

TURKISH JOURNAL of TRAUMA & EMERGENCY SURGERY

Ulusal Travma ve Acil Cerrahi Dergisi



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The journal's impact factor in SCI-E indexed journals is 1.1 according to the 2023 Journal Citation Reports (JCR). In PubMed, the journal is cited as 'Ulus Travma Acil Cerrahi Derg'.

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Priority of publications is given to original studies; therefore, selection criteria are more refined for reviews and case reports.

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Chapter in book: Jurkovich GJ. Duodenum and pancreas. In: Mattox KL, Feliciano DV, Moore EE, editors. *Trauma*. 4th ed. New York: McGraw-Hill; 2000. p. 735-62.

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Impact of the 1,2,3-triazole compound derived from salicylaldehyde on localized and systemic organ injury in an experimental superior mesenteric artery ischemia/reperfusion model

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ABSTRACT

BACKGROUND: Despite several studies indicating the efficacy of different molecules in preventing ischemia/reperfusion (I/R) damage, the most effective treatment remains unknown.

METHODS: This study included 28 male Sprague rats, which were randomly assigned to four equal groups, with seven rats in each group: Group S (Sham), Group C (Control), Group E (Ethanol), and Group T (Triazole). The superior mesenteric arteries of rats in all groups except Group S were exposed and closed with a vascular clamp, and ischemia was induced for one hour. Oxidative stress parameters, ischemia markers, and biochemical tests indicating organ function were examined.

RESULTS: The mean total antioxidant status (TAS) value of Group T was significantly higher than those of Groups C and E, while being significantly lower than that of Group S ($p=0.001$). The mean total oxidant status (TOS) value of Group T was significantly lower than those of Groups C and E and significantly higher than that of Group S ($p<0.001$). Although the mean oxidative stress index (OSI) value of Group T was markedly lower than those of Groups C and E, no statistically significant difference was observed compared to Group S ($p=0.002$, $p<0.001$, and $p=0.721$, respectively). The mean ischemia-modified albumin (IMA) value of Group T was significantly lower than those of Groups C and E and significantly higher than that of Group S ($p<0.001$). The mean malondialdehyde (MDA) value of Group T was significantly lower than those of Groups C and E and significantly higher than that of Group S ($p<0.001$).

CONCLUSION: This study represents the first investigation into the effect of a 1,2,3-triazole compound derived from salicylaldehyde on ischemia/reperfusion injury. The findings provide strong evidence that the 1,2,3-triazole compound significantly enhances the prevention or treatment of experimental I/R injury. We conclude that this triazole derivative may represent a viable therapeutic option for the treatment and prevention of I/R injury, supported by further experimental and clinical research. The triazole is expected to exhibit enhanced protective properties, particularly when solubilized using alternative methods.

Keywords: Ischemia/reperfusion; triazole; liver; small intestine; superior mesenteric artery.

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INTRODUCTION

Ischemia/reperfusion (I/R) injury frequently presents as a clinical condition associated with increased mortality following acute mesenteric ischemia, shock, laparoscopic procedures, and major surgical interventions. The incidence and mortality rates are gradually increasing.^[1,2] I/R injury arises from oxidative stress, lipid peroxidation, and oxygen-derived free radicals.^[3] Reactive oxygen species (ROS) are primarily responsible for the damage induced by ischemia/reperfusion. ROS are generated by four interrelated biochemical mechanisms: xanthine oxidase-mediated processes, the mitochondrial electron transport chain (ETC), nitric oxide synthase, and phagocytic cells.^[4,5] The extent of tissue damage resulting from ischemia/reperfusion depends on variations in ischemia duration and the distinct structural and biochemical metabolic characteristics of tissues and organs.^[4-6] Tissue injury resulting from ischemia/reperfusion may extend beyond the ischemic area, potentially inflicting varying degrees of damage on remote organ systems. Damage to remote organs is believed to result from circulating leukocytes, inflammatory cytokines, and systemic oxidants that induce the migration of polymorphonuclear leukocytes to distant sites, along with reactive oxygen species.^[6-10] This study examined regional damage by analyzing terminal ileum tissue and distant organ damage using liver tissue samples.

Although multiple studies have reported the efficacy of different molecules in mitigating I/R injury, the most effective therapeutic intervention remains unclear.^[3,11] Consequently, further studies are required to improve the prevention of ischemia/reperfusion injury. The primary hypothesis of this study is that ischemia/reperfusion damage can be prevented by inhibiting xanthine oxidase activity during ischemia/reperfusion. The objective was to examine the efficacy of a 1,2,3-triazole derivative as a xanthine oxidase inhibitor in preventing I/R damage.

1,2,3-triazole derivatives are novel compounds identified as inhibitors of xanthine oxidase. The primary xanthine oxidase inhibitor used in the clinical treatment of gout is allopurinol, which is associated with significant side effects due to its involvement in purine metabolism. Consequently, triazole compounds have been identified as xanthine oxidase inhibitors lacking purine analog structures in *in vitro* experiments arising from novel drug research.^[12] Numerous studies have demonstrated that 1,2,3-triazole compounds exhibit antiallergic, antibacterial, and antituberculous activity *in vitro*.^[13-15] Nonetheless, *in vivo* studies demonstrating the effects of these newly identified triazole compounds on xanthine oxidase inhibition and ischemia/reperfusion damage are lacking. This study represents the first *in vivo* investigation demonstrating the effect of a 1,2,3-triazole derivative on xanthine oxidase inhibition and ischemia/reperfusion injury.

The primary hypothesis of this study is that ischemia/reperfusion damage can be prevented by inhibiting xanthine oxidase activity using a 1,2,3-triazole compound. The primary outcome of the investigation was the oxidative stress index (OSI).

MATERIALS AND METHODS

This study was carried out at the University of Health Sciences Hamidiye Animal Experiments Laboratory after approval by the Hamidiye Animal Experiments Local Ethics Committee (Date: 24.07.2024, Approval Number: 02/03). The study included 28 male Sprague rats with an average weight of 200 ± 20 grams and aged 16-20 weeks. Throughout the investigation, all rats were maintained at a standard room temperature of $21 \pm 2^\circ\text{C}$ and humidity levels of 40-60%, under a 12-hour light/12-hour dark cycle. Each cage housed four rats, which were kept in metal cages and provided with standard rat feed and tap water. Cage maintenance was performed routinely with daily inspections. During the study, all rats were treated humanely in accordance with the Guide for the Care and Use of Laboratory Animals. All surgical interventions were performed under anesthesia. For anesthetic induction, ketamine hydrochloride (Ketalar® vial, 50 mg/mL, Eczacıbaşı, İstanbul, Türkiye) was administered intraperitoneally (ip) at a dose of 80 mg/kg, and xylazine hydrochloride (ROMPUN® vial, 23.32 mg/mL, Bayer) was administered intraperitoneally at a dose of 10 mg/kg.

Rats were divided into four equal groups, with seven rats in each group:

Group S (Sham) (n=7): Laparotomy

Group C (Control) (n=7): 1 mL intraperitoneal saline + laparotomy + ischemia/reperfusion

Group E (Ethanol) (n=7): 1 mL intraperitoneal saline/ethanol + laparotomy + ischemia/reperfusion

Group T (Triazole) (n=7): 1 mL intraperitoneal 20 mg/kg triazole/ethanol/saline + laparotomy + ischemia/reperfusion.

After eight hours of fasting, the weights of all rats were recorded under anesthesia. All rats were anesthetized, and vascular access was subsequently obtained using a 26G angiocath inserted into the tail vein. Following shaving of the abdominal regions of all rats and disinfection of the surgical field with povidone-iodine under operating room conditions, 1 mL of saline was administered to the rats in Group C, 1 mL of ethanol/saline (1/9) to the rats in Group E, and 20 mg/kg of triazole/ethanol/saline in 1 mL was administered intraperitoneally to the rats in Group T. After 30 minutes, a 3-cm full-thickness midline abdominal incision was performed in all rats. Immediately after laparotomy, the superior mesenteric arteries of rats in all groups except Group S were exposed and closed with a vascular clamp, and ischemia was induced for one hour. Reperfusion was subsequently performed for one hour (I). At the end of this period, approximately 4-6 mL of blood samples for biochemical analysis were obtained via intracardiac puncture. All rats were sacrificed to obtain liver and terminal ileum tissue samples for histological analysis. The inclusion of the ethanol group in our investigation was due to the use of the 1,2,3-triazole compound as a solvent for intraperitoneal administration. Ethanol was used in Groups E and T at a concentration of 10%.

Biochemical Method (Blood)

The individual performing the blood sample analyses was blinded to group assignments. Blood samples were analyzed for glucose (GLU), aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), and serum creatinine (CR) using an Abbott Architect c16000 analyzer (Abbott, Abbott Park, IL, USA). Total antioxidant status (TAS) and total oxidant status (TOS) were assessed using the Real Assay Total Antioxidant Status Assay Kit (Mega Medikal, Ankara, Türkiye). TAS values were expressed as mmol ascorbic acid equivalent per liter, while TOS values were expressed as $\mu\text{mol H}_2\text{O}_2$ equivalent per liter. The oxidative stress index was calculated using the formula:

$$\text{OSI (AU)} = (\text{TOS } [\mu\text{mol/L}]) / (\text{TAS } [\text{mmol Trolox equivalent/L}] \times 100) \text{ (19)}.$$

Ischemia-modified albumin (IMA) and malondialdehyde (MDA) concentrations were measured using the method described by Ertürk et al.^[11,16]

Histopathological Examination

All assessments were conducted by the same pathologist, who was unaware of the group assignments.

