean ± standard deviation for numerical variables and number and percentage values for categorical variables. Statistical analyses were carried out using the SPSS (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL, USA) version 24.0 software, with a significance level of $P < 0.05$ considered as statistically significant.

RESULTS

In our investigation, it was found that the case and control groups' subject populations' gender distribution and mean ages were comparable ($p > 0.05$). While 84% were female patients, 16% were male patients; 93.8% of female patients were included in the control group. The mean age of the patients was 36.58 ± 9.67, and the mean age of the control group was 34.23 ± 9.35 ($p > 0.05$).

The average number of migraines per patient was 13.56 ± 8.10 years (Table 1). The findings of compar-

Table 1. *Evaluation of socio-demographic and clinical characteristics according to migraine status*

	Patient (n = 50)	Control (n = 64)	Total (n = 114)	p
Female n (%) Male n (%)	42 (84) 8 (16)	60 (93.8) 4 (6.3)	102 (89.5) 12 (10.5)	0.092
Age (mean ± sd)	36.58 ± 9.67	34.23 ± 9.35	35.26 ± 9.52	0.193
Migraine duration (mean ± sd)	13.56 ± 8.10			

Table 2. *Comparison of pretreatment biochemical parameters between groups*

Parameters	Patient mean ± sd	Control mean ± sd	p
WBC	7.44 ± 1.75	7.11 ± 1.73	0.323
MPV	9.64 ± 1.85	9.92 ± 0.94	0.319
NLR	2.26 ± 1.41	2.29 ± 1.25	0.915
PLR	154.18 ± 53.97	126.64 ± 46.61	**0.005**
SII	761.88 ± 1539.28	650.61 ± 350.11	0.576

P value obtained from Student t test sd: standard deviation

ing the pre-treatment biochemical parameters between the patient and control groups are shown in Table 2. It was determined that the subjects in the patient group's mean platelet and PLR values were considerably greater than those of the patients in the control group ($p < 0.05$). The patient and control groups were found to share other parameters ($p > 0.05$). Pre-treatment values refer to the parameters checked just before the GON block.

The findings of comparing the biochemical parameters of the subjects before and after the GON block treatment are shown in Table 3. This led to the observation that the decrease in attack frequency, severity, and length was statistically significant ($p < 0.001$). No significant differences were discovered when compared to post-treatment values ($p > 0.05$), despite the fact that the ratios were greater prior to GON block therapy in other measures.

Table 4 provides an evaluation of the patients' relationships after treatment. The connection between the cases' SII value and neutrophil values was found to be moderately significant ($r = 0.536$; $P = 0.001$). SII values also rise as a result of the rise in neutrophil values. Between the cases' SII values and their lymphocyte values, there was a weakly significant negative association ($r = -0.489$; $P = 0.001$) discovered. A drop in SII values is brought on by an increase in lymphocyte values.

The connection between the cases' SII values and platelet values was found to be moderately significant

Table 3. *Comparison of biochemical parameters pre/post-treatment in cases*

	Pre-treatment	Post-treatment	p
	mean ± sd	mean ± sd	
WBC	7.44 ± 1.75	7.21 ± 1.5	0.309
MPV	9.64 ± 1.85	9.66 ± 1.97	0.832
NLR	2,27 ± 1,42	1.94 ± 0.83	0.121
PLR	126.64 ± 46.61	118.38 ± 47.93	0.252
SII	761.88 ± 1539.28	506.32 ± 237.9	0.239
attack frequency	11.62 ± 8.8	2.78 ± 3.2	**< 0.001**
Vas	8.36 ± 1.48	4.98 ± 2.46	**< 0.001**
attack duration	37.3 ± 24.35	14.98 ± 22.58	**< 0.001**

P value obtained from paired t-test.

Table 4. *The relationship of post-treatment biochemical parameters in cases*

		WBC	neutrophil	lympho-cyte	Platelet	MPV	NLR	PLR	SII	Attack frequency	Attack severity	Attack duration	MigPatient Duration
Age	r	-0.053	-0.155	0.117	0.042	-0.035	-0.052	-0.031	-0.073	-0.012	0.175	0.113	0.512
	p	0.715	0.282	0.420	0.770	0.809	0.722	0.832	0.616	0.936	0.223	0.435	0.001
WBC	r	1	0.857	0.607	0.238	0.086	0.081	-,283	0.200	-0.223	-,333	-0.226	-,386
	p		0.001	0.001	0.096	0.553	0.578	0.047	0.164	0.119	0.018	0.114	0.006
neutrophil	r		1	0.171	0.149	0.091	0.492	-0.006	0.536	-0.220	-,288	-0.190	-,303
	p			0.236	0.300	0.531	0.001	0.968	0.001	0.125	0.043	0.187	0.032
lymphocyte	r			1	0.243	-0.097	-0.643	-0.609	-0.489	-0.109	-0.122	-0.206	-0.232
	p				0.089	0.504	0.001	0.001	0.001	0.453	0.399	0.150	0.105
Platelet	r				1	-0.162	-0.061	0.458	0.429	0.047	0.213	0.270	0.006
	p					0.262	0.676	0.001	0.002	0.746	0.137	0.058	0.969
MPV	r					1	0.124	-0.014	0.039	-,650	-,478	-,323	-0.162
	p						0.391	0.922	0.788	0.001	0.001	0.022	0.261
NLR	r						1	0.623	0.850	-0.144	-0.130	-0.009	-0.050
	p							0.001	0.001	0.319	0.366	0.949	0.728
PLR	r							1	0.793	0.061	0.201	-.340	0.132
	p								0.001	0.673	0.163	0.016	0.361
SII	r								1	-0.107	0.003	0.178	-0.034
	p									0.460	0.982	0.217	0.813
attack frequency	r									1	-.422	-.430	0.090
	p										0.002	0.002	0.534
attack severity	r										1	-.441	-.328
	p											0.001	0.020
attack duration	r												0.185
	p												0.198

r: Pearson correlation coefficient (n=50)

($r = 0.458$; $P = 0.001$). An increase in SII values is anticipated as platelet values rise.

DISCUSSION

Previous research has indicated that individuals suffering from migraines often exhibit elevated levels of platelet activation and interactions between platelets and leukocytes. This interaction is believed to contribute to the inflammatory vascular process underlying migraines, facilitating the spread of infection and inflammation (17, 18). Our study also supports this notion, revealing significantly higher levels of platelets and platelet-to-lymphocyte ratio (PLR) in individuals with migraines compared to the control group. Notably, mean platelet volume (MPV) serves as a highly accurate predictor of platelet activation and has shown promise as a predictive and therapeutic measure for conditions involving thrombosis and inflammation (19). Recent research has even explored its potential in gauging prothrombotic and proinflammatory potentials (19). Similarly, Çelikbilek et al (20) found elevated platelet values in individuals with migraines compared to the control group, with no significant difference in MPV values. Our study similarly detected no significant difference in MPV values, despite notable variation in platelet counts between the pre-treatment migraine patient group and the control group. Additionally, like the findings from Bas et al (21), we observed no statistically significant difference in either platelet count or MPV between adult migraine and control groups. Comparing platelet levels among female migraine sufferers and controls, Peatfield et al. (22) discovered slightly higher levels in females, though the difference was not statistically significant. The MPV values were slightly elevated in the migraine group compared to the control group.

Elevated neutrophil-to-lymphocyte ratio (NLR) values have been shown to independently predict the risk of cardiovascular diseases, cancer, and stroke (23,24). Karabulut et al's 2016 study (13) found higher NLR values during migraine episodes in 92 migraine patients compared to 67 healthy controls. Saricam et al (25) observed significantly elevated values for C-reactive protein (CRP), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-monocyte ratio (NMR) in migraine without aura, and an even greater NMR in migraine with aura, compared to the control group. Our study found no statistically significant differences compared to the control group. Importantly, Eryiğit et al (11) demonstrated higher NLR levels in patients with subarachnoid hemorrhage compared to those with migraines or other headache types. The authors concluded that these findings suggest systemic inflammation in migraine sufferers, indicating the presence of a persistent inflammatory process even between migraine attacks. Inan et al's study in 2015 (26) revealed a statistically significant decrease in headache severity, duration, and monthly frequency in 84 patients treated with greater occipital nerve (GON) block therapy, which was deemed a safe and effective treatment. Other observational studies also indicate the potential benefits of GON block therapy in reducing migraine attack frequency, duration, and severity (27, 28). In our study, the reduction in the number of attacks, visual analog scale (VAS) scores, and attack duration post-GON block treatment was statistically significant, confirming the efficacy of this treatment. Despite the small number of patients in our prospective investigation, other inflammatory markers exhibited higher values without a statistically significant difference. Notably, high levels of the systemic immune-inflammation index (SII), combining inflammatory cells (neutrophils and platelets) and thrombotic factors (platelets), have been linked to recurrence and mortality in pancreatic cancer and gastroesophageal adenocarcinoma (29, 30). A connection has also been established between high SII levels and postoperative adverse cardiovascular events in individuals with coronary heart disease (31). While research has explored neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in various headache types (12), our study found a higher albeit not statistically significant rate of SII in migraine patients, both before and after GON treatment, compared to control patients. This suggests a potential link between neuroinflammation development and migraines.

Our study has several notable limitations, including its retrospective nature and the lack of comparison with other migraine subgroups. Additionally, we didn't explore the association between these biomarkers and migraine intensity or their impact on quality of life. Further research with larger patient groups is warranted to examine inflammatory parameters across all migraine subgroups. We believe our findings support the concept of systemic inflammation in migraines and its association with a persistent inflammatory process, even in the absence of episodes. To understand the detailed pathophysiological components of migraines, comprehensive and controlled investigations are essential.

CONCLUSION

These findings, in our opinion, are related to the occurrence of a continuous inflammatory process even in the absence of episodes and support systemic inflammation in migraineurs. SII is a cheap and simple

to assess marker in peripheral blood, and it may be a helpful prediction marker for migraine patients who are scheduled for GON treatment even though our results are not conclusively significant. SII may be a standalone prognostic factor in migraine patients. Our findings demonstrate the clinical significance of inflammatory markers in migraine sufferers. More extensive clinical research is required to define the function of SII in patients receiving GON block therapy and to enhance our understanding of it.

Conflict of Interests: The authors declare no conflicts of interest related to this article.

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Ethics approval

The present study was approved by the Ethics Committee of Istanbul Medipol University of Medical Sciences, Istanbul, Turkey.

Author contribution

Idea/Concept: Sevil Sadri contributed to the conception and design of the research. Design: Sevil Sadri contributed to the design of the research. Data Collection/Processing: Gözde Ülfer contributed to the interpretation of the data. Analysis/Interpretation: Sevil Sadri contributed to the acquisition and analysis of the data. Literature Review and Drafting/Writing: Sevil Sadri and Burcu Polat drafted the manuscript.

Sažetak

VREDNOST INDEKSA SISTEMSKOG IMUNOG INFLAMATORNOG ODGOVORA (SII) KOD PACIJENATA SA MIGRENOM TRETIRANIH TERAPIJOM VEĆEG OKCIPITALNOG BLOKA

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Uvod: Neuroinflamacija ima ključnu ulogu u različitim neurološkim stanjima, uključujući i migrenu. Blokada većeg okcipitalnog nerva (GON) se koristi kako za akutno, tako i za preventivno lečenje osoba koje boluju od migrene. Istraživanje da li ova lokalna terapija blokadom nerva utiče na znakove sistemskog zapaljenja moglo bi biti korisno.

Materijali i metode: U studiju je uključeno ukupno 50 osoba koje boluju od migrene (uključujući osobe sa visokofrekventnom epizodnom i hroničnom migrenom) i 60 zdravih kontrolnih volontera istog uzrasta i pola. Upoređivani su odnos neutrofila i limfocita (NLR), odnos trombocita i limfocita (PLR) i nivoi SII kod osoba koje boluju od migrene i zdravih pojedinaca. Ova studija je analizirala hematološke parametre i nivoe SII koji se koriste kao inflamatorni markeri kod osoba sa dijagnostikovanom migrenom.

Rezultati: Utvrđeno je da su prosečne vrednosti trombocita i PLR vrednosti kod ispitanika slučajne grupe znatno niže od vrednosti kod ispitanika grupe pacijenata ($p < 0.05$). Biohemijske karakteristike slučajeva su ispitane pre i posle tretmana većom blokadom okcipitalnog nerva (GON), što je otkrilo statistički značajno smanjenje u učestalosti napada, ozbiljnosti i trajanju ($p < 0.001$). Nisu otkrivene značajne razlike u poređenju sa vrednostima nakon tretmana ($p > 0.05$), iako su odnosi bili veći pre primene terapije GON blokadom kod drugih mera.

Zaključak: Naša mišljenja su da su ovi rezultati povezani sa prisustvom kontinuiranog inflamatornog procesa čak i u odsustvu epizoda, podržavajući sistemsku inflamaciju kod osoba sa migrenom. Stoga, SII, pristupačan i lako merljiv marker u perifernoj krvi, može poslužiti kao koristan prediktivni marker za pacijente sa migrenom koji su zakazani za tretman blokadom većeg okcipitalnog nerva (GON). Dalja opsežna istraživanja su neophodna kako bi se utvrdilo da li SII može biti nezavisan prognostički faktor kod pacijenata sa migrenom.

Ključne reči: migrena, neuroinflamacija, sistemski indeks imunog zapaljenja.

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Original article

WOUND CHANGES FOLLOWING DELAYED ADMISSION TO THE BURN CENTER

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Abstract: **Introduction:** This retrospective clinical study aimed to investigate patient profiles and wound degree changes, as well as cultural details, resulting from delayed admissions to burn centers following burn trauma.

Methods: Patients were categorized into five groups based on the time of hospital admission after the burn trauma: 0 days, 1st day, 2nd day, 3rd day, and 4th day and beyond.

Results: During the study period, 1092 patients were admitted to the hospital on the day of their burn trauma. A total of 324 (22.8%) patients — 131 (40.4%) women and 193 (59.6%) men — were admitted to the hospital 1 day or more after the trauma. These patients were admitted to the hospital 3.77 (min = 1, max = 27) days after receiving the burn, on average.