Liver: One-hour post-reperfusion, tissue samples were obtained from the right lobe of the liver. Liver tissue samples were immersed in a 10% formaldehyde solution, embedded in paraffin blocks, sectioned at 5 μm thickness, and stained with hematoxylin-eosin. Biopsy specimens were evaluated at 200 magnification using a sequential scale to determine the severity of liver injury:

- Grade 0: No evidence of mild injury or any injury present.
- Grade 1: Minor damage characterized by cytoplasmic vacuolation and localized nuclear pyknosis.
- Grade 2: Widespread nuclear pyknosis, cytoplasmic hyperosinophilia, intercellular loss, and mild neutrophilic infiltration.
- Grade 3: Significant injury characterized by disintegration of hepatic cords, hemorrhage, and pronounced polymorphonuclear neutrophil infiltration.

Each sample was evaluated using an average of 100 adjacent points on a 1 mm^2 grid.^[17]

Small Intestine: Tissue samples designated for histopathological analysis were stained with hematoxylin and eosin, examined under light microscopy at 10 $\times$ and 40 $\times$ magnification, and scored according to the modified Chiu scoring system.^[18] The scoring criteria were as follows:

- Grade 0: Normal,
- Grade 1: Desquamation and necrosis involving one-third of the villi,
- Grade 2: Progressive desquamation in the center of the villi,

- Grade 3: Necrosis with desquamation and involvement of crypt cells beneath one-third of the villi,
- Grade 4: Necrosis of one-third of the crypt cells,
- Grade 5: Total loss of the basal lamina.

Preparation of 1,2,3-Triazole

The target compound, a 1,2,3-triazole derivative derived from salicylaldehyde and previously synthesized by a member of our group member,^[19] was re-synthesized as reported in the literature and re-characterized using various spectroscopic techniques for this study.^[19] Initially, 4-chloroaniline was treated with chloroacetyl chloride in the presence of NaHCO_3 in MeCN at 0°C to obtain 2-chloro-N-(4-chlorophenyl)acetamide. Subsequently, 2-chloro-N-(4-chlorophenyl)acetamide was reacted with NaN_3 in dimethyl sulfoxide (DMSO) at room temperature to obtain 2-azido-N-(p-tolyl)acetamide. On the other hand, salicylaldehyde was reacted with propargyl bromide in the presence of K_2CO_3 in MeCN, yielding the 2-(prop-2-yn-1-yloxy)benzaldehyde compound at the end of the reaction. Finally, to synthesize the target 1,2,3-triazole compound, the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) method was utilized.^[20-23] In this step, 2-azido-N-(p-tolyl)acetamide (azide) and 2-(prop-2-yn-1-yloxy)benzaldehyde compound (alkyne) were reacted in the presence of sodium L-ascorbate and $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ in a MeOH/ H_2O (1:1) solvent system at room temperature, resulting in the synthesis of the target compound.^[19]

Sample Calculation

MedCalc® Statistical Software version 19.7.2 (MedCalc Software Ltd., Ostend, Belgium; <https://www.medcalc.org>; 2021) was used. According to Kartal et al.,^[3] the analysis indicated a type I error rate of $\alpha=0.05$ and a statistical power of $1-\beta=80\%$. The sample size was determined to be five rats per group. Due to the absence of experimental studies involving the combination of ethanol and triazole, and because the anticipated difference was expected to be comparable to that between the control and triazole groups, the sample size for the other groups was also set at five. Considering possible losses, seven rats were ultimately included in each group.

Statistical Analysis

SPSS version 15.0 software for Windows was used for statistical analysis. Descriptive statistics included numbers and percentages for categorical variables and mean, standard deviation, minimum, and maximum values for numerical variables. The Kruskal-Wallis test was applied when numerical variables did not show a normal distribution, whereas one-way analysis of variance (ANOVA) was used when the normality assumption was met across groups. Subgroup analyses in nonparametric tests were performed using the Mann-Whitney U test and interpreted with Bonferroni adjustment. Differences in rates among groups were analyzed using the chi-square test. The level of statistical significance was set at $p<0.05$.

RESULTS

During the study, rats no. 2 and 6 from the Sham group and rat no. 3 from the Ethanol group were excluded due to death following anesthesia induction.

No statistically significant difference was observed in the mean body weight of the rats among the groups ($p=1.000$). Statistically significant differences were observed among the groups in oxidative stress parameters (mean TAS, TOS, and

OSI) and ischemia markers (mean IMA and MDA) ($p<0.001$). Table 1 presents the mean body weights of the rats in each group, along with oxidative stress parameters and ischemia markers.

Significant differences were also detected in the biochemical parameters (GLU, AST, ALT, BUN, and CR) among the groups ($p<0.001$). The biochemical parameters of the rats are presented in Table 2.

Table 1. Body weight, oxidative stress parameters, and ischemia markers of rats in the study groups

Parameter	Sham	Ethanol	Triazole	Control	p*
	Mean±SD (Min-Max)	Mean±SD (Min-Max)	Mean±SD (Min-Max)	Mean±SD (Min-Max)	
Weight	193.9±7.2 (181.9-204)	193.8±4.1 (188-199)	193.9±14.0 (180-215.7)	194.0±10.5 (182.3-212)	1.000
TAS	0.69±0.10 (0.60-0.85)	0.18±0.06 (0.11-0.27)	0.39±0.05 (0.32-0.48)	0.22±0.06 (0.12-0.29)	<0.001
TOS	2.85±0.42 (2.39-3.25)	16.25±1.17 (15.46-18.53)	9.57±1.27 (8.27-11.78)	13.88±1.79 (12.06-16.89)	<0.001
OSI	4.22±0.91 (2.85-5.31)	99.98±33.66 (61.37-142.11)	24.92±4.56 (17.86-30.16)	68.98±26.46 (52.49-124.14)	<0.001**
IMA	0.32±0.04 (0.28-0.38)	1.79±0.07 (1.71-1.88)	1.19±0.09 (1.10-1.34)	1.64±0.03 (1.61-1.69)	<0.001
MDA	0.74±0.09 (0.65-0.86)	3.01±0.28 (2.70-3.34)	1.67±0.16 (1.44-1.97)	2.70±0.29 (2.36-3.06)	<0.001

**Mann-Whitney U test; $p<0.017$. SD: Standard deviation; Min: Minimum; Max: Maximum; TAS: Total antioxidant status; TOS: Total oxidant status; OSI: Oxidative stress index; IMA: Ischemia-modified albumin; MDA: Malondialdehyde.

Table 2. Biochemical parameters of rats in the study groups

Parameter	Sham	Ethanol	Triazole	Control	p*
	Mean±SD (Min-Max)	Mean±SD (Min-Max)	Mean±SD (Min-Max)	Mean±SD (Min-Max)	
GLU	83.0±8.2 (73-92)	142.7±30 (139-147)	110.7±4.1 (105-116)	127.6±13.1 (108-148)	<0.001
AST	69.0±4.9 (65-77)	104.5±7.0 (92-112)	85.0±6.2 (73-91)	94.9±6.3 (86-105)	<0.001
ALT	54.6±5.7 (45-60)	93.3±3.8 (88-98)	79.7±5.0 (75-90)	86.3±8.1 (76-99)	<0.001**
BUN	31.0±5.5 (25-38)	75.0±7.1 (66-87)	56.7±6.2 (50-68)	66.1±8.4 (53-77)	<0.001
CR	0.51±0.06 (0.44-0.57)	0.85±0.07 (0.74-0.93)	0.74±0.07 (0.62-0.85)	0.82±0.10 (0.69-0.99)	<0.001

**Mann-Whitney U test; $p<0.017$. SD: Standard deviation; Min: Minimum; Max: Maximum; GLU: Glucose; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; BUN: Blood urea nitrogen; CR: Creatinine.

Analysis of the biochemical parameters revealed that the mean GLU value in Group T was significantly lower than those in Groups C and E and significantly higher than that in Group S ($p=0.006$, $p<0.001$, and $p<0.001$, respectively). The mean AST value in Group T was significantly lower than those in Groups C and E and significantly higher than that in Group S ($p=0.043$, $p<0.001$, and $p=0.001$, respectively). The mean ALT value in Group T was lower than that in Group C without reaching statistical significance, showed a statistically significant decrease compared to Group E, and a statistically significant increase compared to Group S ($p=0.061$, $p=0.005$, and $p=0.004$, respectively). The mean BUN value in Group T was lower than that in Group C without statistical significance, significantly lower than that in Group E, and significantly higher than that in Group S ($p=0.119$, $p=0.001$, and $p<0.001$, respectively). The mean CR value in Group T was lower than those of Groups C and E without reaching statistical significance and significantly higher than that of Group S ($p=0.424$, $p=0.140$, and $p<0.001$, respectively). Subgroup analyses are summarized in Table 3.

Upon examination of oxidative stress parameters, the mean TAS value of Group T was significantly higher than those of Groups C and E, while being significantly lower than that of Group S ($p=0.001$). The mean TOS value of Group T was significantly lower than those of Groups C and E and significantly higher than that of Group S ($p<0.001$). Although the mean OSI value of Group T was markedly lower than those of Groups C and E, no statistically significant difference

was observed compared to Group S ($p=0.002$, $p<0.001$, and $p=0.721$, respectively).

Evaluation of the ischemia markers demonstrated that the mean IMA value of Group T was significantly lower than those of Groups C and E and significantly higher than that of Group S ($p<0.001$). The mean MDA value of Group T was also significantly lower than those of Groups C and E and significantly higher than that of Group S ($p<0.001$). Subgroup analyses of oxidative stress parameters and ischemia markers are presented in Table 4.

Histological evaluation revealed no liver damage in any of the rats across the groups, precluding statistical comparison of the mean liver histopathological scores (LHS). No statistically significant difference was observed among the intestinal histopathological scores (IHSs) of the groups ($p=0.345$). The mean histopathological scores of the groups are summarized in Table 5.

DISCUSSION

In this study, the mean TAS values of Group T were statistically significantly higher than those of Groups C and E. The mean TOS, OSI, IMA, MDA, GLU, and AST values of Group T were statistically significantly lower than those of Groups C and E. The mean ALT and BUN values of Group T were statistically significantly lower than those of Group E.

Despite being a critical clinical condition associated with significant mortality, an effective treatment strategy for I/R

Table 3. Subgroup analyses of biochemical parameters among the groups

Group		Sham	Ethanol	Triazole
		P	P	P
GLU	Ethanol	<0.001		
	Triazole	<0.001	<0.001	
	Control	<0.001	0.022	0.006
AST	Ethanol	<0.001		
	Triazole	0.001	<0.001	
	Control	<0.001	0.065	0.043
ALT	Ethanol	<0.001		
	Triazole	0.004**	0.005**	
	Control	<0.001	0.270	0.061**
BUN	Ethanol	<0.001		
	Triazole	<0.001	0.001	
	Control	<0.001	0.201	0.119
CR	Ethanol	<0.001		
	Triazole	<0.001	0.140	
	Control	<0.001	1.000	0.424

**Mann-Whitney U test; $p<0.017$. GLU: Glucose; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; BUN: Blood urea nitrogen; CR: Creatinine.

Table 4. Subgroup analyses of oxidative stress parameters and ischemia markers among the groups

Group		Sham	Ethanol	Triazole
		P	P	P
TAS	Ethanol	<0.001		
	Triazole	<0.001	<0.001	
	Control	<0.001	1.000	0.001
TOS	Ethanol	<0.001		
	Triazole	<0.001	<0.001	
	Control	<0.001	0.024	<0.001
OSI	Ethanol	<0.001		
	Triazole	0.721	<0.001	
	Control	0.004**	0.032**	0.002**
IMA	Ethanol	<0.001		
	Triazole	<0.001	<0.001	
	Control	<0.001	0.002	<0.001
MDA	Ethanol	<0.001		
	Triazole	<0.001	<0.001	
	Control	<0.001	0.143	<0.001

**Mann-Whitney U test; p<0.017. TAS: Total antioxidant status; TOS: Total oxidant status; OSI: Oxidative stress index; IMA: Ischemia-modified albumin; MDA: Malondialdehyde.

Table 5. Histopathological findings of rats in the study groups

	Sham	Ethanol	Triazole	Control	p
LHS, n (%)					
No damage	5 (100)	6 (100)	7 (100)	7 (100)	-
IHS					
No damage	5 (100)	4 (66.7)	7 (100)	6 (85.7)	0.345
Damage	0 (0.0)	2 (33.3)	0 (0.0)	1 (14.3)	

LHS: Liver histopathological score; IHS: Intestinal histopathological score.

damage has yet to be established.^[3] The incidence and mortality rates are increasing.^[1,2] Consequently, the prevention and/or treatment of I/R injury is of paramount therapeutic importance. Although the literature suggests that I/R damage can be reduced using various medications, the underlying mechanisms remain inadequately elucidated in these studies.^[1,2] Therefore, inhibiting ROS production, which contributes to I/R damage through multiple formation pathways, is considered crucial for the development of effective treatment strategies. Xanthine oxidase, an enzyme involved in ROS production, is implicated in organ damage through endothelial dysfunction.^[8] Accordingly, compounds that inhibit xanthine oxidase are anticipated to effectively reduce I/R damage.

Ethanol has a narrow therapeutic window, and both low and high doses can produce opposing effects. Studies in the lit-

erature report that acute ethanol exposure causes ischemia.^[24, 25] Our investigation revealed that acute ethanol exposure negatively affected all oxidative stress parameters, ischemia markers, and biochemical indicators, with statistically significant changes observed in TOS, IMA, and GLU values. These results indicate that acute ethanol exposure exacerbates I/R damage, which is consistent with existing research.^[24,25]

This study demonstrated no statistically significant difference in mean IHSs among the groups. Due to the absence of liver injury in any rat with respect to LHS, statistical comparison was not possible. These findings were attributed to the short I/R duration and insufficient time for damage to manifest in regional and distant organs.

Triazole derivatives have recently been investigated as alter-

native therapeutic agents due to the side effects of allopurinol (e.g., hepatotoxicity and hypersensitivity reactions), which is commonly used in the treatment of gout.^[12] The present study aimed to examine the efficacy of the triazole derivative outside its original development context, suggesting its potential to alleviate I/R damage through xanthine oxidase inhibition. No in vivo studies were identified in the literature concerning the impact of the 1,2,3-triazole derivative on I/R injury. Consequently, this research is considered the first study of its kind in the literature.

Due to the absence of studies evaluating the effects of triazole derivatives on I/R damage, the findings were compared with those from investigations involving other compounds and analyzed accordingly. Dexmedetomidine (Dex) is one of the most commonly investigated compounds for this purpose in research studies. Some studies examining the effects of Dex on I/R damage indicate that it generally exerts favorable effects on oxidative stress parameters, although these effects are not always statistically significant. Nevertheless, despite numerous investigations on Dex, evidence supporting its use in the treatment of I/R damage remains limited.^[1,3] Our investigation demonstrated that all oxidative stress markers were significantly improved in the triazole group compared to Groups C and E. Given that ethanol administration in Group E adversely affected the mean oxidative stress parameters relative to Group C, it is noteworthy that triazole treatment substantially reduced oxidative stress compared to Group C, despite the presence of ethanol. This finding indicates that triazole may serve as an effective agent in reducing I/R damage. The reported effects of Dex on IMA and MDA levels are controversial.^[1,26,27] In contrast, our study showed that triazole significantly decreased mean IMA and MDA values, suggesting a potential protective effect. The effects of Dex on biochemical indicators of organ function remain unclear in the existing literature.^[1,26] In our study, triazole significantly reduced GLU and AST levels compared to Groups C and E, and ALT and BUN levels compared to Group E. These findings indicate that triazole may have a significant organoprotective effect. Dexamethasone is another compound commonly used to reduce I/R damage.^[2,28] These investigations primarily assessed cellular immune suppression, and sufficient data regarding oxidative stress indicators, ischemia markers, and biochemical parameters were not presented. Sun et al.^[2] reported that dexamethasone resulted in reductions in BUN and CR levels.

Although experimental studies in the literature report that allopurinol may be effective in preventing I/R injury through inhibition of the xanthine oxidase enzyme, sufficient clinical evidence has not yet been presented.^[29-32] Given the significant adverse effects associated with allopurinol, a purine analog, the use of newly synthesized non-purine analog triazole derivatives for this indication may be promising. In this study, the 1,2,3-triazole compound significantly improved all oxidative stress parameters, ischemia markers, and some biochemical indicators of organ function in an experimental superior

mesenteric artery (SMA) I/R model. These results strongly suggest that the 1,2,3-triazole compound may be useful in the prevention and/or treatment of I/R injury. This study represents the first investigation in the literature examining the impact of a 1,2,3-triazole compound on I/R injury. Since 1,2,3-triazole compounds are already used in humans for other therapeutic indications, these findings suggest promising potential for accelerated clinical application in I/R injury. Moreover, because ethanol was used as the solvent for the triazole compound in our study, it is noteworthy that, despite the immediate adverse effects of ethanol, I/R damage was significantly reduced compared to the control group. Consequently, these findings indicate that triazole may exhibit even greater protective effects when dissolved in alternative solvents other than ethanol that do not exacerbate tissue injury.

Limitations of the Study

1. Experimental study design
2. As this is the first study, comparison with other results was not possible
3. The mechanism could not be fully elucidated due to a focus on clinical outcomes
4. Use of ethanol as a solvent.

CONCLUSION

In conclusion, I/R injury is a critical clinical condition following major surgical and laparoscopic procedures, with its incidence increasing. Despite numerous compounds being tested for its treatment and prevention, I/R injury remains a significant health problem due to the lack of an effective therapy. In response to the substantial adverse effects of allopurinol, novel 1,2,3-triazole derivatives have recently been developed as alternative therapeutic agents for gout management. However, there is a lack of research in the literature regarding the effects of 1,2,3-triazole derivatives on I/R injury. This study represents the first investigation into the effects of a 1,2,3-triazole derivative on ischemia/reperfusion injury. The findings of this study provide strong evidence that the 1,2,3-triazole compound significantly enhances the prevention or treatment of experimental I/R injury. We support the notion that 1,2,3-triazole derivatives may offer a viable therapeutic option for the treatment and prevention of I/R injury, supported by further experimental and clinical research. Triazole is anticipated to exhibit enhanced protective properties, particularly when dissolved using alternative methods.

Ethics Committee Approval: This study was approved by the Hamidiye Animal Experiments Local Ethics Committee (Date: 24.07.2024, Decision No: 02/03).

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DENEYSEL ÇALIŞMA - ÖZ

Deneysel superior mezenterik arter iskemi/reperfüzyon modelinde salisilaldehitten türetilmiş 1,2,3 triazol bileşiğinin lokalize ve sistemik organ hasarı üzerindeki etkisi

AMAÇ: Farklı moleküllerin iskemi/reperfüzyon (I/R) hasarını önlemede etkili olduğunu gösteren birçok çalışmaya rağmen, en etkili tedavi yöntemi henüz bilinmemektedir.

GEREÇ VE YÖNTEM: Bu çalışmada 28 erkek Sprague sıçanı kullanılmıştır. Sıçanlar, her grupta yedi sıçan olacak şekilde dört eşit gruba ayrılmıştır. Gruplar; Grup S (Sham), Grup C (Kontrol), Grup E (Etanol), Grup T (Triazol). Grup S hariç tüm gruplardaki sıçanların superior mezenterik arterleri açığa çıkarılıp vasküler klem ile kapatılmış ve 1 saat boyunca iskemi oluşturulmuştur. Oksidatif stres parametreleri, iskemi belirteçleri ve organ fonksiyonlarını gösteren biyokimyasal testler incelenmiştir.