Of the 324 patients admitted to the hospital after 1 day, 57.9% were rural residents, and 42.1% were urban residents. The most common cause of wound site infection was Staphylococcus aureus, with 20.18%.

No statistically significant difference existed between the number of days of delayed hospital admission and the duration of hospitalization.

Conclusion: Delays in hospital admission significantly influence changes in burn wound conditions.

Keywords*:* Burn, admission delay, mortality, morbidity.

INTRODUCTION

Burn injuries result in skin loss and can lead to various infections, heat loss, and immune suppression. The treatment of burn wounds has significantly improved over time, substantially enhancing the survival rates of patients. Infection prevention for burn patients starts promptly following the injury. Despite advancements in the utilization of antimicrobial therapy, escharotomy, and tangential excision, bacterial infections and associated complications persist as crucial contributors to burn morbidity and mortality (1, 2 3).

Burn injuries represent one of the most significant health problems faced by both developing and developed countries (4, 5). However, a significant gap exists between the number of burn patients and available burn units in the developing world. Limited functional specialized burn units mean that even severe burn patients cannot receive necessary treatment. Lack of knowledge, inadequate and inappropriate treatment, and limited access to tertiary centers (6) result in inadequate wound care until hospitalization in the burn care unit. Consequently, these patients are at high risk of developing systemic infections. Performing early treatment and skin grafting for these wounds (7) is sometimes impossible.

The present retrospective clinical study aimed to examine the demographic structure of burn patients who sought immediate treatment after burn trauma occurred at a tertiary care center in Turkey, as well as burn cases that sought treatment more than a day later. The study's purpose is to demonstrate the impact of delayed admission to the burn center on wound changes.

MATERIALS AND METHODS

The current study investigated all burn cases that occurred between January 1, 2014, and January 1, 2020. A total of 1415 patients were included in this retrospective follow-up analysis, focusing on their admission as inpatients to the hospital.

Patients were categorized into five groups based on their hospital admission date after the burn trauma: 0 days, 1st day, 2nd day, 3rd day, and 4th day and above. The collected data encompassed patient demographics, admission date, burn mechanism, burn degree, burn percentage, and average duration of hospitalization. The collected data were then analyzed and grouped according to the admission day.

Categorical variables were assessed using chi-square tests, while normally distributed continuous variables were subjected to one-way analysis of variance. Post hoc tests utilizing Tukey's honestly significant difference method were conducted following the one-way analysis of variance. Multiple comparisons were corrected using Bonferroni corrections. The Statistical Package for the Social Sciences for Windows (version 10.0; SPSS Inc., Chicago, IL, USA) was used for statistical analyses. P values below 0.05 were considered to be statistically significant.

RESULTS

Throughout the study duration, a total of 1415 patients were hospitalized due to burn injuries. Among them, 704 patients were admitted through the emergency room, while 711 patients were admitted from the outpatient clinic. The study cohort included 798 men (56.4%) and 617 women (43.6%).

Among the hospitalized patients, 1092 were admitted to the hospital on the same day as their burn trauma. Additionally, 324 patients (22.8%), consisting of 131 women (40.4%) and 193 men (59.6%), were admitted to the hospital one day or more after the burn trauma. On average, these patients were admitted to the hospital 3.77 days (min = 1, max = 27) after sustaining the burn injury (Table 1). The patients' mean age was 12.86 ± 17.34 years (min = 1, max = 94). Burn degrees ranged from second to fourth.

When examining age distribution, similar trends were observed between patients who applied within the first 24 hours and those who applied after the first 24 hours. Notably, there was a higher number of patients in the +65 age group who presented to the hospital at a later time (Figure 1).

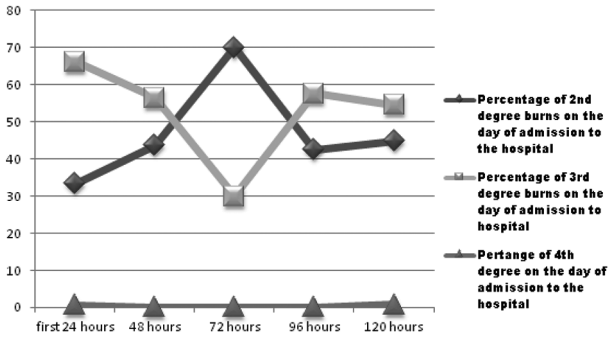

Figure 1. *Distribution of age groups of those who were admitted on the same day and those who were admitted with a delay of 1 day or more*

The time of admission varied according to the etiology of the burns. When examining the causes of burns in cases of late admission, the causes were as follows: scalding burns accounted for 72.1%, flame burns for 12.7%, burns from contact with hot objects for 9.9%, electrical burns for 3.1%, chemical burns for 0.9%, and other causes for 1.3%. Analyzing the applicants with emergency burns did not yield statistically significant results (p = 0.75). In cases of late applicants, the most commonly burned areas were the right and left extremities (Table 2).

Of the 1,092 patients admitted within the first 24 hours, 55.1% were urban residents and 44.9% were

Table 1. *Patient information overview*

	Immediate applicants	Applicants in 24–48 hours	Applicants in 49–72 hours	Applicants in 73–96 hours	Applicants in 97 hours or more
Number of patients	1092	55	40	85	143
Percentage of patients	77.2%	3.9%	2.8%	6.0%	10.1%
Average percentage of burns ± SD	9.09 ± 6.325	10.58 ± 9.251	10.15 ± 6.542	10.72 ± 9.711	8.66 ± 6.301
Average length of hospital stay	5.46 ± 4.657	5.13 ± 3.278	6.65 ± 10.712	5.16 ± 5.442	5.78 ± 6.911

SD: standard deviation

Table 2. *Burn areas in early and late admissions*

Burn site	Percentage in first 24 hours	Percentage of applicants after 24 hours	Total	Pearson chi-square
Head neck	16.3%	5.1%	21.4%	0.680
Right upper extremity	25.1%	6.9%	32.0%	0.654
Left upper extremity	24.9%	7.8%	32.8%	0.493
Chest anterior face + abdomen	20.6%	7.2%	27.8%	0.179
Chest back + back	5.7%	1.9%	7.6%	0.639
Perineum	3.7%	1.6%	5.3%	0.335
Right lower extremity	32.5%	10.0%	42.5%	0.635
Left lower extremity	31.1%	9.5%	40.6%	0.805

rural residents. Among the 324 patients admitted to the hospital after 24 hours, 57.9% were rural residents, and 42.1% were urban residents.

In admissions occurring up to 72 hours after the burn trauma, there was a gradual increase in the percentage of second-degree burns, while the percentage of third-degree burns gradually decreased. However, this change was not statistically significant (p = 0.08) as shown in Figure 2. Beyond the 72-hour mark, the percentage of second-degree burns decreased, and the percentage of third-degree burns increased.

When considering patients with positive wound culture results, 90.1% of these cases were among those who presented to the hospital a day or more after the burn. Among patients who arrived a day or more after the burn, gram-positivebacteria were the most commonly isolated organisms (65.14%). Within this group, Staphylococcus aureus was the most prevalent, accounting for 20.18% of cases (Table 3).

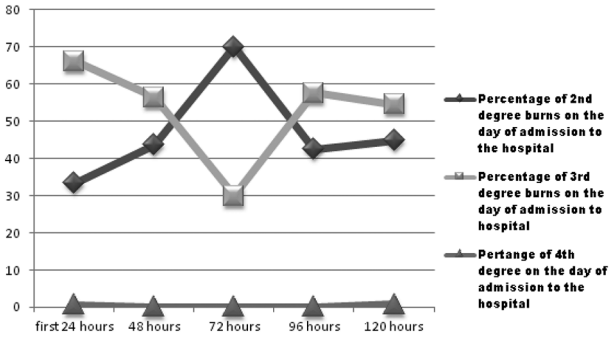

***Figure 2**. The degree of burn patients based on the time of admission to hospital*

The mean hospital stay of all patients was 5.50 ± 5.189 days. There was no statistically significant difference between the number of days of late admission and the duration of hospitalization. p = 0.548, (Figure 3).

Out of the total patients, 21 (1.48%) died, with two (9.5%) due to insufficient fluid replacement within

***Table 3.** Culture results of some microorganisms of early and late admitted patients*

Main pathogen	Subgroup	Number of applicants in 24 hours	Number of applicants in 1-2 days	Number of applicants in 2-3 days	Number of applicants after > 3 days
Gram(-)					
Acinetobacter	Baumannii	7			1
Escherichia	coli	27	2	2	3
	faecalis		1	2	2
Klebsiella	pneumoniae	5			
Pantoea	agglomerans	3			
Proteus	mirabilis	4		1	1
pseudomonas	aeruginosa	28	1	2	5
	putida				2
Serratia	marcescens	1			1
Gram(+)					
Enterococcus	avium	1			
Kocuria	kristinae	4			
Lactococcus	garvieae				1
Staphylococcus	aureus	49	4	3	8
	epidermidis	67	2	2	8
	hemolyticus	21	2	2	2
	hominis	23	1	1	8
	lugdunensis	2			
	xylosus	3		1	1
Streptococcus	Spp.	1			2
	Agalactia	1			
	Mutis	1			
	pyogenes	1	1		1

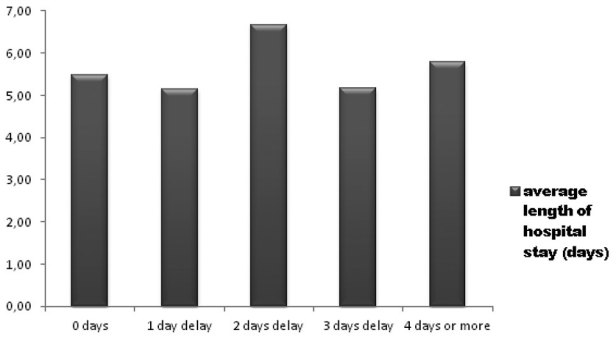

Figure 3. *Comparison of patients' late admission and hospitalization time*

the first 24 hours, and the remaining 19 (90.5%) after 1 day or more, primarily from wound site infections.

DISCUSSION

A burn is a devastating form of trauma affecting both developed and developing countries. Delayed presentation affects the prognosis by delaying fluid resuscitation, burn wound management, pain control, and wound infection control. In our study, the incidence of burn injuries was higher in men (56.4%) than women (43.6%), probably because the predominance of males in this study is due primarily to the fact that men are income-generating members of the family and are the most exposed to outdoor activities in our country. Males are less concerned about their health because of their large family (6). In the study conducted by Tasnim and Hubab et al. (8, 9), the incidence of men with burn trauma was found to be higher. Our work is in line with this.

Delays in burn treatment pose a significant issue in developing countries. Burn patients residing in rural areas may experience delays in gaining admission to burn units (10). This can be attributed to factors such as remote rural locations, lengthy travel distances, lack of accessible roads and transportation options, andlimited availability of burn care facilities (11). For instance, burn survivors in Ghana often seek medical attention at local hospitals, and it takes an average of 60 days to reach burn units in the country. Unfortunately, burn wounds are frequently infected by the time patients receive treatment in such cases (11). Notably, only 48% of childhood burns in Ghana receive treatment in modern healthcare facilities, with 68% of these being addressed within 24 hours of the burn incident. Various factors contribute to treatment delays, including a lack of awareness regarding the severity of the condition and financial constraints (11).

In our study, 77.2% of patients were admitted to the hospital on the same day as their burn trauma, with 3.9% admitted within 24–48 hours, 2.8% within 49–72 hours, 6% within 73–96 hours, and the remaining 10.1% experiencing an admission delay of 97 hours or more. Among the 323 patients admitted after 24 hours, 57.9% were residents of rural areas, while 42.1% resided in urban settings.

In the study by Duzgun et al., 50% of the patients were admitted 1 day or later (12). In our study, 22.8% of all patients were admitted to the hospital after a day. The rate of delayed admission was 36.4% in the 65+ age group. In the current study, we attribute this to living alone, which correlates with previous reports (12).

In our study, the average hospital admission occurred 3.77 days after the burn incident (min = 1, max = 27). In a study conducted by Duzgun et al. (12), this duration was reported as 5.4 days. We attribute the shorter duration in our study to improved accessibility of transportation options and a higher number of available burn centers.

In Khurramet al.'s study, the most common cause of burns in late admission was flash flame burn (67.30%), followed by scalding burn (7.69%) (6). In our study, scalding burns were the most common cause, and the most common burn sites were the right and left extremities.

In our study, the burn degree ranged from second to fourth in patients who were admitted more than 1 day after the trauma, while the percentage of second-degree burns in the group increased gradually in those admitted from the first hour to 72 hours, but the percentage of third-degree burns in the group gradually decreased. The percentage of patients with third-degree burns increased after 72 hours, while the percentage of patients with second-degree burns decreased.

Here, 72 hours is an important reason for the burn degree to be fully settled. At the same time, alternative medicine treatments are common in Turkey, generally in rural areas, where second-degree burns are treated with alternative medicine.

When looking at patients with positive wound culture results, 90.1% of these werepositive in those who came to the hospital after 1 day or more. In the wound culture results of patients who came after 1 day or more, gram-positive bacteria were the most common (65.14%). The most common of these was Staphylococcus aureus (20.18%). In the study by Özbek et al (7), the most commonly cultured microorganism from infected burn wounds was Pseudomonas aeruginosa (38%), followed by Staphylococcus aureus (18.3%) and coagulase-negative staphylococci (13.6%).

The factors that will most affect the estimation of hospital stay in acute burn patients are infection incidence, wound depth, TBSA%, and inhalation injury (13). In our study, the mean hospital stay of all patients was 5.50 ± 5.189. There was no statistically significant

difference between the number of days of late admission to the hospital and length of hospital stay. In a study by Goswami et al., The length of stay was significantly low in the early excision group (14.9 ± 6.37 days vs. 26.4 ± 20.16 days, p = 0.003) as compared with the late excision group (14).

The limitations of this study are specific to its retrospective methodology. The analyzed data were from a single burn center in the Diyarbakir province and might thus be subject to presentation bias. Patients who sought treatment at burn units and plastic surgery polyclinics in the surrounding provinces were not included in the analysis.