BULGULAR: Grup T ortalama Total antioksidan seviye (TAS) değeri Grup C ve E'ye göre istatistiksel olarak anlamlı düzeyde yüksek, Grup S'ye göre anlamlı düzeyde düşük tespit edildi ($p=0.001$). Grup T ortalama Total oksidan seviye (TOS) değeri Grup C ve E'ye göre istatistiksel olarak anlamlı düzeyde düşük, Grup S'ye göre anlamlı düzeyde yüksek tespit edildi ($p<0.001$). Grup T ortalama Oksidatif stres indeksi (OSI) değeri Grup C ve E'ye göre istatistiksel olarak anlamlı düzeyde düşük, Grup S'ye göre yüksek olmasına rağmen istatistiksel olarak anlamlı fark tespit edilmedi (Sırasıyla; $p=0.002$, $p<0.001$, $p=0.721$). Grup T ortalama skemi modifiye albümin (İMA) değeri Grup C ve E'ye göre istatistiksel olarak anlamlı düzeyde düşük, Grup S'ye göre anlamlı düzeyde yüksek tespit edildi ($p<0.001$). Grup T ortalama Malendialdehit (MDA) değeri Grup C ve E'ye göre istatistiksel olarak anlamlı düzeyde düşük, Grup S'ye göre anlamlı düzeyde yüksek tespit edildi ($p<0.001$).

SONUÇ: Bu çalışma, salisilaldehitten türetilmiş 1,2,3-triazol bileşiğinin iskemi/reperfüzyon hasarı üzerindeki etkisine ilişkin ilk araştırmayı temsil etmektedir. Bu çalışmanın bulguları, 1,2,3-triazol bileşiğinin deneysel I/R hasarının önlenmesini veya tedavisini önemli ölçüde artırdığına dair güçlü kanıtlar sunmaktadır. Kapsamlı deneysel ve klinik araştırmalarla desteklenen triazol türevinin I/R hasarının tedavisi ve önlenmesi için uygulanabilir bir tedavi seçeneği sunabileceğini savunuyoruz. Triazolün, özellikle alternatif yöntemlerle çözündürüldüğünde gelişmiş koruyucu özelliklere sahip olması beklenmektedir.

Anahtar sözcükler: İskemi/reperfüzyon, triazol, karaciğer, ince bağırsak, superior mezenterik arter.

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Investigation of the protective effects of hydroxytyrosol on erythrocyte deformability during hind limb ischemia-reperfusion injury in rats

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ABSTRACT

BACKGROUND: Ischemia-reperfusion (IR) injury significantly reduces erythrocyte deformability, leading to increased oxidative stress, inflammation, and impaired microvascular perfusion. This study aimed to examine the protective effects of hydroxytyrosol (HT), a powerful antioxidant derived from olives, on erythrocyte deformability and related oxidative stress markers in a rat model of hind limb ischemia-reperfusion injury.

METHODS: Twenty-four rats were randomly divided into four groups: Sham, HT-Sham, ischemia-reperfusion (IR), and IR treated with HT (IR-HT). HT was administered intraperitoneally at a dose of 10 mg/kg prior to ischemia induction. Following reperfusion, biochemical parameters, including malondialdehyde (MDA), superoxide dismutase (SOD), endothelial nitric oxide synthase (eNOS), erythrocyte deformability, and morphology, were evaluated.

RESULTS: HT administration significantly improved erythrocyte deformability, decreased MDA levels, increased SOD activity, and moderated eNOS expression in the IR-HT group compared to the untreated IR group ($p < 0.001$). Morphological analysis demonstrated substantial preservation of erythrocyte integrity, with fewer pathological changes such as echinocytes and dacryocytes.

CONCLUSION: This study provides preliminary insights into the protective mechanisms of HT, highlighting its therapeutic potential in reducing erythrocyte dysfunction and oxidative damage during ischemia-reperfusion events. Further research exploring comprehensive signaling pathways and long-term clinical outcomes is advisable.

Keywords: Hydroxytyrosol; ischemia-reperfusion injury; erythrocyte deformability; oxidative stress; rats.

INTRODUCTION

Ischemia-reperfusion (IR) injury initially results from ischemia-induced hypoxia and worsens significantly upon res-

toration of blood flow. During ischemia, reduced oxygen delivery causes anaerobic glycolysis, adenosine triphosphate (ATP) depletion, lactic acidosis, and intracellular Ca^{2+} accu-

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mulation due to impaired ATP-dependent ion pumps.^[1-4] Elevated intracellular Ca^{2+} triggers proteolytic enzymes, causes mitochondrial dysfunction, and leads to the opening of mitochondrial permeability transition pore (mPTP), promoting apoptosis and necrosis.^[2,4,5] Reperfusion introduces oxygen, which increases reactive oxygen species (ROS) production through mitochondrial electron transport chains, xanthine oxidase, and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, leading to significant oxidative stress.^[4] This stress causes endothelial nitric oxide synthase (eNOS) to become uncoupled, decreasing nitric oxide (NO) levels and impairing vasodilation.^[4,5] Endothelial dysfunction promotes leukocyte-endothelial interactions, initiating inflammation through neutrophils, macrophages, lymphocytes, and cytokines (tumor necrosis factor- α [TNF- α], interleukin-1 [IL-1], IL-6, IL-8, and platelet-activating factor [PAF]), thereby worsening tissue damage. Complement activation enhances leukocyte chemotaxis, causes vascular leakage, and leads to edema. Adhesion molecules (intercellular adhesion molecule-1 [ICAM-1], vascular cell adhesion molecule-1 [VCAM-1], and selectins) facilitate leukocyte migration into tissues.^[1,2] Malondialdehyde (MDA), a marker of lipid peroxidation, accumulates during reperfusion, indicating membrane oxidative damage.^[1-3] Reduced superoxide dismutase (SOD) activity impairs ROS detoxification, leading to increased oxidative damage.^[2,3] Additionally, erythrocyte deformability, which is crucial for microcirculatory perfusion, declines significantly due to oxidative damage to the membrane and cytoskeleton, as well as disrupted calcium balance, leading to microvascular obstruction.^[1-3] Elevated inflammatory cytokines and oxidative stress further damage erythrocytes, exacerbating tissue hypoxia and injury.^[2,4,6]

Erythrocyte deformability, which is essential for effective microcirculation and tissue oxygenation, allows red blood cells (RBCs) to change shape dynamically when passing through narrow capillaries.^[6,7] This property depends on membrane elasticity, cytoskeletal integrity, intracellular viscosity, and cellular geometry, which are largely influenced by proteins such as spectrin, ankyrin, band 3, and glycophorin.^[8] During reperfusion, excessive ROS-hydroxyl radicals, hydrogen peroxide, and superoxide anions damage RBC membranes through lipid peroxidation, altering membrane fluidity and increasing rigidity, as reflected by elevated MDA levels.^[1,2,9] Oxidative stress also damages cytoskeletal proteins (spectrin and actin), leading to cross-linking and fragmentation, which further decreases RBC flexibility.^[8,10] NO, primarily synthesized by eNOS, maintains vascular tone and erythrocyte deformability. Endothelial dysfunction during IR injury impairs NO synthesis, leading to increased vascular resistance and decreased erythrocyte deformability.^[11] Enhancing NO production shows protective effects on RBC deformability in IR models.^[9,12] Ischemia-induced ATP depletion disrupts ionic gradients essential for maintaining cytoskeletal function, leading to cell swelling, increased intracellular viscosity, and decreased deformability.^[7] Reperfusion initially worsens these metabolic

disturbances before they eventually return to normal. Additionally, intracellular calcium accumulation during ischemia activates enzymes such as calpain, leading to cytoskeletal degradation and membrane stiffening, significantly impairing erythrocyte deformability.^[13] Several pharmacological agents, including alprostadil, dexmedetomidine, thymoquinone, and esmolol, reduce oxidative stress and lipid peroxidation, thereby improving erythrocyte deformability during IR and highlighting the therapeutic potential of targeting oxidative pathways to preserve erythrocyte deformability and attenuate IR injury.^[9,14-17]

Hydroxytyrosol (HT) is a potent phenolic compound predominantly found in olives, olive leaves, and extra virgin olive oil, chemically known as 3,4-dihydroxyphenylethanol. It is characterized by robust antioxidant and anti-inflammatory properties, primarily through its capacity to neutralize ROS, thereby mitigating oxidative stress.^[18] Studies have consistently demonstrated that HT significantly reduces oxidative markers such as MDA, a marker of lipid peroxidation, and enhances endogenous antioxidant enzyme activities, notably SOD, thereby safeguarding cellular integrity under oxidative conditions.^[19-22] Moreover, HT has been shown to improve vascular function by upregulating eNOS expression and increasing NO bioavailability, which is critical for maintaining vascular homeostasis and promoting vasodilation.^[22-26] Its anti-inflammatory effects are mediated by inhibition of nuclear factor-kappa B (NF- κ B) signaling pathways, leading to reduced production of pro-inflammatory cytokines, including tumor necrosis factor- α , interleukin-1 beta, and interleukin-6, as well as adhesion molecules such as vascular cell adhesion molecule-1 and intercellular adhesion molecule-1.^[18,20,25] HT's protective mechanism against IR injury also involves inhibition of mPTP opening, a critical event leading to apoptosis and cellular damage during reperfusion.^[22,27] Additionally, HT's protective effects on erythrocyte deformability highlight its crucial role in reducing blood viscosity and maintaining microcirculatory flow under oxidative stress conditions, thus improving overall microvascular function during IR events.^[19,21,28,29] Collectively, these multi-targeted protective mechanisms position HT as a promising therapeutic agent for conditions involving oxidative stress and inflammation, particularly IR injuries.

The primary aim of this study is to evaluate the potential protective effects of HT on erythrocyte deformability and related oxidative stress parameters in a rat model of hind limb IR injury. Specifically, the study seeks to determine whether HT administration can reduce erythrocyte dysfunction, maintain cellular integrity, and improve microcirculatory flow during IR conditions. Using comprehensive biochemical, hematological, and histological methods, this investigation aims to uncover the underlying protective mechanisms of HT, providing important insights into its therapeutic potential and guiding future dietary strategies for managing and preventing IR injury.

MATERIALS AND METHODS

Ethical Approval

The experimental protocol of this study received approval from the Local Ethics Committee of the Kobay Experimental Animals Laboratory in Ankara, Türkiye, dated November 24, 2023 (Approval No: 692). All procedures involving animal handling, surgery, and sampling were meticulously performed in accordance with the ethical guidelines and standards established by the approving ethics committee.

The HT used in this study was obtained from Sigma-Aldrich (Sigma-Aldrich, St. Louis, MO, USA; CAS No. 10597-60-1). All reagents and materials were supplied by the researchers, and no external funding sources supported this study.

Experimental Design and Animals

The study utilized a total of 24 rats, systematically allocated into four experimental groups (n=6 per group): Sham, HT-Sham, IR, and ischemia-reperfusion treated with hydroxytyrosol (IR-HT). Sample sizes for each group were determined using Mead's method to ensure sufficient statistical power to detect meaningful differences in primary outcomes, including MDA, SOD, eNOS, erythrocyte morphology assessed via May-Grünwald-Giemsa (MGG) staining, and erythrocyte deformability.

Animals were housed individually under carefully regulated environmental conditions, with room temperature consistently maintained at 20–21°C and relative humidity kept between 45% and 55%. A standardized 12-hour light/dark cycle was used to align with circadian rhythms. Throughout the study, all rats had free access to standardized laboratory rodent chow and purified drinking water to ensure optimal nutrition and hydration.

Induction of Hind Limb Ischemia-Reperfusion Injury

The hind limb IR injury model was used to evaluate the protective effects of HT on erythrocyte deformability and oxidative stress parameters. Before the procedure, all rats fasted overnight but had free access to water. Anesthesia was induced by intraperitoneal injection of ketamine (80 mg/kg) combined with xylazine (10 mg/kg). The level of anesthesia was confirmed by the absence of withdrawal reflexes upon paw pinch. Rats were then placed on a heated surgical table in a supine position, with body temperature maintained at approximately 37°C throughout the procedure.

Hydroxytyrosol was administered intraperitoneally at a dose of 10 mg/kg, 30 minutes prior to ischemia induction, in the HT-Sham and IR-HT groups to assess its potential protective effects against erythrocyte dysfunction and oxidative stress during IR injury.

The right hind limb was carefully prepared by shaving and then disinfected with povidone-iodine solution. A small longitudinal incision was made in the right inguinal area to access the femoral artery. For rats in the IR and IR-HT groups,

the femoral artery was gently isolated and occluded with a non-traumatic microvascular clamp. Complete ischemia was visually confirmed by pallor and decreased temperature of the distal limb. The ischemic period was strictly maintained for two hours. In the Sham and HT-Sham groups, the femoral artery was similarly exposed but left unclamped, serving as surgical controls.

Following the ischemic period, reperfusion was initiated by gently removing the microvascular clamp. Successful reperfusion was confirmed by the restoration of normal limb color and temperature. Afterwards, the surgical incision was closed with 4-0 silk sutures, and the animals were carefully monitored during recovery. The reperfusion phase lasted an additional two hours for all relevant groups.

Measurement of Biochemical and Hematological Parameters

At the end of the reperfusion period, blood samples were collected via cardiac puncture, and gastrocnemius muscle tissue from the affected limb was harvested for subsequent biochemical, hematological, and histological analyses.

Erythrocyte Deformability: Erythrocyte deformability was evaluated to determine the flexibility of RBCs under different treatment conditions. To reduce the risk of hemolysis, blood samples were carefully collected, and measurements were performed promptly. The samples were initially centrifuged at $1,000 \times g$ for 10 minutes. The serum and buffy coat layers above the erythrocyte pellet were then gently removed and discarded. The erythrocyte pellet was washed with isotonic phosphate-buffered saline (PBS), followed by centrifugation at $1,000 \times g$ for an additional 10 minutes. This washing process was repeated three times to ensure the isolation of pure erythrocytes. The purified erythrocytes were resuspended in PBS to achieve a final hematocrit of 5%, creating a standardized erythrocyte suspension used for deformability measurements, which were consistently performed at 22°C.

The evaluation of erythrocyte deformability was performed using a constant-flow filtration system. For each sample, a 10 mL suspension of erythrocytes in PBS was prepared. A steady flow rate of 1.5 mL/min was maintained using an infusion pump. The filtration setup included a nucleoporin polycarbonate filter with a pore size of 5 μm and a diameter of 28 mm. Pressure changes caused by erythrocytes passing through the filter were continuously monitored with a pressure transducer, and the data were recorded digitally using an MP30 data acquisition system (BIOPAC Systems Inc., Goleta, CA).

Before each measurement, the system's pressure calibration was performed to ensure accuracy. Initially, the PBS buffer alone was passed through the filtration apparatus to establish a baseline measurement. The erythrocyte suspension was then introduced, and pressure values were recorded. Relative resistance (R_{rel}) was calculated as the ratio of the pressure generated by the erythrocyte suspension to that of the PBS buffer alone. The deformability index was interpreted in-

versely; higher R_{rel} values indicated decreased erythrocyte deformability.

Measurement of Malondialdehyde Levels: MDA levels were measured as a marker of lipid peroxidation and oxidative stress using a commercially available ELISA (enzyme-linked immunosorbent assay) kit (SunRed Biological Technology Co. Ltd., Cat. No. 201-11-0157, Shanghai, China; Ref: DZE201110157, Lot: 202311). The assay was performed strictly according to the manufacturer's protocol. Briefly, all reagents were equilibrated to room temperature prior to use. Serial dilutions of the standard stock solution were prepared at concentrations of 40, 20, 10, 5, 2.5, and 1.25 ng/mL. Then, 50 μ L of each standard solution was pipetted into the respective wells. Since the standard solutions already contained a biotin-labeled antibody, no additional antibody was added to these wells. For experimental samples, 40 μ L of each sample was dispensed into separate wells, followed by the addition of 10 μ L of anti-MDA antibody.

Subsequently, 50 μ L of streptavidin-horseradish peroxidase conjugate was added to all standard and sample wells. The plate was incubated at 37°C for 60 minutes. After incubation, the wells underwent five washing cycles with 350 μ L of washing solution per well using an automated ELISA plate washer. Next, 50 μ L of Chromogen A and 50 μ L of Chromogen B solutions were added sequentially to each well, followed by incubation in the dark at 37°C for an additional 10 minutes. The reaction was stopped by adding 50 μ L of stop solution to each well, resulting in a color change from blue to yellow. Absorbance was measured at 450 nm using a microplate reader, with readings taken within 15 minutes of stopping the reaction.

Measurement of Superoxide Dismutase Activity: SOD activity was measured to evaluate antioxidant enzyme status using a commercial ELISA kit (SunRed Biological Technology Co. Ltd., Cat. No. 201-11-0169, Shanghai, China; Ref: DZE201110169, Lot: 202311). The assay was performed strictly according to the manufacturer's instructions. Briefly, all reagents were brought to room temperature before starting. SOD standards were serially diluted from a stock solution to concentrations of 64, 32, 16, 8, 4, and 2 ng/mL. Then, 50 μ L of each standard dilution was added to the respective wells of the microplate. Since the standard solutions already contained a biotin-labeled antibody, no additional antibody was added to these wells. For the experimental samples, 40 μ L of each sample was added to individual wells, followed by the addition of 10 μ L of anti-SOD antibody solution.

Thereafter, 50 μ L of streptavidin-horseradish peroxidase conjugate was added to all wells containing standards and samples, followed by incubation at 37°C for 60 minutes. After incubation, each well was washed five times with 350 μ L of wash solution using an automated ELISA plate washer to remove unbound components. Subsequently, 50 μ L of Chromogen A and 50 μ L of Chromogen B solutions were added

sequentially to all wells. The plate was then incubated in the dark at 37°C for an additional 10 minutes. The enzymatic reaction was stopped by adding 50 μ L of stop solution to each well, resulting in a color change from blue to yellow. Absorbance was immediately measured at 450 nm using a microplate reader, with readings taken within 15 minutes of stopping the reaction.

Histological Analysis

To examine erythrocyte morphology, blood smear samples were stained using the MGG method. Photomicrographs were taken at 1000 $\times$ magnification to allow detailed visualization of cell structure and changes.

Immunohistochemical Analysis

Blood smear samples fixed in ethanol underwent antigen retrieval, followed by washing with Tris-buffered saline containing Tween 20. Subsequently, the samples were treated with hydrogen peroxide to inhibit endogenous peroxidase activity and minimize nonspecific staining. Slides were incubated overnight at 4°C with a primary antibody specific for eNOS, diluted 1:100. The following day, the slides were incubated with a biotinylated secondary antibody and then treated with a streptavidin-peroxidase complex. Diaminobenzidine was used as the chromogenic substrate for visualization, and Mayer's hematoxylin served as the counterstain. Immunoreactivity for eNOS was quantitatively assessed using the H-score method.

Statistical Analysis

Data were expressed as mean $\pm$ standard deviation. Statistical comparisons of continuous variables among treatment groups were conducted using one-way analysis of variance (ANOVA). When ANOVA indicated statistically significant differences, pairwise comparisons between individual groups were performed using Tukey's post hoc test. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics software version 25 (IBM Corp., Armonk, NY, USA).