CONCLUSION

Delays in hospital admission stand out as the critical factor impacting burn wound treatment. Swift patient transportation, addressing hypovolemic shock upon initial hospitalization through appropriate pre-treatment, early wound debridement, protein-calorie support, and prompt infection management are pivotal prognostic elements.

Author Contributions

Ebral Yiğit- Concept, Design, Data collection &/or processing, Literature search, Writing, Critical review; **Yasemin Demir Yiğit-** Supervision, Analysis and/or interpretation, Critical review

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Sažetak

PROMENE U RANAMA NAKON ODLOŽENOG PRIJEMA U CENTAR ZA OPEKOTINE

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Uvod: Ova retrospektivna klinička studija sprovedena je kako bi se ispitali profili pacijenata i promene u ranama u zavisnosti od stepena opekotine i izolovanim bakterijama, nakon kasnog prijema u centre za opekotine, a nakon trauma izazvanih opekotinama.

Metode: Pacijenti su kategorisani u pet grupa na osnovu datuma prijema u bolnicu nakon traume izazvane opekotinama: 0 dana, 1. dana, 2. dana, 3. dana i 4. dana i više.

Rezultati: Tokom perioda istraživanja, 1092 pacijenta je primljeno u bolnicu istog dana kada su zadobili opekotine. Ukupno 324 (22,8%) pacijenata — 131 (40,4%) žena i 193 (59,6%) muškaraca — je primljeno u bolnicu jedan ili više dana nakon traume. Ovi pacijenti su primljeni u bolnicu prosečno 3,77 dana (min = 1, max = 27) nakon što su zadobili opekotine.

Od 324 pacijenta koji su primljeni u bolnicu nakon jednog dana, 57,9% su bili ruralni stanovnici, dok je 42,1% bilo urbanog porekla. Najčešći uzrok infekcije mesta povrede bio je Staphylococcus aureus sa 20,18%.

Nije postojala statistički značajna razlika između broja dana kašnjenja pri prijemu u bolnicu i dužine hospitalizacije.

Zaključak: Kašnjenje u prijemu u bolnicu značajno utiče na promene u stanju opekotina.

Ključne reči: Opekotine, kašnjenje pri prijemu, smrtnost, morbiditet.

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ORAL TOPICAL TIMOLOL MALEAT OR ORAL PROPRANOLOL TREATMENT FOR INFANTILE HEMANGIOMAS: CLINICAL ANALYSIS OF 403 PATIENTS

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Abstract: **Objective:** Infantile hemangiomas (IH) are the most common benign vascular tumors of infancy. Propranolol (P), a nonselective beta-blocker, has been successfully used in managing IHs. Ongoing studies investigate the efficacy of the topical β-antagonist timolol maleate (TM) in IHs. The aim of this study is to assess the effects of interventions for managing infantile hemangiomas in children.

Material and Methods: We retrospectively reviewed a total of 403 IH patients from March 2021 to March 2022. The patients were stratified into three groups. Patients in Group 1 were given TM at a dose of one drop topically twice a day, 0.5%. Patients in Group 2 were given P at a dose of 1 mg/kg twice a day. The patients in Group 3 did not receive any treatment, and observation was conducted solely by contacting the controls.

Results: The median age of diagnosis was 5 months (range 0-60), with 57.1% of the cases being male. While TM treatment was applied to 32% of the children and P treatment was applied to 46.9% of the children, no treatment was administered in 21.1%. The most common location of hemangiomas was the face, accounting for 39.2%. Hemangiomas were observed in more than one location in 48 (12%) children. The median follow-up period for the patients was 4 months (range 0-28). Hemangiomas remained unchanged in 28.3% of all cases, shrank in 60.3%, and continued to grow in 11.4%. The primary indication for initiating TM was superficial hemangiomas and infants younger than 6 months. The leading reason for starting P significantly higher than in the other groups (p : 0.001). No statistically significant differences were observed between the groups regarding bleeding and ulceration rates ($p > 0.05$).

Conclusion: The efficacy of propranolol in treating IH was higher than that of TM.

Keywords: timolol maleate, infantile hemangioma, propranolol.

INTRODUCTION

Infantile hemangiomas (IH) are proliferative hamartomas that originate from the vascular endothelium, representing the most prevalent benign tumors of childhood (1, 2, 3). Their incidence varies between 4-12% (3, 4). The assumed cell of origin for Ihs is progenitor endothelial cells originating from the chorionic villi of the placenta. Factors like the glucose transporter protein, particularly expressed by chorionic villi, and the inappropriate distribution of chorionic villus cells during fetal development have been implicated in IH development (5 ,6). Vascular endothelial growth factor A, associated with angiogenesis, is considered a primary driver of IH proliferation and contributes to treatment responses involving corticosteroids and P (7). Moreover, although rare, genetic factors might play a role in the pathogenesis of IHs (8).

IHs typically emerge in the first few weeks of life, with the most rapid growth occurring in the second postnatal month (9, 10). Growth continues until 12 months of age, after which it slows down in parallel with the child's general growth (7, 9). Approximately half of IH cases experience complete involution

by the age of 5, with 70% disappearing by age 7 and 95% regressing between ages 10 to 12 (11). However, complications such as ulceration, bleeding, functional impairment, and cosmetic issues may arise in about a quarter of cases (7). Various treatment methods have been employed, ranging from corticosteroids to propranolol, and from surgical interventions to sirolimus (12 ,13).

Presently, oral P is the preferred first-line treatment option (2, 14). It's the sole treatment for IH endorsed by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (15, 16). Although the precise mechanism of action remains uncertain, it's believed that P acts by inhibiting vasoconstriction and angiogenesis in endothelial cells, leading to apoptosis (15). Additionally, recent studies have indicated that P hinders the differentiation of hemangioma stem cells into hemangioma endothelial cells (17). Most cases experience complete resolution, with response rates reaching up to 100% (15, 18). Nonetheless, adverse effects such as hypoglycemia, bradycardia, and hypotension have been associated with propranolol (19).

However, considering the unfavorable side effects of propranolol, topical timolol maleate has also been attempted as a treatment (20).

Timolol maleate is a non-selective beta-adrenergic receptor antagonist. It may prove beneficial for treating thin, superficial Ihs (15, 16). Studies have revealed noteworthy response rates, leading to a reduction in both IH color and size (21). Nevertheless, a recent study indicated no substantial effect when using timolol for IH treatment during the early proliferative phase (16). In a cohort study, it was documented that only two patients experienced apnea or bradycardia, necessitating the discontinuation of timolol. Notably, these two patients had a history of symptomatic bradycardia prior to using the medication (22).

The primary goal of this study was to determine the most effective treatment approach for IH management.

MATERIAL AND METHODS

Pediatric patients diagnosed with infantile hemangioma, aged between 3-82 months, at a single Pediatric Oncology Clinic between 01 .03. 2021 and 01. 03. 2022 were included. Demographic and clinical data of the patients were retrospectively obtained from patient records. The patients were categorized into three groups. Patients in Group 1 were administered TM 0.5% solution at a dose of one drop topically twice a day (22). Patients in Group 2 were given P at a dose of 1 mg/kg twice a day (23). The patients in Group 3 did not receive any treatment, and observation was conducted solely by contacting the controls. In the study, a reduction of 50% or more in the size of the hemangioma after treatment was considered a reduction. Echocardiography was conducted prior to treatment due to the arrhythmia side effect of P (16, 21). Abdominal and transfontanel USG were requested to evaluate the extent of the hemangioma.

The study was approved by the Başakşehir Çam and Sakura City Hospital Clinical Research Ethics Committee (Number: 2021.12.274).

Statistical analysis

Data were analyzed using IBM SPSS, version 23 (IBM Inc., Armonk, NY, USA). Through the Kolmogorov-Smirnov test, it was determined that parameters did not exhibit normal distribution. The Kruskal-Wallis test was employed to compare parameters among groups. Dunn's test was used to identify the group responsible for the differences. The Mann-Whitney U test was utilized to compare parameters between the two groups. The Chi-square test and Fisher Freeman Halton Exact Chi-square test were applied to compare qualitative data. Statistical significance was considered when $p < 0.005$.

RESULTS

A total cohort size of 403 patients was identified, with 57.1% of the cases being male. The median age was 24 months (range 3-82) (Table 1). The median age at diagnosis was 5 months (range 0-60). While TM treatment was administered to 32% of the children and P treatment was given to 46.9% of the children, no treatment was administered in 21.1% of cases. The most common location of hemangiomas was the face, accounting for 39.2%. Other sites of occurrence are indicated in Table 2. Hemangiomas were observed in more than one location in 48 (12%) children (Table 1).

The median follow-up period was 4 months (range 0-28). The median age at the onset of treatment was 6 months (1-53 months). Hemangioma remained unchanged in 28.3% of all cases, shrank in 60.3%, and continued to grow in 11.4% (Table 2). Timolol maleate and P were administered to 129 and 189 patients, respectively. The most common indication for initiating TM was superficial hemangiomas and infants younger than 6 months (Table 2). The leading indication for starting P was facial hemangiomas (Table 2). Bleeding occurred in 1.5% of hemangioma cases, and ulceration was observed in 3.7% (Table 2). Some of the patients underwent ultrasonography and echocardiography, and the results are summarized in Table 2.

Table1. *General characteristics of the patients*

	n	Median age (months)
Age (months)	403	24 (3-82)
Age of diagnosis (months)	403	5 (0-60)
		n (%)
Group 1 Group 2 Group 3	Timolol maleate Propranolol No treatment	129 (32) 189 (46.9) 85 (21.1)
Gender	Female Male	280 (69.5) 123 (30.5)
One Location	Face Neck Extremity Scalp Body Visceral Genitalia	158 (39.2) 15 (3.7) 76 (18.9) 50 (12.4) 85 (21.1) 4 (1) 15 (3.7)
2./3. location (n = 48)	Neck Extremity Scalp Scalp + body Body Visceral Genitalia	2 (4.2) 9 (18.8) 12 (25) 1 (2.1) 19 (39.6) 1 (2.1) 4 (8.3)

Table2. *Distribution of information on follow-up and treatments*

	n	Median (range)
Follow-up time (months)	403	4 (0-28)
Treatment start age	318	6 (1-53)
		n (%)
During follow-up	stabilized shrunk grew up	114 (28.3) 243 (60.3) 46 (11.4)
TM initiation indication (n = 129)	Superficial hemangioma age < 6 months age = 6-12 months	43 (33.3) 64 (49.6) 22 (17.1)
P initiation indication (n = 189)	Facial hemangioma hemangioma in the neck Hemangioma larger than 2 cm Tends to grow bleeding ulceration Family request	92 48.7) 7 (3.7) 62 (32.8) 10 (5.3) 5 (2.6) 8 (4.2) 5 (2.6)
bleeding (n = 403)	none positive	397 (98.5) 6 (1.5)
ulceration (n = 403)	none positive	388 (96.3) 15 (3.7)
Abdomen USG (n = 403)	none No pathology Hemangioma positive	152 (37.7) 243 (60.3) 8 (2)
Cranial USG (n = 403)	none No pathology	216 (53.6) 187 (46.4)
Superficial USG (n = 403)	none No definitive diagnosis Hemangioma positive	297 (73.7) 27 (6.7) 79 (19.6)
ECO (n = 274)	none No pathology	143 (52.2) 131 (47.8)

TM: Timolol Maleate. **P**: Propranolol. **USG**: Ultrasonography. **ECO**: Echocardiography.

There was a significant difference between the groups regarding the mean age and mean age at diagnosis ($p < 0.05$). The mean age of children treated with P was significantly higher than that of those treated with TM (p: 0.030; $p < 0.05$). Additionally, the mean age at diagnosis of children treated with P was found to be significantly higher than that of those treated with TM (p: 0.036; $p < 0.05$). There were no significant differences among the other groups ($p > 0.05$) (Table 3).

No significant difference was observed between the groups concerning gender distribution ($p > 0.05$) (Table 3). The follow-up period for untreated children was significantly shorter compared to those treated with P (p: 0.001) and TM (p: 0.001) ($p < 0.05$). No significant difference existed between the P and TM groups ($p > 0.05$) (Table 3).

The age of treatment initiation in children treated with TM was statistically significantly lower than that in those treated with P (p: 0.001; $p < 0.05$). A statistically significant difference was observed among the groups concerning hemangioma locations (p: 0.001; $p < 0.05$). Facial IHs (54%) were significantly more prevalent in Group 2. The incidence of hemangiomas on the scalp (20.2%) in those treated with TM was significantly higher compared to those treated with P (6.9%). Furthermore, the proportion of hemangiomas on the trunk (12.2%) was significantly lower in individuals treated with P (Table 3).

Table 3. *Evaluations according to groups*

		TM Group 1	**PP Group 2**	**No Treatment Group 3**	**p**
Age (months) median		23	27	22	*
Age of diagnosis (months)		4	6	5	[1]0.039*
Follow-up time (months)		5	5	3	[1]0.001*
Age to start treatment (months)		5	6	-	[2]0.001*
Gender n (%)	Female Male	93 (%72.1) 36 (%27.9)	131 (%69.3) 58 (%30.7)	56 (%65.9) 29 (%34.1)	[3]0.626
Hemangioma location n (%)	Face Neck extremity Scalp Body Visceral Genitalia	38 (%29.5) 2 (%1.6) 24 (%18.6) 26 (%20.2) 34 (%26.3) 0 (%0) 5 (%3.9)	102 (%54) 10 (%5.3) 30 (%15.9) 13 (%6.9) 26 (%13.8) 2 (%1.1) 6 (%3.2)	18 (%21.2) 3 (%3.5) 22 (%25.9) 11 (%12.9) 25 (%29.5) 2 (%2.4) 4 (%4.7)	[3]0.001*
Response to treatment/no treatment n (%)	Stabil shrunk grew up	33 (%25.6) 70 (%54.3) 26 (%20.2)	37 (%19.6) 144 (%76.2) 8 (%4.2)	44 (%51.8) 29 (%34.1) 12 (%14.1)	[3]0.001*
Bleeding (%)	None pozitive	127 (%98.4) 2 (%1.6)	185 (%97.9) 4 (%2.1)	85 (%100) 0 (%0)	[4]0.493
Ulceration n (%)	None pozitive	123 (%95.3) 6 (%4.7)	180 (%95.2) 9 (%4.8)	85 (%100) 0 (%0)	[4]0.107
Abdomen USG n (%)	None no pathology Hemangioma	35 (%27.1) 93 (%72.1) 1 (%0.8)	86 (%45.5) 98 (%51.9) 5 (%2.6)	31 (%36.5) 52 (%61.2) 2 (%2.4)	[4]0.005*
Cranial USG n (%)	None No pathology	55 (%42.6) 74 (%57.4)	115 (%60.8) 74 (%39.2)	46 (%54.1) 39 (%45.9)	[3]0.006*
Superficial USG n (%)	None No definitive diagnosis Hemangioma	89 (%69) 12 (%9.3) 28 (%21.7)	142 (%75.1) 9 (%4.8) 38 (%20.1)	66 (%77.6) 6 (%7.1) 13 (%15.3)	[3]0.390
ECO n (%)	None no pathology		80 (%42.3) 109 (%57.7)	63 (%74.1) 22 (%25.9)	[3]0.001*

[1]Kruskal Wallis Test; [2]Mann Whitney U Test; [3]Ki-kare test; [4]Fisher Freeman Halton Exact Test
p < 0.05.* **TM: Timolol Maleate. **P**: Propranolol. **USG**: Ultrasonography. **ECO**: Echocardiography.