RESULTS

The results of biochemical, hematological, and histopathological analyses across the experimental groups are summarized comprehensively in Table 1. Statistically significant differences were observed among the groups for all measured parameters ($p<0.001$).

Erythrocyte Deformability

Erythrocyte deformability was significantly reduced in the IR group (3.12 ± 0.35) compared to the Sham group (1.74 ± 0.12 , $p<0.001$), indicating decreased red blood cell flexibility under ischemic conditions. However, HT administration notably preserved erythrocyte deformability in the IR-HT group (2.02 ± 0.24) compared to the untreated IR group ($p<0.001$), demonstrating a significant protective effect of HT against IR-induced erythrocyte rigidity.

Table 1. Mean $\pm$ standard deviation values of deformability, May-Grünwald-Giemsa (MGG) score, endothelial nitric oxide synthase (eNOS) expression, malondialdehyde (MDA) levels, and superoxide dismutase (SOD) activity according to treatment groups

Groups	DEFORMABILITY	MGG	E-NOS	MDA	SOD
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Sham	1.74 $\pm$ 0.12	2.11 $\pm$ 0.47	70.18 $\pm$ 14.15	12.91 $\pm$ 1.41	4.68 $\pm$ 0.96
HT-Sham	1.91 $\pm$ 0.06	2.93 $\pm$ 0.33	152.53 $\pm$ 16.24	15.09 $\pm$ 1.59	9.18 $\pm$ 0.88
IR	3.12 $\pm$ 0.35	4.42 $\pm$ 0.52	222.05 $\pm$ 23.34	21.97 $\pm$ 5.72	9.69 $\pm$ 1.36
IR-HT	2.02 $\pm$ 0.24	3.09 $\pm$ 0.41	161.67 $\pm$ 18.36	16.02 $\pm$ 1.76	12.45 $\pm$ 1.91
p [†]	<0.001	<0.001	<0.001	<0.001	<0.001
p ^{††}					
1 vs. 2	0.59	0.02	0.001	0.63	0.001
1 vs. 3	0.001	0.001	0.001	0.001	0.001
1 vs. 4	0.18	0.005	0.001	0.34	0.001
2 vs. 3	0.001	0.001	0.001	0.006	0.91
2 vs. 4	0.83	0.92	0.91	0.96	0.002
3 vs. 4	0.001	0.001	0.002	0.02	0.01

[†]One-Way ANOVA; ^{††}Tukey post hoc test ($p < 0.05$: statistical significance). SD: Standard deviation.

Malondialdehyde (MDA) Levels

Malondialdehyde, a key biomarker of lipid peroxidation and oxidative damage, was significantly higher in the IR group (21.97 $\pm$ 5.72) compared to the Sham group (12.91 $\pm$ 1.41,

$p < 0.001$). HT treatment significantly lowered MDA levels in the IR-HT group (16.02 $\pm$ 1.76) compared to untreated IR animals ($p = 0.02$), demonstrating effective attenuation of oxidative stress.

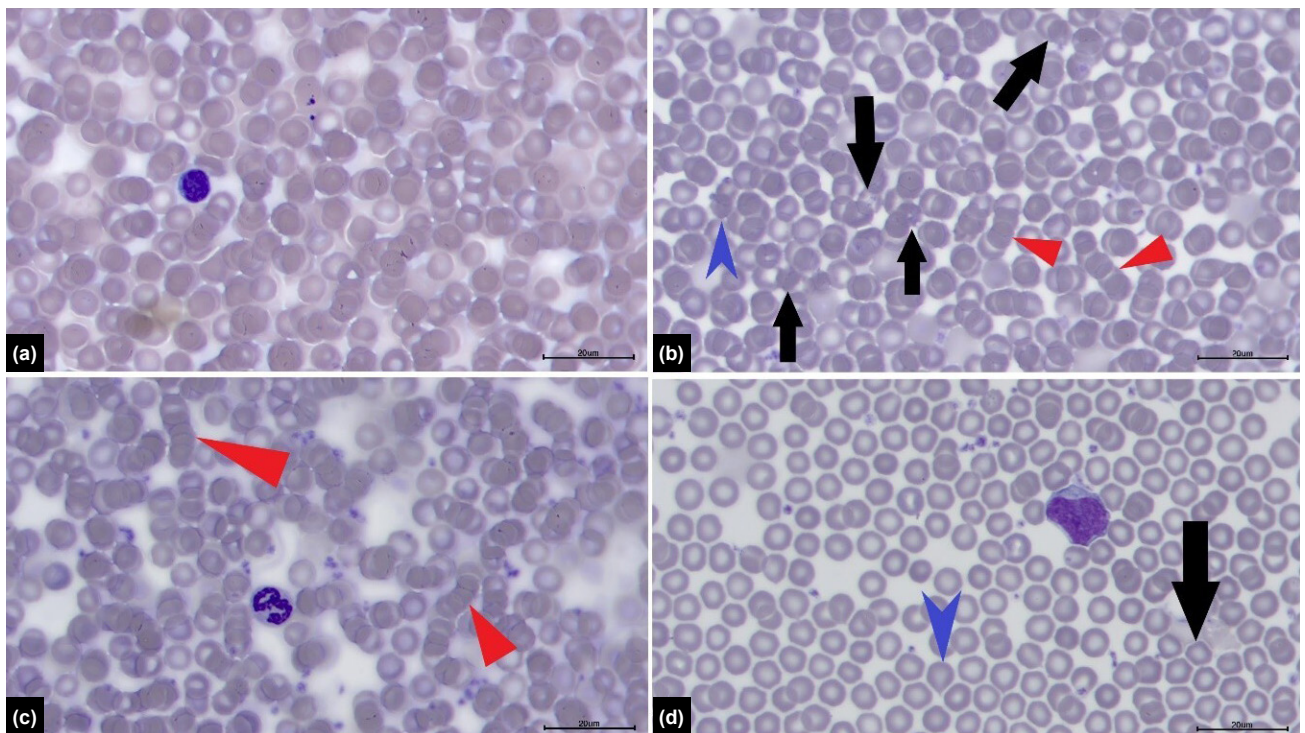


Figure 1. May-Grünwald-Giemsa (MGG)-stained photographs of the experimental groups Control, IR, HT-Sham, and HT-IR are shown in a, b, c, and d, respectively. Black arrows indicate echinocytes, blue arrowheads indicate dacrocytes, and red arrowheads indicate rouleaux formation (magnification $\times 1000$).

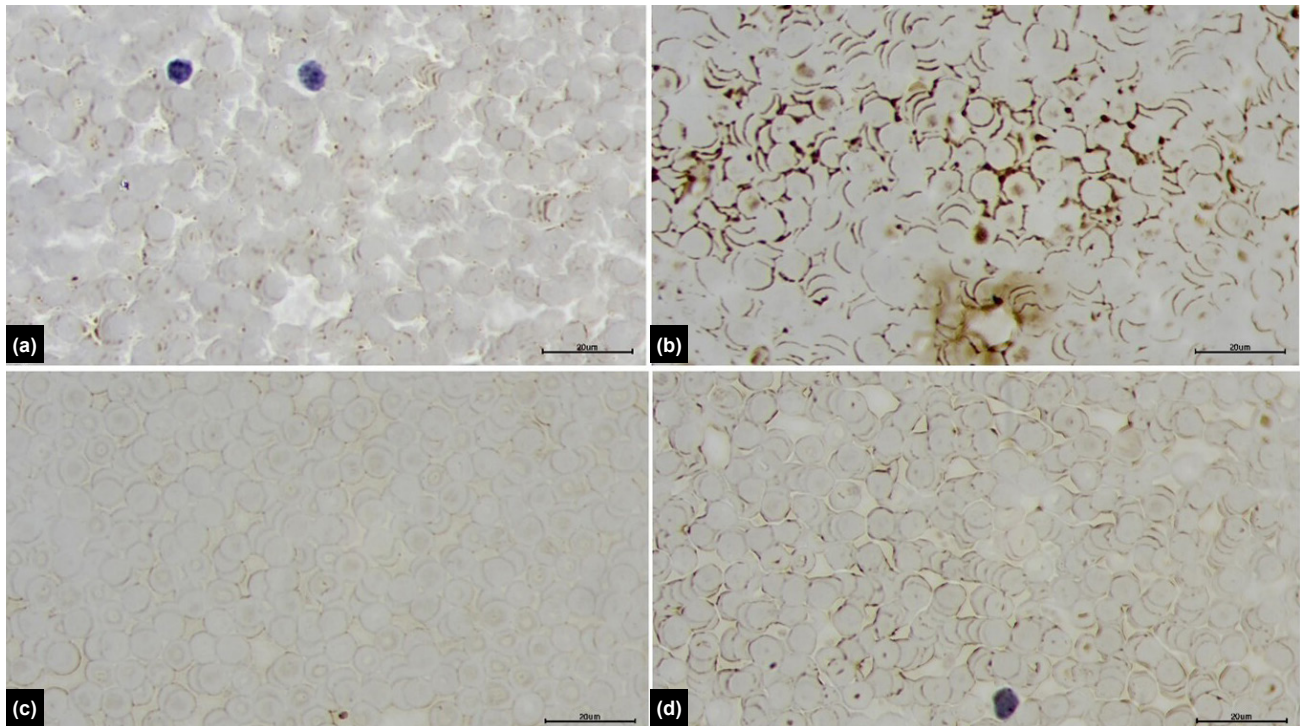


Figure 2. Immunohistochemically-stained photographs of the experimental groups Control, IR, HT Control, and HT-IR are shown in **a, b, c, and d**, respectively (magnification $\times 1000$).

Superoxide Dismutase (SOD) Activity

Superoxide dismutase activity, a key antioxidative enzyme, was significantly higher in the IR-HT group (12.45 ± 1.91) compared to the IR group (9.69 ± 1.36 , $p=0.01$). This increase underscores the protective antioxidative effect of HT during IR injury.