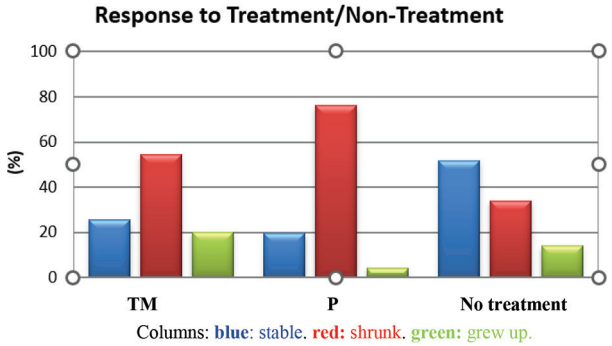

Figure 1. *Response toTreatment/Non-Treatment*

A significant difference emerged among the groups in terms of responses to treatment or lack thereof (p: 0.001; $p < 0.05$) (Table 3). The rate of hemangioma shrinkage in those treated with P (76.2%) was markedly higher than in those treated with TM (54.3%) and those who received no treatment (34.1%). Additionally, the shrinkage rate of hemangiomas in those treated with TM (54.3%) was significantly higher than in those who were untreated (34.1%) (Figure 1). No statistically significant differences were noted among the groups concerning bleeding and ulceration rates ($p > 0.05$) (Table 3). Notably, no side effects were reported.

DISCUSSION

Infantile hemangioma is one of the most common benign vascular endothelial tumors. Various approaches, including steroids, oral propranolol, topical timolol maleate, and laser therapy, are employed for treating infantile hemangioma (12, 13).

Since 2008, oral propranolol has gained widespread use for IH treatment (24). Numerous clinical trials have assessed the efficacy of oral propranolol for IH treatment. A meta-analysis has demonstrated that oral propranolol surpasses other therapies in improving the response rate of IH, thus being considered a first-line therapy for IH in children (25). In another study, P treatment achieved a therapeutic response with at least a 50% mean percentage reduction in size in 84.6% of patients (26). A study by Zhang et al. showed a response to oral propranolol treatment in 96.9% of 578 IH patients (27).

Although oral propranolol remains the primary IH therapy, topical timolol maleate offers a well-tolerated alternative. A study by Jha et al. confirmed the safety and effectiveness of topical timolol maleate for IH treatment (28). Another study involving 145 patients reported that only 8.3% showed no response to topical 0.5% timolol maleate treatment (29). Jha et al. also demonstrated that laser-assisted drug delivery of timolol maleate 0.5% is an effective and safe approach for treating deep IHs (30).

Despite these treatment options, infantile hemangiomas often regress spontaneously without complications (7, 9, 11). Thus, cases without complications, growth tendencies, or functional/cosmetic concerns can be managed without drug treatment (7).

According to our study results, oral propranolol emerged as the most effective IH treatment. No patient reported side effects. Topical timolol maleate therapy was primarily administered to infants under 6 months (p : 0.001) or for treating superficial IH, consistent with other studies. TM's treatment success rate was also high. However, P was predominantly administered to patients with growth tendencies and complications. If TM had been the initial treatment for these patients, TM's success rate might have been lower. Ongoing research investigates enhancing success rates by varying P and TM doses across different age groups. In our study, a dose of 2mg/kg/day proved effective for oral P. Larger studies are essential for assessing efficacy across various age groups.

The retrospective nature of our study limits it to information within patient records, constituting a study limitation.

CONCLUSION

Oral propranolol has demonstrated both effectiveness and safety in treating IH, whereas the efficacy of TM appears to be lower compared to P.

Author Contributions

Conceived and designed the analysis: OT; Collected the data: CNB, EA, AGK, EPU, HAS, DY, AOK, SE, ST, AA; Contributed data or analysis tools: OT; Performed the analysis: OT; Wrote the paper: OT.

Abbreviations

IH — Infantile hemangioma
P — Propranolol
TM — Timolol Maleate
USG — Ultrasonography.
ECO — Echocardiography

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Sažetak

ORALNI TOPIKALNI TIMOLOL MALEAT ILI ORALNI PROPRANOLOL U LEČENJU INFANTILNIH HEMANGIOMA: KLINIČKA ANALIZA 403 PACIJENTA

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Uvod: Infantilni hemangiomi (IH) predstavljaju najčešće benigne vaskularne tumore kod odojčadi. Propranolol (P), neselektivni beta-blokator, uspešno se primenjuje za tretiranje IH. Trenutno se istražuje efikasnost topikalnog β-antagoniste timolol maleata (TM) kod IH. **Cilj** ovog istraživanja je proceniti efekte intervencija u lečenju infantilnih hemangioma kod dece.

Materijal i Metode: Retrospektivno je analizirano ukupno 403 pacijenta sa IH dijagnozom u periodu od marta 2021. do marta 2022. godine. Pacijenti su podeljeni u tri grupe. Pacijenti u Grupi 1 su dobijali TM u dozi od jedne kapi topikalno, dva puta dnevno, 0,5%. Pacijenti u Grupi 2 su dobijali P u dozi od 1 mg/kg dva puta dnevno. Pacijenti u Grupi 3 nisu primili nikakav tretman, već je praćenje vršeno isključivo kontaktiranjem kontrolne grupe.

Rezultati: Srednja vrednost uzrasta pri postavljanju dijagnoze iznosila je 5 meseci (raspon 0-60), pri čemu je 57,1% slučajeva bilo muškog pola. Dok je TM tretman primenjen kod 32% dece, a P tretman kod 46,9% dece, 21,1% nije dobilo nikakav tretman. Najčešća lokacija hemangioma bilo je lice, što je činilo 39,2%. Hemangiomi su primećeni na više od jedne lokacije kod 48 (12%) dece. Srednja vrednost perioda praćenja pacijenata iznosila je 4 meseca (raspon 0-28). Hemangiomi su ostali nepromenjeni kod 28,3% svih slučajeva, smanjili su se kod 60,3%, a nastavili su rast kod 11,4%. Osnovni pokazatelj za započinjanje TM bio je površinski hemangiom i bebe mlađe od 6 meseci. Vodeći razlog za početak P tretmana bio je hemangiom na licu (p : 0,001). Stopa smanjenja IH kod osoba koje su tretirane P bila je značajno veća nego u drugim grupama (p : 0,001). Nisu primećene statistički značajne razlike između grupa u pogledu stope krvarenja i ulceracija (p > 0,05).

Zaključak: Efikasnost propranolola u tretiranju IH bila je veća u poređenju sa TM.

Ključne reči: timolol maleat, infantilni hemangiom, propranolol.

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RISK FACTORS FOR MORTALITY IN INTENSIVE CARE UNIT-ACQUIRED PNEUMONIA DUE TO KLEBSIELLA PNEUMONIAE

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Abstract: **Objective**: Hospital-acquired pneumonia (HAP) developing in intensive care units (ICU) is an important problem. Gram-negative bacteria are the most important cause of HAP. Among these bacteria, *Klebsiella pneumoniae* is among the most important pathogens. The mortality rate for infections caused by carbapenem-resistant *Klebsiella pneumoniae* is high. Identifying mortality risk factors is crucial to prevent potential deaths. The aim of this study was to determine the risk factors associated with mortality in HAP due to *Klebsiella pneumoniae* in intensive care unit patients.

Material and Methods: This cross-sectional study was conducted between 01. May 2021. and 01. May 2023. in the Anesthesia and Reanimation Intensive Care Unit of Izmir Tepecik Training and Research Hospital. Patients aged 18 years who were diagnosed with hospital-acquired pneumonia due to *Klebsiella pneumoniae* were included in the study. The dependent variable of the study was 14-day mortality due to *Klebsiella pneumoniae* pneumonia. Independent variables were presence of COVID-19, bacteremia, ceftazidime/avibactam treatment, intubation, sepsis, Charlson comorbidity score, and laboratory parameters. We conducted logistic regression analysis using the backward elimination method to identify independent predictors of mortality.

Results: A total of 176 patients were included in the study. The mean age of the patients was 64.6 ± 16.2 years and 64.2% were male. The 14-day mortality rate was 29% (n:51). In the regression analysis performed to determine the risk factors for mortality; in the univariate regression analysis, day 0 leukocyte count > 10.600/mm^3 (OR: 2.31; 95% CI: 1.10-4.84), platelet value < 140.000/mm^3 (OR: 2.26; 95% CI: 1.06-4.81), AST > 50 U/L (OR: 2.40; 95% CI: 1.20-4.79) and creatinine > 1.3 mg/dL (OR: 1.96; 95% CI: 1.006-3.82) were associated with mortality. In multivariate regression analysis, a leukocyte count > 10.600/mm^3 (OR: 2.30; 95% CI: 1.03-5.14) and an AST > 50 U/L (OR: 2.23; 95% CI: 1.04-4.75) were found to be independent predictors of mortality.

Conclusion: In conclusion, leukocytosis and high AST levels were found to be independent risk factors associated with mortality in cases of *Klebsiella pneumoniae* in the intensive care unit. Taking these factors into account, in addition to other parameters and scores that determine the prognosis of patients, may be useful in reducing mortality.

Keywords: *Klebsiella pneumoniae*, mortality, pneumonia, risk factors, intensive care units.

INTRODUCTION

Hospital-acquired pneumonia (HAP) in intensive care units (ICU) is a significant problem due to its high frequency and mortality (1). Gram-negative bacteria are the most important cause of HAP developing in ICUs (2). Among these bacteria, multidrug-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae (K. pneumoniae)* are among the most important pathogens. The main resistance mechanism in these microorganisms is beta-lactamase enzyme production. Carbapenem group antibiotics are increasingly used in these units due to high extended-spectrum beta-lactamase (ESBL) rates. As a result, carbapenem resistance among these bacteria has increased significantly in recent years (3). The mortality rate for infections associated with carbapenem-resistant *K. pneumoniae* is as high as 50% (4, 5). Several new antibiotics have been introduced for the

treatment of carbapenemase-producing *K. pneumoniae* infections. Before the introduction of these agents or in countries without access to them, "second-line" antibiotics such as aminoglycosides, tigecycline, fosfomycin, and colistin are used in the treatment. Among the newer antibiotics, ceftazidime/avibactam stands out. In the treatment of infections due to carbapenemase-producing Enterobacteriaceae, mortality rates were lower with ceftazidime/avibactam treatment compared with conventional treatment regimens (6). Ceftazidime/avibactam received approval in our country in October 2019 and has been in use since April 28, 2021(7).

Several factors influence mortality in ICU-acquired pneumonia caused by gram-negative bacteria. In additon to coronary heart disease, diabetes, renal failure, shock, venous catheterization, mechanical ventilation, high Charlson comorbidity, and quick Sepsis Related Organ Failure Assessment (qSOFA) scores have all been associated with poor prognosis (8, 9).

However, there have been only a limited number of studies on pneumonia caused by *K. pneumoniae* indicating the risk factors for mortality. Identifying mortality risk factors is crucial to prevent potential deaths.

Aim: The aim of this study was to determine the risk factors associated with mortality in HAP due to *K. pneumoniae* infection in intensive care patients.

MATERIAL AND METHODS

This cross-sectional study was conducted between 01. May 2021. and 01. May 2023. in the Anesthesia and Reanimation Intensive Care Unit of Izmir Tepecik Training and Research Hospital. Patients aged 18 years who were diagnosed with hospital-acquired pneumonia due to *K.pneumoniae* were included in the study. The diagnosis of pneumonia was made according to the Infectious Diseases Society of America (IDSA) guideline criteria (10).

Electronic medical records were used to collect data. The study was approved by the Ethics Committee of the Tepecik Training and Research Hospital on September 15, 2022, under the number 2022/09-13.

The study's dependent variable was 14-day mortality due to *K.pneumoniae* pneumonia. Independent variables included demographic characteristics of the patients, the presence of COVID-19, bacteremia, ceftazidime/avibactam treatment, comorbidity, intubation, sepsis, Charlson comorbidity score, as well as levels of leukocytes, platelets, hemoglobin, C-reactive protein, procalcitonin, creatinine, albumin, AST, and ALT. Laboratory results were categorized using either the upper/lower limits of normal values or the median/intermediate values in the study database.

Descriptive statistics are presented as a number and percentage for categorical variables, the mean and standard deviation for continuous variables that fit the normal distribution, and median and 25%-75% interquartile range for those that do not. We used Pearson's chi-square or Fisher's exact test to compare categorical data, the t-test to compare continuous variables that followed a normal distribution, and the Mann–Whitney U test for those that did not.

Logistic regression analysis with the backward elimination method was performed to determine the independent predictors of mortality. To select the variables to be included in the model, a univariate regression analysis was first performed with the variables that were statistically significant in the univariate analysis or had a relationship found in the literature and with biological probability, and a crude odds ratio (OR) was calculated. The adjusted OR was calculated by multivariate regression analysis, and predictors were determined. Analyses were performed with SPSS 22.0 (IBM Corporation, Armonk, New York, United States) and a two-way p value < 0.05 was considered statistically significant.

RESULTS

A total of 176 patients were included in the study. The mean age of the patients was 64.6 ± 16.2 years and 64.2% were male. The 14-day mortality rate was 29% (n:51). *K. pneumoniae* growth in blood culture was found in 21.6% (n:37), sepsis in 64.1% (n:107), and COVID-19 in 41.5% (n:73) of the patients. 94.5% of COVID-19 cases and 84.5% of other cases were intubated. The demographic and clinical characteristics, laboratory findings, and treatment results of the patients are shown in Table 1.

Table 1. *Demographic and clinical characteristics, laboratory findings, and treatment results of the patients*

Demographic and clinical characteristics	n (%)
Age (mean ± SD)	64.6 ± 16.2
Gender (n:176)	
Female	63 (35.8)
Male	113 (64.2)
Co-morbidity (n:176)	
Yes	147 (83.5)
No	29 (16.5)
COVID-19 (n:176)	
Yes	73 (41.5)
No	103 (58.5)
Sepsis (n:167)	
Yes	107 (64.1)
No	60 (35.9)
Bacteremia (n:171)	
Yes	37 (21.6)
No	134 (78.4)
Invasive mechanical ventilation (n:175)	
Yes	156 (89.1)
No	19 (10.9)

Charlson score (n:176) [median (IQR)]	3 (2-5)
Length of stay (n:176) [median (IQR)]/days	31 (16-51)
Laboratory	
Day 0 WBC/mm^3 [median (IQR)]	12.400 (9.000-18.500)
Day 7 WBC/mm^3 [median (IQR)]	11.100 (8.100-15.300)
Day 0 CRP/mg/L [median (IQR)]	139.5 (78.5-219.8)
Day 7 CRP/mg/L [median (IQR)]	125.5 (81.3-191.5)
Day 0 Procalcitonin mcg/L [median (IQR)]	0.6 (0.17-3.6)
Day 7 Procalcitonin mcg/L [median (IQR)]	0.36 (0.12-1.5)
Day 0 Haemoglobin g/dL (mean ± SD)	9.7 ± 2.2
Day 0 Trombocyte/mm^3 [median (IQR)]	231.000 (156.000-310.000)
Day 0 Albumin g/dL (mean ± SD)	2.3 ± 0.5
Day 0 ALT U/L [median (IQR)]	28 (17-61)
Day 0 AST U/L [median (IQR)]	29.5 (18-58.8)
Day 0 Creatinin mg/dL [median (IQR)]	1.1 (0.7-1.8)
Treatment	
Ceftazidime/avibactam (n:176)	
Yes	26 (14.8)
No	150 (85.2)
Mortality	
14-day mortality (n:176)	
Yes	51 (29)
No	125 (71)

CRP: C-reactive protein; WBC: White blood cell count

Ceftazidime/avibactam (88.2%) was the most susceptible antibiotic for *K.pneumoniae* isolates from respiratory samples of the patients, followed by fosfomycin (41.7%) and trimethoprim-sulfamethoxazole (41.7%). Resistance to carbapenems was over 80%, whereas resistance to colistin was 95.9%. The antimicrobial susceptibility profiles of the isolates are shown in Table 2.

Ceftazidime/avibactam was used in 14.8% (n:26) of patients. In other patients, various combination regimens were employed according to antibiotic susceptibility results. Although the mortality rate was lower in patients treated with ceftazidime/avibactam than in those not treated with ceftazidime/avibactam, the difference was not statistically significant (23.1% vs 30%; p:0.47). In bacteremic cases (n:37), the mortality rate was 9.1% in those treated with ceftazidime/avibactam (n:11) and 30.8% in those treated with other antibiotics (n:26), but the difference was not statistically significant (p:0.22). Although the mortality rate was higher in COVID-19 cases than in non-COVID-19 cases, the difference was not statistically significant (34.2% vs. 25.2%; p:0.19).

Mortality rates of patients were compared in terms of various variables. The mortality rate was found to be statistically significantly higher in the presence of sepsis (34% vs 20%), leukocyte count > 10,600/mm^3 (34.8% vs 18.8%), platelet value < 140,000/mm^3 (43.2% vs 25.2%), AST value > 50 U/L (42.3% vs 23.4%), and creatinine value > 1.3 mg/dL (38.1% vs 23.9%) ($p < 0.05$).

A comparison of the mortality rates of the patients in terms of clinical and laboratory findings is presented in Table 3.

Table 2. *The antimicrobial susceptibility of K.pneumoniae isolates*

Antibiotic	Susceptible n (%)	Susceptible, increased exposure n (%)	Resistant n (%)	Total n (%)
Ceftazidime/avibactam	75 (88.2)		10 (11.8)	85 (100)
Meropenem	28 (16.9)		138 (83.1)	166 (100)
Imipenem	30 (18.9)	1 (0.6)	128 (80.5)	159 (100)
Ertapenem	13 (8.3)		144 (91.7)	157 (100)
Fosfomycin	10 (41.7)		14 (58.3)	24 (100)
Colistin	2 (4.1)		47 (95.9)	49 (100)
Tigecycline	-	-	5 (100)	5 (100)
Amikacin	30 (18.9)	1 (0.6)	128 (80.5)	159 (100)
Gentamicin	13 (8.3)		144 (91.7)	157 (100)
Trimethoprim-Sulfamethoxazole	10 (41.7)		14 (58.3)	24 (100)
Ciprofloxacin	19 (11)		154 (89)	173 (100)
Levofloxacin	9 (5.6)		152 (94.4)	161 (100)
Piperacillin/tazobactam	17 (10)		153 (90)	170 (100)
Ceftriaxone	18 (10.4)		155 (89.6)	173 (100)
Ceftazidime	15 (8.9)		154 (91.1)	169 (100)
Cefuroxime	12 (7.3)		152 (92.7)	164 (100)

Table 3. *Comparison of mortality rates according to demographic, clinical, and laboratory findings of patients*

	Mortality		P value
	Yes n (%)	No n (%)	
Gender Female Male	 15 (23.8) 36 (31.9)	 48 (76.2) 77 (68.1)	0.26
Co-morbidity Yes No	 44 (29.9) 7 (24.1)	 103 (70.1) 22 (75.9)	0.53
COVID-19 Yes No	 25 (34.2) 26 (25.2)	 48 (65.8) 77 (74.8)	0.19
Sepsis Yes No	 37 (34.6) 12 (20)	 70 (65.4) 48 (80)	0.04
Bacteremia Yes No	 9 (24.3) 40 (29.9)	 28 (75.7) 94 (70.1)	0.5
Invasive mechanical ventilation Yes No	 49 (31.4) 2 (10.5)	 107 (68.6) 17 (89.5)	0.06
Ceftazidime/avibactam Yes No	 6 (23.1) 45 (30)	 20 (76.9) 105 (70)	0.47
Day 0 WBC/mm^3 4.200–10.600 > 10.600	 12 (18.8) 39 (34.8)	 52 (81.3) 73 (65.2)	0.02
Day 7 WBC/mm^3 4.200–10.600 > 10.600	 10 (15.2) 9 (12.3)	 56 (84.8) 64 (87.7)	0.63
Day 0 CRP mg/L 5-100 100-200 > 200	 15 (25.4) 16 (25.8) 20 (36.4)	 44 (74.6) 46 (74.2) 35 (63.6)	0.34
Day 7 CRP mg/L 5-100 100-200 > 200	 6 (11.8) 9 (15.3) 4 (13.3)	 45 (88.2) 50 (84.7) 26 (86.7)	0.86
Day 0 Procalcitonin mcg/L < 0.25 0.25–1.5 > 1.5	 12 (20.3) 20 (35.1) 19 (31.7)	 47 (79.7) 37 (64.9) 41 (68.3)	0.18
Day 7 Procalcitonin mcg/L < 0.25 0.25–1.5 > 1.5	 4 (7.4) 10 (19.6) 5 (14.7)	 50 (92.6) 41 (80.4) 29 (85.3)	0.18
Haemoglobin g/dL > 9 < 9	 26 (27.7) 25 (30.5)	 68 (72.3) 57 (69.5)	0.68

Thrombocyte/mm^3 < 140.000 > 140.000	 16 (43.2) 35 (25.2)	 21 (56.8) 104 (74.8)	 0.03
Albumin (< 3.5 g/dL) Yes No	 51 (30.4) 0 (0)	 117 (69.6) 7 (100)	 0.10
ALT U/L < 50 > 50	 32 (25.2) 19 (38.8)	 95 (74.8) 30 (61.2)	 0.07
AST U/L < 50 > 50	 29 (23.4) 22 (42.3)	 95 (76.6) 30 (57.7)	 0.01
Creatinine mg/dL < 1.3 > 1.3	 27 (23.9) 24 (38.1)	 86 (76.1) 39 (61.9)	 0.04
Age (mean ± SD)	67.6 ± 16.8	63.4 ± 15.8	0.12
Charlson comorbidity index [median (IQR)]	4 (2-5)	3 (2-4)	0.15

Table 4. *Risk factors for mortality determined by univariate and multivariate logistic regression analyzes*

	Univariate Crude OR 95% CIp value			Multivariate* Adjusted OR 95% CIpvalue		
Age	1.01	(0.99-1.04)	0.12			
Gender Female Male	 1 0.66	 (0.33-1.35)	 0.26			
Sepsis	2.11	(1.001-4.46)	0.05			
Day 0 WBC/mm^3 4200–10600 > 10600	 1 2.31	 (1.10-4.84)	 **0.02**	 1 2.30	 (1.03-5.14)	 **0.04**
Thrombocyte/mm^3 > 140000 < 140000	 1 2.26	 (1.06-4.81)	 **0.03**			
AST U/L < 50 > 50	 1 2.40	 (1.20-4.79)	 0.01	 1 2.23	 (1.04-4.75)	 **0.03**
Creatinin mg/dL < 1.3 > 1.3	 1 1.96	 (1.006-3.82)	 **0.04**			

OR: odds ratio; CI: Confidence Interval
*Only statistically significant variables are shown.

In the regression analysis performed to determine the risk factors for mortality; in the univariate regression analysis, day 0 leukocyte count >10.600/mm^3 (OR: 2.31; 95% CI: 1.10-4.84), platelet value < 140.000/mm^3 (OR: 2.26; 95% CI: 1.06-4.81), AST > 50 U/L (OR: 2.40; 95% CI: 1.20-4.79) and creatinine > 1.3 mg/dL (OR: 1.96; 95% CI: 1.006-3.82) were associated with mortality. In multivariate regression analysis, a leukocyte count > 10.600/mm^3 (OR: 2.30; 95% CI: 1.03-5.14) and an AST > 50 U/L (OR: 2.23; 95% CI: 1.04-4.75) were found to be independent predictors of mortality (Table 4).

DISCUSSION

In our study, the mortality rate was found to be 29% in patients who were followed up in the ICU with a diagnosis of HAP due to *K. pneumoniae*, and leukocytosis and AST elevation were found to be independent risk factors associated with mortality. However, the presence of sepsis, comorbidities, COVID-19 infection, bacteremia, and antibiotic treatment regimens were not associated with mortality.

In a study conducted in China with *K. pneumoniae*-related pneumonia cases developing in intensive

care units, the mortality rate was found to be 18%, and the risk factors associated with mortality were low Glasgow Coma Scale, low platelet count, low albumin concentration, high lactate levels, and inappropriate antibiotic treatment (1). In another study conducted in hospital-acquired pneumonia cases with bacteremia, the 28-day mortality rate was found to be 60.2%. High severe organ failure assessment score (SOFA) and inappropriate antibiotherapy were found to be factors associated with mortality (11). Jiao et al. found that the presence of ventilator-associated pneumonia, pressure ulcers, and several comorbidities were associated with high mortality in patients with hospital-acquired pneumonia (12). In our study, the mortality rate was found to be higher in intubated patients, but the difference was not statistically significant. No difference was found between the Charlson comorbidity index and mortality.

Our patients in the study were elderly, intubated, and generally in poor clinical condition with sepsis. Approximately one-fifth of the patients had simultaneous *K. pneumoniae* growth in blood culture. The presence of bacteremia in cases of pneumonia worsens the disease course and leads to increased mortality (13). Similarly, in a study conducted in Japan in 2015, the mortality rate was found to be significantly higher (34.8% vs. 11.3%) in patients with bacteremia (14). However, there was no difference in the mortality rate between patients with and without bacteremia in our study. These results should be evaluated with caution because the number of patients with blood culture growth was low in our study. Further studies are needed with a larger number of patients to investigate mortality in cases of bacteraemic pneumonia caused by *K. pneumoniae*.

In previous studies, conflicting data have been presented in research examining the effect of the appropriateness of antibiotic treatment on mortality. In addition to studies reporting that mortality decreased with appropriate treatment, there are also studies reporting that it did not affect mortality (1, 14, 15). In our study, very high resistance rates, including carbapenems and colistin, were found in *K. pneumoniae* isolates. Ceftazidime/avibactam exhibited the highest susceptibility rate (88.2%). In a study conducted in critically ill patients, ceftazidime/avibactam treatment was found to be associated with higher survival (16). Similarly, in our study, a lower mortality rate was observed in the group receiving ceftazidime/avibactam treatment compared with the group receiving other combination regimens, but the difference was not statistically significant. In the study by Rivera-Espinar et al., 30-day mortality in ventilator-associated pneumonia due to *K. pneumoniae* was higher in the presence of carbapenem resistance due to KPC than in susceptible isolates. However, even in cases of VIP caused by resistant isolates, a similar prognosis has been observed with appropriate antibiotic treatment (15). Ceftazidime/avibactam is indicated according to the specific rules in our country. It can only be used for infections in vitro resistant to carbapenems, aminoglycosides, and third-generation cephalosporins and susceptible to ceftazidime/avibactam. Ceftazidime/avibactam was used in only 14.8% of cases. Therefore, randomized trials with larger numbers of patients should be conducted.