Histological and Immunohistochemical Observations

Morphological changes in erythrocytes, assessed by MGG staining, showed significantly increased pathological features, including more echinocytes, dacrocytes, and rouleaux formations, in the IR group (4.42 ± 0.52) compared to the Sham (2.11 ± 0.47) and HT-Sham (2.93 ± 0.33) groups (both $p<0.001$). HT treatment notably reduced these morphological changes in the IR-HT group (3.09 ± 0.41) compared to the IR group ($p<0.001$), highlighting its protective effects on erythrocyte structure (Fig. 1).

Immunohistochemical staining showed markedly increased eNOS immunoreactivity in the IR group, indicating vascular endothelial activation under ischemic stress. In contrast, the IR-HT group exhibited moderate immunoreactivity, which aligns with biochemical data indicating improved endothelial function due to hydroxytyrosol treatment (Fig. 2). The IR group had significantly higher eNOS levels (222.05 ± 23.34), suggesting increased endothelial activity in response to ischemic stress compared to all other groups ($p<0.001$). HT treatment significantly lowered eNOS levels in the IR-HT group (161.67 ± 18.36) compared to the IR group ($p<0.001$).

DISCUSSION

Ischemia-reperfusion injury is a complex pathological process characterized by cellular and vascular damage that occurs not only during ischemia but also paradoxically increases upon reperfusion. The initial ischemic event results in hypoxia-related metabolic disturbances, including a shift from aerobic to anaerobic glycolysis, leading to lactic acidosis, ATP depletion, and dysfunction of ATP-dependent ion pumps.^[1-3] This energy failure causes accumulation of intracellular calcium (Ca^{2+}), which activates proteolytic enzymes and contributes to mitochondrial dysfunction and opening of the mPTP, ultimately leading to cell death through necrosis or apoptosis.^[4,5] Paradoxically, reperfusion amplifies injury due to the sudden reintroduction of oxygen, significantly increasing ROS production via mitochondrial electron transport, xanthine oxidase, and NADPH oxidase pathways.^[2,3] This increase in ROS results in eNOS uncoupling, reducing NO bioavailability and impairing vascular relaxation and homeostasis.^[3,5] At the cellular level, oxidative stress during reperfusion causes extensive lipid peroxidation, which can be measured by increased MDA levels, a reliable marker of membrane oxidative damage.^[3-5] Concurrently, the activity of SOD, a crucial antioxidant enzyme, decreases markedly, impairing the body's ability to detoxify ROS and exacerbating oxidative injury.^[4] These redox imbalances significantly affect RBC physiology, particularly erythrocyte deformability, a key determinant of microcirculatory flow and oxygen delivery.^[6]

Erythrocyte deformability describes the ability of RBCs to

change shape as they pass through capillaries smaller than their normal diameter. This feature is mainly governed by membrane elasticity, cytoskeletal structure, internal viscosity, and cell shape, and is largely maintained by cytoskeletal proteins such as spectrin, ankyrin, and band 3.^[6-8] IR injury-induced oxidative stress damages both lipid membranes and cytoskeletal proteins, leading to cross-linking, fragmentation, and stiffening of RBCs, thereby impairing their ability to navigate microvascular beds.^[1,2,10] Elevated MDA levels are associated with reduced deformability and increased membrane rigidity.^[9] Simultaneously, ischemic ATP depletion disrupts ionic gradients, resulting in increased cytoplasmic viscosity and alterations in cell shape.^[7] Furthermore, intracellular Ca^{2+} overload activates calpain and other calcium-dependent enzymes, accelerating cytoskeletal breakdown and increasing cell stiffness.^[13] NO, produced by eNOS, plays a key role in maintaining erythrocyte deformability by promoting vasodilation, inhibiting platelet aggregation, and preserving cytoskeletal integrity.^[11] However, eNOS uncoupling during IR injury markedly reduces NO bioavailability, worsening vascular tone regulation and decreasing RBC flexibility. Restoring NO synthesis or availability has been shown to improve deformability and microcirculatory flow.^[9,12]

This study demonstrates that HT significantly improves erythrocyte deformability, reduces oxidative stress, and increases eNOS expression in a rat model of hind limb IR injury. These findings support a growing body of research indicating HT's protective role against oxidative damage through multiple mechanisms, including antioxidant, anti-apoptotic, anti-inflammatory, and gene-regulatory pathways.

Hydroxytyrosol's ability to significantly reduce MDA levels and enhance SOD activity observed in our study highlights its potent antioxidant capacity. These findings align with those of Manna et al.,^[19] who reported that HT protected erythrocytes against hydrogen peroxide-induced oxidative stress, thereby preserving membrane integrity. The antioxidant effects of HT stem not only from direct radical scavenging but also from activation of mitochondrial SOD, which is crucial for reducing intracellular superoxide buildup during reperfusion, as previously shown by Pei et al.^[22] in myocardial IR models. Additionally, HT's role in maintaining mitochondrial integrity and activating anti-apoptotic signaling pathways is well documented; Pei et al.^[22] demonstrated that HT significantly inhibited apoptosis in cardiomyocytes after IR injury by lowering cleaved caspase-3 expression and promoting phosphorylation of Akt and glycogen synthase kinase-3 beta (GSK3 β), thereby stabilizing mitochondrial membranes. Although mature erythrocytes lack mitochondria, these systemic protective mechanisms may extend beneficial effects to erythroid precursors and endothelial cells, ultimately supporting overall hemorheological stability. Importantly, HT also plays a key role in preventing eryptosis, the programmed cell death pathway specific to erythrocytes. Tortora et al.^[28] showed that HT counteracts lysophosphatidic acid-induced

eryptosis by restoring intracellular ATP and glutathione levels and maintaining calcium balance. These mechanistic insights closely match our morphological findings, in which HT administration reduced echinocyte and dacrocyte formation, indicating membrane stabilization and preservation of erythrocyte deformability under IR conditions.

Consistent with our results showing reduced impairment in erythrocyte deformability, decreased MDA levels, and increased SOD activity after HT treatment, Pan et al.^[21] also reported that HT administration significantly lowered oxidative stress markers (ROS and MDA) and increased the activity of antioxidative enzymes such as SOD and catalase through increased expression of SOD1, SOD2, and catalase in a mouse model of liver IR injury. Although our study does not involve direct hepatoprotective outcomes, the underlying antioxidative mechanisms identified by Pan et al.^[21] align closely with our observed improvements in erythrocyte oxidative status and deformability, suggesting a similar protective pathway mediated through upregulation of endogenous antioxidant defense. Additionally, the anti-inflammatory effects of HT demonstrated by Pan et al., through decreased levels of pro-inflammatory cytokines (TNF- α , IL-6, and macrophage inflammatory protein-2 [MIP-2]), may further explain our findings of improved endothelial function and reduced inflammatory responses following HT administration. Collectively, these mechanisms offer a plausible molecular basis for the beneficial effects of HT on protecting erythrocytes and the endothelium in our IR model.

At the cellular signaling level, HT activates key redox-sensitive pathways, including phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), nuclear factor erythroid 2-related factor 2/heme oxygenase-1 (Nrf2/HO-1), and sirtuin 1 (SIRT1), which are essential for maintaining vascular homeostasis.^[22,30,31] Zrelli et al.^[31] provided further mechanistic evidence supporting HT's protective effects by demonstrating its potent antioxidant properties in vascular endothelial cells. Their study revealed that HT significantly increased endothelial cell proliferation, promoted cytoprotection against H_2O_2 -induced oxidative damage, and enhanced wound repair through activation of the PI3K/Akt and extracellular signal-regulated kinase 1/2 (ERK1/2) signaling pathways. Importantly, HT treatment led to activation and nuclear translocation of nuclear factor-E2-related factor-2 (Nrf2), a crucial transcription factor that regulates antioxidant enzyme expression. Once activated, Nrf2 induced expression of heme oxygenase-1, thereby strengthening the cellular antioxidant defense system. These findings align well with our results, in which HT administration considerably reduced MDA levels and increased SOD activity, along with improvements in erythrocyte deformability and morphology, indicating an antioxidative mechanism. The enhanced HO-1 induction through Nrf2 activation, as highlighted by Zrelli et al.,^[31] may represent a central pathway through which HT provides protection against oxidative stress and inflammation observed in our IR model. Specifically, HT-induced Nrf2 translocation promotes upregulation

of HO-1, a cytoprotective enzyme responsible for degrading pro-oxidant heme, thereby reducing oxidative stress and inflammation. These effects are consistent with the notable improvements in erythrocyte deformability and morphological preservation observed in our findings, suggesting improved membrane integrity.

In another study, Zrelli et al.^[30] provided valuable mechanistic insights into the cytoprotective effects of HT, highlighting its role in vascular endothelial cells. They showed that HT increased HO-1 expression in a dose- and time-dependent manner through activation and nuclear accumulation of Nrf2. This effect required new synthesis and stabilization of Nrf2, mediated through the PI3K/Akt and ERK1/2 pathways. Additionally, their findings suggested that HO-1 induction was crucial for HT-mediated endothelial wound repair, largely dependent on HO-1-derived carbon monoxide production. Although our study does not directly examine endothelial wound repair, the mechanisms described by Zrelli et al.^[30] are consistent with the improved endothelial function and reduced oxidative stress observed in our IR model. Therefore, activation of the Nrf2/HO-1 pathway, stabilization of Nrf2, and the ensuing antioxidative and anti-inflammatory actions outlined by Zrelli et al.^[30] are likely key mechanisms underlying the protective effects of HT observed in our research.