Garcia-Vidal et al. found that the presence of community or hospital-acquired superinfection was associated with a worse prognosis in patients with COVID-19 infection (17). In a meta-analysis study, it was found that co-infection or superinfection increased mortality in those infected with COVID-19 (18). In our study, although the mortality rate was higher in COVID-19 cases, there was no statistically significant difference. This was considered to be because the patient population in the study was elderly, intubated, and sepsis patients. Standard treatment and care protocols applied to critically ill patients may have caused similar mortality rates.

In our study, leukocytosis, thrombocytopenia, elevated creatinine levels, and elevated AST levels were significantly associated with mortality in univariate analysis. However, only leukocytosis and high AST levels remained significant in multivariate analysis. In a study conducted in hospitalized patients with community-acquired pneumonia, age, leukocytosis, high urea level, and hypotension were found to be associated with mortality (19). In the study by Sönmez et al. examining mortality predictors for COVID-19, high AST levels and leukocytosis were found to be independent risk factors (20). This may be compatible with the fact that the presence of sepsis and organ dysfunction in patients is associated with mortality.

In order to prevent mortality due to nosocomial infections, it is essential to maintain infection control measures, personnel training, early diagnosis, and appropriate treatment of developing infections (21).

Our study has several limitations. The study was conducted in a single center with a relatively small number of patients. Treatment regimens could not be adequately compared because antibiotic treatments included different combinations and the number of patients receiving ceftazidime/avibactam was low.

CONCLUSION

In conclusion, leukocytosis and high AST levels were found to be independent risk factors associated with mortality in cases of *K. pneumoniae* in the intensive care unit. Taking these factors into account, in addition to other parameters and scores that determine the prognosis of patients, may be useful in reducing mortality.

Abbreviations

HAP — Hospital-acquired pneumonia
IDSA — Infectious Diseases Society of America
qSOFA — quick Sequential Organ FailureAssessment
WBC — White blood cell count
CRP — C-reactive protein
AST — Aspartat aminotransferase
ALT — Alanine aminotransferase
OR — odds ratio
CI — Confidence Interval
IQR — Inter QuantileRange
COVID-19 — Coronavirus Disease 2019
ICU — Intensive care unit

Authors contributions:

US: Study design, data collection, writing the manuscript, analyzing data

DÇ: Analyzing data, writing the manuscript, data collection

SS: Data collection, writing the manuscript

GE: Analyzing data, data collection

SA: Study design, writing the manuscript, analyzing data

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Sažetak

FAKTORI RIZIKA ZA SMRTNOST U SLUČAJEVIMA PNEUMONIJE IZAZVANE KLEBSIELOM U JEDINICI INTENZIVNE NEGE

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Uvod: Bolnički stečena pneumonija (BSP) koja se razvija u jedinicama intenzivne nege (JIN) predstavlja značajan problem. Gram-negativne bakterije su najvažniji uzrok BSP. Među ovim bakterijama, Klebsiella pneumoniae je jedna od najvažnijih patogena. Stopa smrtnosti od infekcija izazvanih Klebsiella-om pneumoniae otpornom na karbapeneme je visoka. Identifikacija faktora rizika za smrtnost je od suštinskog značaja kako bi se sprečile potencijalne smrti. Cilj ovog istraživanja bio je utvrditi faktore rizika povezane sa smrtnošću kod BSP izazvane infekcijom Klebsiella-om pneumoniae kod pacijenata u jedinicama intenzivne nege.

Materijal i Metode: Ova studija preseka sprovedena je između 01. maja 2021. i 01. maja 2023. godine u Jedinici intenzivne nege za anesteziju i reanimaciju u Bolnici za obuku i istraživanje Izmir Tepecik. U istraživanju su učestvovali pacijenti stariji od 18 godina kod kojih je dijagnostifikovana bolnički stečena pneumonija uzrokovana Klebsiella-om pneumoniae. Zavisna varijabla istraživanja bila je smrtnost u roku od 14 dana usled pneumonije uzrokovane Klebsiella-om pneumoniae. Nezavisne varijable obuhvatile su prisustvo COVID-19, bakterijemiju, tretman sa ceftazidime/avibactam, intubaciju, sepsu, Charlson komorbiditet skor, i laboratorijske parametre. Sproveli smo analizu logističke regresije koristeći metod obrnutog isključivanja kako bismo identifikovali nezavisne prediktore smrtnosti.

Rezultati: U studiju je uključeno ukupno 176 pacijenata. Prosečna starost pacijenata iznosila je 64,6 ± 16,2 godine, a 64,2% su bili muškarci. Stopa smrtnosti u roku od 14 dana iznosila je 29% (n:51). U analizi regresije sprovedenoj kako bi se utvrdili faktori rizika za smrtnost, u univarijatnoj regresiji, leukociti prvog dana > 10.600/mm^3 (OR: 2,31; 95% CI: 1,10-4,84), vrednost trombocita < 140.000/mm^3 (OR: 2,26; 95% CI: 1,06-4,81), AST > 50 U/L (OR: 2,40; 95% CI: 1,20-4,79) i kreatinin > 1,3 mg/dL (OR: 1,96; 95% CI: 1,006-3,82) bili su povezani sa smrtnošću. U multivarijatnoj regresijskoj analizi, leukociti > 10.600/mm^3 (OR: 2,30; 95% CI: 1,03-5,14) i AST > 50 U/L (OR: 2,23; 95% CI: 1,04-4,75) su pronađeni kao nezavisni prediktori smrtnosti.

Zaključak: Ukratko, leukocitoza i visoki nivoi AST su identifikovani kao nezavisni faktori rizika povezani sa smrtnošću u slučajevima Klebsiella pneumoniae u jedinici intenzivne nege. Razmatranje ovih faktora, zajedno sa ostalim parametrima i skorovima koji utiču na prognozu pacijenata, može biti korisno u smanjenju smrtnosti.

Ključne reči: Klebsiella pneumoniae, smrtnost, pneumonija, faktori rizika, jedinice intenzivne nege.

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Case report

PEDIATRIC EMERGENCY OF UNEXPECTED CAUSE: INFANTILE FIBROMATOSIS - CASE REPORT

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Abstract: Introduction: Infantile fibromatosis (IF) is a rare benign mesenchymal tumor of early childhood, located solitarily or multicentrically in the skin, soft tissues, muscles, bones, or visceral organs. The cause is unknown, and some cases are linked to mutations in two different genes. Rapid growth is typical, and while there are reports of spontaneous regression, relapses have also been recorded. Treatment depends on the location of the lesions, with surgery being the main treatment option.

Case report: This paper presents an unusual emergency presentation of infantile fibromatosis in a 16-month-old girl, initially manifested as acute laryngitis. The rapid development of respiratory failure necessitated immediate life-saving treatment. Emergency diagnostics revealed a large mass deep within the neck structures, causing significant compression and endangering the airways. The child's condition was critical, and the multidisciplinary team thoroughly discussed available treatment options. Eventually, after careful preparations, the tumormass was surgically removed on the sixth day. The postoperative course was challenging, but the outcome was positive. Pathohistological diagnosis confirmed infantile fibromatosis, and the treatment was successfully completed.

Conclusion: Despite its rarity, infantile fibromatosis must be considered a potential cause of urgent, life-threatening conditions in children. Treatment requires individual adaptation and collaboration with a multidisciplinary team.

Keywords: infantile fibromatosis, rare diseases, compromised airway, pediatric intensive care.

INTRODUCTION

Infantile fibromatosis (IF) is a rare benign mesenchymal tumor that primarily affects early childhood and can occur solitarily or in multiple locations in the skin, soft tissues, muscles, bones, or visceral organs (1). Initially termed "congenital generalized fibromatosis" by Stout in 1954, it was later referred to as "infantile myofibromatosis" due to the histological similarity of tumor cells to myofibroblasts and its frequent occurrence in newborns and infants (2).

Though IF tumors do not metastasize, their growth can lead to compression and damage to surrounding organs and tissues (3). Being classified as rare diseases, IF manifests with diverse localizations and presentations, sharing a common pathohistological appearance (4).

The exact cause of IF remains unknown, and most cases occur randomly without a discernible reason. However, some rare cases have been associated with mutations in two different genes, PDGFRB and NOTCH3, currently under extensive research (5-8).

Treatment of IF depends on lesion location. While rapid growth is typical, spontaneous regression has been reported, as well as instances of relapse (4). Surgical intervention remains the primary treatment option (9-12). Interestingly, up to 30% of cases involve threatening localization in the head and neck structures (1-4).

This paper presents an exceptional case of infantile fibromatosis in a 16-month-old girl, initially presenting with acute laryngitis, which rapidly progressed to respiratory insufficiency, requiring immediate life-saving treatment.

CASE REPORT

A 16-month-old girl was admitted to the pediatric clinic following an examination by an otolaryngologist for the treatment of acute laryngitis. On admission, she presented as pale, afebrile, and slightly inspiratory dyspnoic, with a hoarse cough and moderate severity of the disease. Her condition seemed similar to other children of the same age being treated for similar problems during the season. Initial biochemical

parameters, including C-reactive protein, complete blood count, urea, creatinine, and electrolytes, showed no significant deviations, except for respiratory acidosis observed in the gas analysis.

Unexpectedly, the patient did not respond to the standard treatment protocol and rapidly deteriorated, developing progressive respiratory insufficiency. Urgent transfer to the intensive care unit (ICU) was necessary for immediate intubation and mechanical ventilation. Due to the complexity of her airway, intubation posed challenges, requiring complete analgosedation, relaxation, and other general supportive therapies and further diagnostics.

Following stabilization, the presence of neck swelling and asymmetry was noted, along with a palpable mass on the right side of the neck, prompting further urgent investigation. Given the critical condition, the multidisciplinary team explored treatment options. Chest X-rays indicated pulmonary infiltration, atelectasis, and an enlarged upper mediastinum. X-ray of the hypopharynx revealed narrowing of the upper esophagus, likely due to external compression. Brain CT results were normal. Subsequent CT and MRI scans of the neck and thorax confirmed a large mass (Figure 1 and 2), which compressed vascular structures and involved the mediastinum. Angiography (Figure 3) suggested a differential diagnosis of hemangioma, leading to the initiation of propranolol therapy along with other treatments.

In the pediatric intensive care unit (PICU), the patient's condition remained critical, with hyperdynamic, febrile, and edematous features, and clinical signs of superior vena cava syndrome and multiorgan

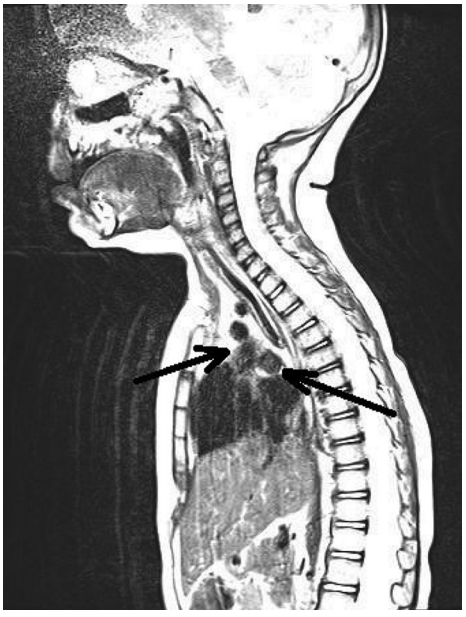

Figure 1. *Presentation of the tumor mass with CT scan*

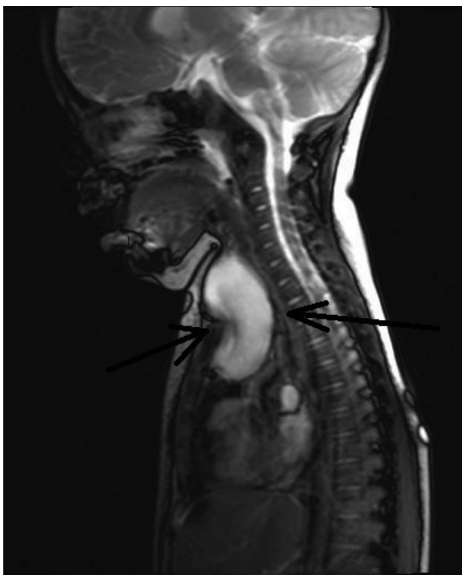

Figure 2. *Magnetic resonance imaging (MRI) of the tumor mass*

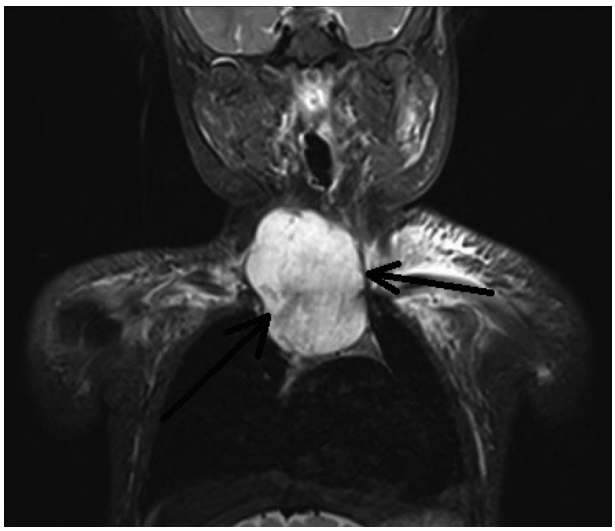

Figure 3. *Imaging of the tumor mass with magnetic resonance angiography (MRA)*

dysfunction. The lungs were particularly challenging, necessitating substantial support to maintain stability. A daily multidisciplinary team reviewed treatment options, including pediatricians, otolaryngologists, pediatric surgeons, hemato-oncologists, anesthesiologists, infectious disease specialists, clinical pharmacologists, cardiologists, endocrinologists, pediatric neurologists, and others. Preoperative preparation was comprehensive, involving detailed biochemical tests and multiorgan assessments.

Most findings from hematological parameters, coagulation status, thyroid hormones, and flow cytometry were normal. A decrease in immunoglobulin G (2.93g/L) led to treatment with intravenous gammaglobulins. Extensive microbiological examinations were generally negative, with only respiratory profile

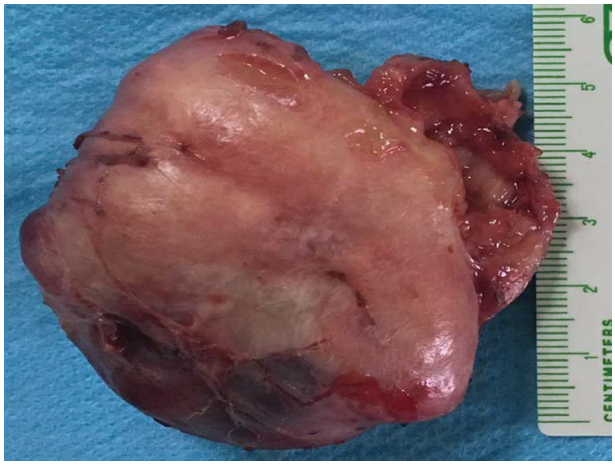

Figure 4. *The tumor mass was successfully removed completely, the size corresponded to the imaging studies*

tests indicating positive Coxyckie virus type A7 and indeterminate Quantiferon TB results, leading to additional gastric lavage testing. Repeated blood, urine, and swab cultures were performed.

Surgery with a high ASA risk was performed collaboratively with an ENT and pediatric surgeon on the 6th day of hospitalization. The tumor mass was completely removed, resembling one of the fibrous tumors of childhood, and sent for Ph.D. verification. The size corresponded to the imaging studies (Figure 4).

In the early postoperative course, the patient remained demanding, with persistent fever and bilateral pulmonary infiltration and atelectasis. On the 5th postoperative day (12th PICU day), after two unsuccessful attempts, she was finally extubated. Following extubation, she showed gradual recovery but with hypotonia and mild neurological deficit (discrete hemiparesis). Physical treatment, under the consultation of a neurologist and physiatrist, was initiated. On the 13th postoperative day (19th PICU day), she became febrile again, with stable cardiorespiratory parameters, but with elevated infection markers, leukopenia, neutropenia, slightly elevated toxic hepatitis parameters, and confirmed Candida sepsis, which was successfully treated.

The final PHD diagnosis was infantile fibromatosis, confirmed by additional molecular genetic testing. Further treatment continued at the Hemato-oncology department. Re-evaluation of the patient's clinical condition, laboratory results, and radiological findings confirmed excellent recovery. She was discharged from the hospital after a total of 6 weeks (25 PICU days) and has been under follow-up care by a pediatrician, hemato-oncologist, physiatrist, and neurologist. So far, her development has been satisfactory, and there have been no signs of disease relapse.

DISCUSSION

Infantile fibromatosis (IF) is in the register of rare diseases and is a benign mesenchymal tumor of early childhood, with varied manifestations (1). Symptoms vary in severity, depending on localization, with possible spontaneous regression (11), but also very complicated presentations if it involves internal organs, as was our case. It is important to note that each case is unique, which can be concluded from the literature, published mainly in the form of case series (2, 3).

Although IF does not metastasize, it grows rapidly, and depending on its localization, can damage nearby structures (1). Single tumors are the most common in up to 80% of cases (2), half of which are described on the head and neck (3), and 60% are reported in children under 2 years of age (4). This all applies to our case as well. The solitary form occurs predominantly in males (1), while in our case it was the opposite. Single bone tumors have been described, but they are extremely rare (11). Multifocal forms are more common in females (2, 3). This form with visceral involvement is considered the most severe form, which can cause severe, life-threatening complications, depending on the exact location (9). Our example, although it was solitary, caused an acute, life-threatening condition by its location

The etiology of IF is unknown and in most published cases there was no previous family history. Mutations in two genes are reported as the cause in some cases: the neurogenic locus protein homolog 3 gene (NOTCH3) (8) and the platelet-derived growth factor receptor beta (PDGFRB) gene (5-7). In our case, there were no previous examples of IF in the family, and additional molecular genetic testing did not confirm the marked genes.

Other soft tissue tumors may resemble IF (1). In our case as well, the postoperative macroscopic appearance of the tumor gave the possibility of guessing. Definitive confirmation of IF is based solely on the pathohistological diagnosis. Imaging studies, including ultrasound, CT, and MRI, are most commonly used to visualize tumor location, size, and extent, to decide on therapeutic options and surgical procedures, and to diagnose tumor recurrence during follow-up,as already evidenced by peer reports (2-4, 13).

Treatment is mostly surgical, but in any case, it should be personalized and may require the coordinated efforts of a team of experts. Genetic counseling is recommended as well as psychosocial support for the family. Due to the rarity of the disease, there are no studies on a large group of patients. Experiences with different treatments have been reported in the medical literature individually or in small series of patients (9-12). There are no standardized treatment protocols or guidelines.

Decisions should be made by a multidisciplinary team with careful consultation with the patient and family.

Surgical removal is the first option in the case of involvement of internal organs or in the case of lesions that are life-threatening due to their location, as in our case. In approximately 10% of cases, lesions may recur after surgery. The postoperative course was complicated by confirmed Candida sepsis, which was expected, given all the existing risk factors for systemic fungal infection (14). Chemotherapy may be used to treat cases (9) where the surgery was unsuccessful, if lesions recur, or if lesions are unresectable due to the location. In similar cases, interferon alfa (12) or cytostatic combination have also been used successfully.

CONCLUSION

Although infantile fibromatosis is very rare, it must be considered a possible cause of urgent, life-threatening conditions in children. Treatment must be individually adapted and with a multidisciplinary team.

Abbreviations

IF — Infantile Fibromatosis (IF)
MV — Mechanical Ventilation
CT — Computerized Tomography
MRI — Magnetic Resonance Imaging
MRA — Magnetic Resonance Angiography
PICU — Pediatric Intensive Care Unit
ASA — American Society of Anesthesiologists
ENT — Ear, Nose, and Throat Doctors (Otolaryngologists)
Ph.D. — Pathohistological Diagnosis
PDGFRB — Platelet-Derived Growth Factor Receptor Beta Gene
NOTCH3 — Neurogenic Locus Notch Homolog Protein 3 Gene

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Sažetak

HITNO STANJE U PEDIJATRIJI NEOČEKIVANOG UZROKA: INFANTILNA FIBROMATOZA - PRIKAZ SLUČAJA

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Uvod: Infantilna fibromatoza (IF) je redak benigni mezenhimalni tumor ranog detinjstva, solitaran ili multicentričan u koži, mekim tkivima, mišićima, kostima ili visceralnim organima. Uzrok je nepoznat, a neki slučajevi su povezani s mutacijama u dva različita gena. Brz rast je tipičan, postoje izveštaji o spontanoj regresiji, ali su zabeleženi i recidivi. Lečenje zavisi od lokacije lezija, a operacija je glavna opcija lečenja.

Prikaz slučaja: U radu je prikazana neobična urgentna prezentacija infantilne fibromatoze kod 16-mesečne devojčice, u početku predstavljena kao akutni laringitis. Veoma brz razvoj respiratorne insuficijencije zahtevao je hitno lečenje koje spašava život. Hitna dijagnostika otkrila je veliku tumorsku masu duboko u strukturama vrata, koja je izrazito, kompresijom, ugrožavala disajne puteve. Stanje deteta je bilo vrlo kritično, a nije bilo drugih bezbednih opcija lečenja, o čemu je odlučivao multidisciplinarni tim. Nakon pažljivih priprema, tumorska masa je hirurški uklonjena šestog dana. Usledio je težak postoperativni tok, ali sa pozitivnim konačnim ishodom. Infantilna fibromatoza je patohistološki potvrđena i lečenje je uspešno završeno.

Zaključak: Iako je infantilna fibromatoza vrlo retka, mora se razmatrati kao mogući uzrok hitnih, životno opasnih stanja kod dece. Tretman mora biti individualno prilagođen i sa multidisciplinarnim pristupom.

Ključne reči: infantilna fibromatoza, retke bolesti, kompromitovani disajni put, pedijatrijska intenzivna nega.

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Case report

SEROTONIN SYNDROME IN A PATIENT WITH DUAL DIAGNOSIS - CASE STUDY

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Abstract: **Introduction**: Serotonin syndrome is a rare but potentially life-threatening condition. In most cases, this complication is caused by taking two serotonergic medications simultaneously, leading to excessive serotonin concentration in the body. Selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine reuptake inhibitors (SNRIs), as well as irreversible monoamine oxidase inhibitors (MAOIs) and their combination with other serotonergic substances, are associated with symptoms of serotonin syndrome.

Case study: A patient who was prescribed sertraline (an SSRI) for a depressive episode suffered fractures in a traffic accident during the treatment, and tramadol was prescribed for her pain. Since both drugs tend to increase serotonin levels in the body, a complication in the form of serotonin syndrome developed. With timely recognition and treatment, the symptoms of serotonin syndrome resolved without lasting consequences.

Conclusion: Numerous drugs and substances can induce serotonin syndrome, often in combination with antidepressants. Therefore, it is of great importance that doctors are aware of comorbid conditions that necessitate the use of the mentioned drugs in order to prevent serotonin syndrome. If it does occur, adequate and successful treatment is crucial.

Keywords: Serotonin syndrome, risk, treatment, SSRI, SNRI.

INTRODUCTION

Serotonin syndrome (SS) represents a not-frequent but potentially life-threatening reaction due to an excessively high concentration of serotonin in both the peripheral and central nervous systems (1-4). Most frequently, serotonin syndrome occurs when two or more medications that affect serotonin levels are administered simultaneously, when the dose of one serotonergic medication is suddenly increased, or due to intoxication or overdoses of various substances with serotonergic properties.

Serotonin syndrome was first described in 1937 as an adverse effect in a patient taking iproniazide, an irreversible monoamine oxidase inhibitor (IMAO). Symptoms can manifest in various patients regardless of age and sex. Serotonin syndrome can even be diagnosed in a newborn if it was exposed in utero to serotonergic substances (4, 5, 6). Usually, antidepressants are the most common drugs that affect serotonin levels, leading to the occurrence of serotonin syndrome. Nevertheless, there are numerous other substances that can cause symptoms of SS either by themselves or in combination. The fact is that under therapeutic dosage and monitoring, a single serotonergic antidepressant will not cause serotonin syndrome if not administered with other serotonergic substances (2-5).

Serotonin (5-HT) was identified in 1937 by Asero Erspamer. Over 90% of the body's serotonin is synthesized in enterochromaffin cells, about 5% in thrombocytes and other organs, and only 5% in the central nervous system (CNS) (1, 6). Nonetheless, serotonin remains one of the most important neurotransmitters, regulating neurophysiological and behavioral processes, pain perception, mood, anger, anxiety, appetite, sleep, libido, and thermoregulation. In peripheral areas of the body, serotonin plays an important role in vasoconstriction, muscle contraction, and thrombocyte aggregation, among other functions (5, 6, 7).

A deficiency of serotonin in CNS synapses is associated with the emergence of depressive and anxiety disorders (5-8). There is an abundance of evidence that

drugs which increase intrasynaptic serotonin concentration in the CNS alleviate symptoms of depression and anxiety (7, 8, 9).

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) are the most commonly prescribed drugs for anxiety and depressive disorders. Most people can safely take antidepressants under the guidance of a healthcare professional. Adverse effects might arise when two or more serotonergic drugs are combined or when they are overdosed (1, 2, 9, 10, 11).

When the combination of serotonergic antidepressants is deemed necessary, doctors should exercise caution and regularly monitor the patient's condition. Symptoms resembling those of serotonin syndrome can be similar to symptoms of a mental disorder, a comorbid somatic problem, or a result of intolerance to a specific medication. The diagnosis of serotonin syndrome in most cases includes mental changes, dysfunction of the neurovegetative system, and neuromuscular changes (clonus, tremor). Nonetheless, it is crucial to gather all data about comorbid somatic disorders and other drugs/supplements prescribed to the patient for somatic issues (painkillers, antibiotics, etc.), as well as any use of illegal psychoactive substances, to avoid adverse reactions such as SS.

Symptoms of serotonin syndrome usually occur within a few hours to a day after an elevated level of serotonin in the CNS. When the serotonergic drug that is causing the rise in serotonin levels is excluded, symptoms typically disappear within 24-72 hours. However, if a prescribed antidepressant has a long half-life elimination time or has active metabolites, some mild symptoms may persist for a few weeks. Cases of chronic, mild clinical features of SS are described in the literature (10-14). Symptoms can vary in intensity, ranging from mild to moderate and severe. When serotonin syndrome remains unrecognized and is left untreated, severe symptoms can escalate to a life-threatening condition. Complications can include seizures, abnormal heartbeat, rhabdomyolysis, renal or heart failure, acidosis, disseminated intravascular coagulation, respiratory insufficiency, coma, and death (15-18). To prevent complications, a prompt diagnosis and treatment of SS should be initiated as soon as symptoms arise.

Most frequently, serotonin syndrome presents as mental confusion, agitation, neurovegetative dysfunction, and various forms of neuromuscular dysfunctions or even coma. The following is a list of the most common symptoms that occur in serotonin syndrome (Table 1).

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Epidemiological data regarding serotonin syndrome (SS) are not well consolidated, but there is evidence suggesting that SS occurs in approximately 15% of cases involving intoxication with selective serotonin reuptake inhibitors (SSRIs). However, there is a suspicion that the actual number might be much higher due to cases of SS going unrecognized (2, 3, 17, 19, 20). There is evidence that various medications, opioids, and many illegal substances, either taken alone or in combination with other serotonergic sub-

Table 1. *Symptoms of Serotonin syndrome*

Symptoms of Serotonin Syndrome
Mild- Hypertension, intermittent tremor, mydriasis, tachycardia, diaphoresis, myoclonus, restlessness
Moderate- Hyperthermia (> 38 °C), psychomotor agitation, confusion, hyperreflexia, tremor, hyperhidrosis, diarrhea, tachycardia, hypertension (> 140/90 mmHg), repeated rotatory movements of head and neck
Serious- Myoclonus, horizontal oculogyric clonus, tachypnea, tremor, seizures, muscle rigidity, rhabdomyolysis, metabolic acidosis, coma or agitation, hypo or hypertension, renal insufficiency, disseminated intravascular coagulation (DIC), hyperthermia (> 41 °C), death

stances, can contribute to serotonin syndrome (SS). As our understanding of SS improves, misdiagnosis and complications can be significantly reduced, which can lead to a decrease in the mortality rate associated with serotonin syndrome.

Here is a list of medications and other substances that could potentially cause serotonin syndrome (SS):

Antidepressants

Selective Serotonin Reuptake Inhibitors (SSRIs): fluoxetine, citalopram, escitalopram, sertraline, paroxetine

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs): venlafaxine, desvenlafaxine, duloxetine, milnacipran, levomilnacipran

Tricyclic Antidepressants (TCAs): clomipramine, amitriptyline, imipramine, desipramine, nortriptyline, doxepin

Monoamine Oxidase Inhibitors (MAOIs): selegiline, tranylcypromine, phenelzine

Serotonin Modulators: trazodone, nefazodone

Norepinephrine Reuptake Inhibitor (NRI): bupropion

There is evidence suggesting that mirtazapine, a noradrenergic and specific serotonergic antidepressant (NaSSa), does not cause SS due to its dual action. However, some articles claim the opposite.

Other medications that can cause SS include:

Opioid painkillers: tramadol, hydrocodone, oxycodone, fentanyl

Migraine headache drugs: sumatriptan, zolmitriptan, eletriptan, rizatriptan, almotriptan

Drugs for treating HIV/AIDS: ritonavir

Cough medication: dextromethorphan

Antibiotics: linezolid

Antiemetics: metoclopramide, droperidol, granisetron, ondansetron

Mood stabilizer: lithium

Illegal substances: LSD, ecstasy, cocaine, amphetamine

Other drugs: olanzapine, risperidone, valproate, tryptophan, levodopa, buspirone

Herbal supplements: Asian and American Ginseng, St. John's wort, Syrian rue

Serotonin syndrome (SS) is not solely attributed to an increased level of serotonin in the synaptic space; it also involves the overstimulation of 5-HT2A receptors, while agonism of 5-HT1A receptors can contribute through pharmacodynamic interaction (18, 19, 20). The mechanisms of serotonin syndrome encompass various factors, including elevated serotonin synthesis, hyperactivation of serotonin receptors, inhibition of serotonin reuptake, slower serotonin metabolism, and potential inhibition of CYP 450 enzymes. However, other neurotransmitters also play a role in the development of serotonin syndrome, such as the increased level of norepinephrine. Alterations in the sensitivity of NMDA receptors and changes in GABA neurotransmission have been observed in serotonin syndrome (7, 11, 20). Evidence suggests that numerous other neurotransmitters influence the clinical signs and symptoms of serotonin syndrome.

Diagnosing SS is typically a process of exclusion, as there is no specific test available for serotonin syndrome. The diagnosis relies on clinical assessment. Other conditions, such as neuroleptic malignant syndrome (NMS), intoxication with anticholinergic drugs or sympathomimetics, neurological disorders, and viral illnesses, should be ruled out in the diagnostic process (2, 4, 7, 11, 15). Diagnostic procedures, including blood and urine tests, toxicology and alcohol screening, electrolyte level assessment, thyroid function testing, spinal tap, chest X-ray, and CT scan of the brain, may be conducted. If all tests yield negative results and the criteria specified by the Hunter criteria are met, a diagnosis of serotonin syndrome can be made.

Distinguishing between SS and NMS is always necessary. This distinction can be difficult, especially if a patient was using both antipsychotics and serotonergic antidepressants. Symptoms of serotonin syndrome can emerge rapidly, often within hours of co-medication or a dose increase of serotonergic substances, particularly when medications affecting serotonin levels are combined. In our patient, symptoms appeared in less than a day, despite not using antipsychotic medication (although even SSRIs can cause NMS). In NMS, symptoms usually arise over a few days after initial antipsychotic use or a dosage increase. Main NMS symptoms include bradykinesia, hyperreflexia, extrapyramidal rigidity, leukocytosis, elevated body temperature, confusion, somnolent consciousness, or psychomotor agitation, often accompanied by increased blood creatine phosphokinase (CPK) enzyme levels (4, 5, 21, 22).

In serotonin syndrome, the most important symptoms include muscle rigidity, tremor, clonus, and dilated pupils along with dryness of the mouth's mucosa. In diagnosis, medical history is crucial, particularly the patient's illness history, medication usage, and observation of symptoms.

The first evaluated criteria were introduced by Sternbach in 1991 (15, 17, 20). For diagnosis, the presence of 3 out of 10 symptoms should be positive: altered consciousness, agitation, hyperreflexion, myoclonus, diaphoresis, hyperthermia, tremor, diarrhea, dyscoordination, and trembling. These should be ac-

companied by the use of serotonergic drugs or an increased dosage within the last 24 hours.

Later, Hunter Toxicity Criteria Decision Rules were introduced, with greater sensitivity (84%) and specificity (over 97%). According to the Hunter criteria, therapy with serotonergic drugs in combination with one of the symptoms is necessary to confirm the diagnosis of serotonin syndrome. The qualifying symptoms are myoclonus, tremor with hyperreflexia, muscle rigidity in combination with hyperthermia, and ocular or induced clonus (12, 14, 15).

CASE REPORT

A 54-year-old female patient has been undergoing psychiatric treatment for 5 years with a diagnosis of depressive disorder. The patient experienced remission for the last three years, but following her mother's passing, she developed symptoms of anxiety, sleep disturbances, and reduced appetite. Her treatment involved increasing the dosage of sertraline up to 150 mg/day and adding mirtazapine at 30 mg/day, which resulted in a decrease in the intensity of her depressive symptoms. During this time, the patient was involved in a car accident resulting in a broken arm and four ribs. At the Surgery unit, she was given tramadol for the severe pain, reaching doses of up to 400 mg/day. After less than a day, the patient reported experiencing intense tremors, anxiety, restlessness, diaphoresis, confusion, and instability. She visited her psychiatrist, who diagnosed serotonin syndrome based on the Hunter criteria. The patient's psychiatric medications were reduced to 50 mg/day of sertraline and 15 mg/day of mirtazapine, and diazepam was added to the therapy at a dosage of 10 mg/day. Tramadol was discontinued and replaced with paracetamol. Over the course of a few days, the symptoms subsided; however, the patient continued to experience insomnia, leading to an increase in the dosage of mirtazapine to 30 mg/day. In the subsequent period, the patient achieved clinical remission without further signs of serotonin syndrome.

DISCUSSION

Upon correct diagnosis, the initial management involves discontinuing the use of precipitating drugs or other contributing substances. Benzodiazepines can be administered to address myoclonus, and supportive measures should be taken based on the type and severity of symptoms. In the first hour, intestinal decontamination with activated charcoal may be prescribed if the patient has ingested large doses of serotonergic medication. If hypotension is evident, sympathomimetics are recommended, while short-acting antihypertensive drugs like nitroprusside are preferable in cases of hypertension or tachycardia. Hyperthermia treatment includes using benzodiazepines to reduce myoclonus and applying cold compresses; however, antipyretic agents are ineffective as the elevated body temperature results from muscular activity. Severe cases may call for the administration of serotonin antagonists such as cyproheptadine. Hospitalization is necessary when symptoms are of moderate to severe intensity. In our patient's case, her symptoms were mild to moderate, and with adjustments in sertraline and mirtazapine dosages, discontinuation of tramadol, and additional supportive measures like diazepam, her serotonin syndrome symptoms lessened.

In most cases, prompt recognition and treatment of serotonin syndrome lead to symptom resolution without lasting consequences. Supportive measures should be continued until symptoms abate, usually within 24 hours after discontinuation of serotonergic substances. This was the case with our patient.

Accurate diagnosis is crucial, as misdiagnosing serotonin syndrome as neuroleptic malignant syndrome (NMS) might lead to inappropriate treatment. For example, bromocriptine, a drug used in NMS, can be contraindicated and worsen the clinical presentation of serotonin syndrome due to its interaction with D2 receptors.

Medical personnel should remain vigilant about the potential for serotonin syndrome. When there is a need for two serotonergic medications in higher doses, close monitoring becomes essential. Patients with comorbid mental disorders, particularly anxiety and depressive symptoms alongside chronic pain, require careful observation. If feasible, the effective dosage of pain-relieving medication (e.g., tramadol) and serotonergic antidepressants should be minimized.

CONCLUSION

Serotonin syndrome can develop in approximately 14-16% of patients who overdose on serotonergic drugs or substances. Early identification plays a crucial role in preventing the progression to more severe symptoms. When symptoms and signs of serotonin syndrome are recognized, it is advisable for medical practitioners to consider prescribing serotonergic antidepressants, if necessary, at the lowest effective dosage or to explore alternative classes of antidepressants. It is essential to avoid combining two medications that affect serotonin, particularly in higher dosages. However, in most cases, SSRI or SNRI antidepressants, even at higher dosages when administered individually, do not typically induce serotonin syndrome. Various other drugs have the potential to influence serotonin levels in the human body, and the best approach to prevent-

ing serotonin syndrome is to minimize the combination of different medications in patients. Combining opioids with other serotonergic drugs, due to their serotonin-norepinephrine reuptake inhibition, tends to pose the most significant concern in this regard.

Abbreviations

CNS — Central Nervous System
CT scan — Computerised Tomography scanning
CPK — Creatinine Phosphocinase
GABA — Gama-amynobutricaccide
Imao — Irreversible Monoaminooxidase inhibitors
5HT — 5-Hydroxytryptophan
5HT1a, 5HT2a — 5-Hydroxytryptophan receptors
NaSSA — Noradrenergic and specific serotonergic antidepressants
NMDA — N-methyl-D-aspartate receptor
NMS — Neuroleptic Malignant Syndrome
NRI — Norepinephrine reuptake inhibitor antidepressants
SNRI — Serotonin and norepinephrine reuptake inhibitor antidepressant
SS — Serotonin Syndrome
SSRI — Selective Serotonin Reuptake Inhibitor antidepressant
X-RAY — Radiation

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Sažetak

SEROTONINSKI SINDROM KOD PACIJENTKINJE SA DUALNOM DIJAGNOZOM — PRIKAZ SLUČAJA

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Uvod: Serotoninski sindrom predstavlja retko, ali po život potencijalno ugrožavajuće stanje. Najčešće do ove komplikacije dolazi kod istovremene primene dva serotonergična leka koji prekomerno povise nivo serotonina u organizmu. Najčešće se primena SSRI (selektivni inhibitori ponovnog preuzimanja serotonina) i SNRI (inhibitori ponovnog preuzimanja serotonina i noradrenalina), kao i IMAO (ireverzibilni inhibitori monoaminooksidaze) povezuju sa pojavom serotoninskog sindroma, najčešće u kombinaciji sa drugim serotonergičnim sredstvima.

Prikaz slučaja: Pacijentkinja kojoj je zbog depresivne epizode ordiniran sertralin (SSRI) tokom lečenja je u saobraćajnoj nesreći zadobila prelome, te joj je zbog bolova ordiniran tramadol. Obzirom da oba leka imaju tendenciju da povećaju nivo setotonina u telu, razvila se komplikacija u vidu serotoninskog sindroma. Pravovremenim prepoznavanjem i tretmanom, simptomi serotoninskog sindroma su se povukli bez trajnih posledica.

Zaključak: Brojni lekovi i supstance mogu da uzrokuju serotoninski sindrom, najčešće u kombinaciji sa antidepresivima. Od velike važnosti je stoga da se lekari informišu o komorbidnim stanjima koje iziskuju primenu navedenih lekova kako bi se serotoninski sindrom prevenirao, a ukoliko se javi kako bi se adekvatno i uspešno lečio.

Ključne reči: serotoninski sindrom, rizik-lečenje, serotonin, SSRI, SNRI.

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Diskusija. Ne treba činiti obiman pregled literature. Treba diskutovati glavne rezultate u vezi sa rezultatima objavljenim u drugim radovima. Pokušati da se objasne razlike između dobijenih rezultata i rezultata drugih autora. Hipoteze i spekulativne zaključke treba jasno izdvojiti. Diskusija ne treba da bude ponovo iznošenje zaključaka.

Literatura. Reference numerisati rednim arapskim brojevima prema redosledu navođenja u tekstu. Broj referenci ne bi trebalo da bude veći od 30, osim u pregledu literature, u kojem je dozvoljeno da ih bude do 50.

Izbegavati korišćenje apstrakta kao reference, a apstrakte starije od dve godine ne citirati.

Reference se citiraju prema tzv. Vankuverskim pravilima, koja su zasnovana na formatima koja koriste *National Library of Medicine* i *Index Medicus*.

Primeri:

1. **Članak:** (svi autori se navode ako ih je šest i manje, ako ih je više navode se samo prvih šest i dodaje se *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Knjiga:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Poglavlje ili članak u knjizi:**

Latković Z. Tumori očnih kapaka. U: Litričin O i sar. Tumori oka. 1. izd. Beograd: Zavod za udžbenike i nastavna sredstva, 1998: 18–23.

Tabele. Tabele se označavaju arapskim brojevima po redosledu navođenja u tekstu, sa nazivom tabele iznad.

Slike. Sve ilustracije (fotografije, grafici, crteži) se smatraju slikama i označavaju se arapskim brojevima u tekstu i na legendama, prema redosledu pojavljivanja. Treba koristiti minimalni broj slika koje su zaista neophodne za razumevanje rada. Slova, brojevi i simboli moraju biti jasni, proporcionalni, i dovoljno veliki da se mogu reprodukovati. Pri izboru veličine grafika treba voditi računa da prilikom njihovog smanjivanja na širinu jednog stupca teksta neće doći do gubitka čitljivosti. Legende za slike se moraju dati na posebnim listovima, nikako na samoj slici.

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Each manuscript component (title page, etc.) begins on a separate page. All pages are numbered consecutively beginning with the title page.

References in the text are designated with Arabic numerals in parentheses, and the order in which they appear in the text.

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A short title of less than 50 spaces, for use as a running head, is included.

A brief acknowledgment of grants and other assistance, if any, is included.

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1. **Article:** (all authors are listed if there are six or fewer, otherwise only the first six are listed followed by *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Book:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Chapter or article in a book:**

Trier JJ. Celiac sprue. In: Sleisenger MH, Fordtran J5, eds. Gastro-intestinal disease. 4 th ed. Philadelphia: WB Saunders Co, 1989: 1134–52.

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