Our findings show a significant decrease in eNOS expression in the IR-HT group compared to the untreated IR group. Elevated eNOS expression usually indicates compensatory endothelial activation in response to ischemic stress; however, persistently high eNOS levels in the IR group may also reflect pathological endothelial activation driven by severe oxidative stress and inflammation. The decrease in eNOS expression following HT administration suggests normalization of endothelial function and reduced vascular stress. This observation aligns with evidence from a review by Serreli et al.,^[23] who reported that HT enhances eNOS activity by promoting phosphorylation at Ser1177 through PI3K/Akt and AMP-activated protein kinase (AMPK) signaling pathways, thereby increasing NO bioavailability.^[22] Therefore, the balanced regulation of eNOS expression by HT observed in our study likely contributes to improved NO-mediated vascular responses, including increased erythrocyte flexibility via downstream cyclic guanosine monophosphate-dependent (GMP-dependent) mechanisms. Overall, these positive effects of HT may reduce vascular resistance and enhance microcirculatory outcomes during IR injury.

A significant body of research has demonstrated the vascular protective effects of HT, highlighting its ability to counteract endothelial dysfunction induced by inflammatory stimuli.^[25] Specifically, these studies showed that HT significantly reduces TNF- α -induced endothelial cell damage by decreasing apoptosis and promoting cell survival. These protective effects are mediated through suppression of caspase-3 activation and inhibition of the NF- κ B signaling pathway. Additionally, HT treatment increases eNOS phosphorylation and NO production, leading to inactivation of NF- κ B and enhanced

endothelial cell viability.

Moreover, Wang et al.^[26] reported that HT directly activates SIRT1, which subsequently enhances antioxidant pathways such as SIRT1-FOXO1-SOD1, reduces ROS production, and preserves endothelial health. HT-mediated activation of SIRT1—a NAD⁺-dependent deacetylase—may also explain the moderated eNOS expression observed in our study, as SIRT1 activation increases eNOS activity through deacetylation and simultaneously inhibiting NF- κ B-mediated inflammatory signaling.^[32,33] This interpretation is consistent with the balanced decrease in eNOS expression observed in the IR-HT group, indicating normalized endothelial function.

Clinically relevant, these cellular mechanisms likely also underlie the reduced erythrocyte rigidity and vascular resistance observed in our findings, highlighting HT's ability to inhibit platelet aggregation and thrombosis. López-Villodres et al. and Muñoz-Marin et al.^[35] reported that HT plays a role in suppressing platelet activation and thromboxane B2 production, mechanisms that are particularly beneficial under IR conditions, where platelet-endothelial interactions exacerbate microvascular occlusion.^[34] Moreover, HT's nutrigenomic and epigenetic modulation further supports the sustained vascular protection observed in our experimental findings. Carluccio et al.^[36] demonstrated HT's ability to modify endothelial transcriptomic profiles and regulate microRNA expression, thereby positively influencing inflammatory suppression and vascular repair. These molecular changes align with the preserved erythrocyte morphology and reduced oxidative stress observed in the IR-HT group. Finally, HT's potential to prevent endothelial-to-mesenchymal transition (EndMT), as shown by Terzuoli et al.,^[37] may further explain the improved endothelial function and reduced vascular stress indicated by our eNOS expression data, highlighting its regenerative therapeutic potential in IR injury.

Our findings regarding HT's protective effects align well with related research on structurally similar compounds such as p-tyrosol, which has demonstrated significant antioxidative and hemorheological benefits in IR models. Osipenko et al.^[38] showed that intravenous administration of p-tyrosol markedly reduced blood and plasma viscosity, enhanced erythrocyte deformability, and subsequently improved oxygen delivery to cerebral tissues following global cerebral IR injury in rats. They attributed these protective effects to substantial reductions in lipid peroxidation products, including diene and triene conjugates, as well as fluorescent lipid oxidation products, which effectively lowered the lipid oxidation index in brain tissues. Correspondingly, our results demonstrate that HT exhibits a similar capacity to mitigate lipid peroxidation, as indicated by significantly reduced MDA levels and improved erythrocyte deformability, highlighting comparable antioxidative mechanisms. This parallel suggests that both tyrosol derivatives may exert their beneficial effects through similar pathways by reducing oxidative stress, stabilizing erythrocyte membranes, and enhancing microvascular perfusion. Conse-

quently, the neuroprotective effects of p-tyrosol described by Osipenko et al.^[38] provide additional mechanistic insights that support and reinforce the vascular protective mechanisms identified in our study with HT, indicating broad potential for these phenolic compounds in IR injury management.

A limitation of this study is that it assessed a limited range of biochemical, hematological, and morphological parameters without directly exploring detailed molecular signaling pathways. Specifically, although antioxidant status, erythrocyte deformability, eNOS expression, and oxidative stress markers were measured, crucial signaling pathways such as Nrf2/HO-1, PI3K/Akt, SIRT1, and NF- κ B were not examined. Additionally, the study employed only a single dosage and route of HT administration, which limits conclusions regarding optimal dosing strategies or dose-dependent effects. Another limitation was the relatively short reperfusion period, which may not fully reflect long-term progression and delayed effects associated with IR injury. Furthermore, the study utilized a rat hind limb IR model, which, despite its experimental relevance, may not fully represent the complexity of clinical IR injury in humans. Therefore, caution is needed when applying these preliminary results to clinical settings. Future research incorporating broader molecular assessments, multiple dosages, longer observation periods, and translational clinical models is necessary to fully understand HT's therapeutic potential and practical applicability.

CONCLUSION

In conclusion, this study demonstrates that HT effectively reduces erythrocyte dysfunction in a rat model of hind limb IR injury by preserving erythrocyte deformability, lowering lipid peroxidation, enhancing antioxidant enzyme activity, and regulating eNOS expression. Given the limited research specifically addressing lower limb IR injury, these findings provide initial insights into HT's protective mechanisms and emphasize its therapeutic potential. Further research is necessary to verify these results and investigate the underlying molecular pathways in greater detail, ultimately supporting the potential clinical application of HT in the management of IR injury.

Ethics Committee Approval: The experimental protocol of this study received approval from the Local Ethics Committee of the Kobay Experimental Animals Laboratory in Ankara, Türkiye (Date: 24.11.2023, Decision No: 692).

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ORIJİNAL ÇALIŞMA - ÖZ

Şıçanlarda alt ekstremitte iskemi-reperfüzyon hasarı sırasında hidrokstitirozolün eritrosit deformabilitesi üzerindeki koruyucu etkilerinin araştırılması

AMAÇ: İskemi-reperfüzyon (İR) hasarı, eritrosit deformabilitesini anlamlı derecede azaltarak oksidatif stresin ve inflamasyonun artmasına, buna bağlı olarak da mikrovasküler perfüzyonun bozulmasına yol açan karmaşık bir patofizyolojik süreçtir. Bu çalışmada, zeytinden elde edilen güçlü bir fenolik antioksidan olan hidrokstitirozolün (HT), şıçan alt ekstremitte iskemi-reperfüzyon modeli üzerinde eritrosit deformabilitesi ve ilişkili oksidatif stres belirteçleri üzerindeki koruyucu etkilerinin incelenmesi amaçlanmıştır.

GEREÇ VE YÖNTEM: Toplam 24 şıçan rastgele dört gruba ayrılmıştır: Sham, HT-Sham, İR ve hidrokstitirozol ile tedavi edilen İR grubu (İR-HT). Hidrokstitirozol, iskemi indüksiyonundan önce 10 mg/kg dozunda intraperitoneal olarak uygulanmıştır. Reperfüzyon döneminin ardından malondialdehit (MDA), süperoksit dismutaz (SOD), endotelial nitrik oksit sentaz (e-NOS) düzeyleri ile eritrosit deformabilitesi ve morfolojisi gibi biyokimyasal parametreler değerlendirilmiştir.

BULGULAR: Hidrokstitirozol uygulaması, tedavi edilmeyen İR grubuna kıyasla İR-HT grubunda eritrosit deformabilitesini anlamlı düzeyde artırmış, MDA düzeylerini belirgin şekilde düşürmüş, SOD aktivitesini yükseltmiş ve e-NOS ekspresyonunu dengeleyici yönde düzenlemiştir ($p<0.001$). Morfolojik analiz sonuçları, eritrosit bütünlüğünün büyük ölçüde korunduğunu, ekinosit ve dakrosit gibi patolojik şekil değişikliklerinin belirgin şekilde azaldığını göstermiştir.

SONUÇ: Bu çalışma, hidrokstitirozolün iskemi-reperfüzyon sürecinde eritrosit disfonksiyonunu azaltma ve oksidatif hasarı sınırlama konusundaki koruyucu mekanizmalarına ilişkin öncü bulgular sunmaktadır. Bulgular, HT'nin terapötik bir ajan olarak potansiyelini vurgulamakta olup, daha geniş moleküler yollar ve uzun dönemli klinik sonuçları değerlendiren ileri düzey çalışmalara ihtiyaç olduğunu göstermektedir.

Anahtar sözcükler: Hidrokstitirozol, İskemi-Reperfüzyon Hasarı, Eritrosit Deformabilitesi, Oksidatif Stres, Şıçanlar

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A hybrid machine learning approach to improve the diagnostic accuracy of acute appendicitis

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ABSTRACT

BACKGROUND: Acute appendicitis is the most common diagnosis considered in patients presenting to the emergency department with right lower quadrant pain. However, atypical presentations often lead to unnecessary surgeries and increased healthcare costs. This study aimed to improve diagnostic accuracy in acute appendicitis using a hybrid machine learning (ML) model.

METHODS: A retrospective analysis was performed on 395 patients who underwent appendectomy for suspected acute appendicitis between 2020 and 2024 at Ankara University Faculty of Medicine, Department of General Surgery. Demographic, clinical, laboratory, and radiological variables were collected. ML algorithms, including NaiveBayes, MultilayerPerceptron, IBk, AdaBoost, RandomForest, and a hybrid model combining NaiveBayes, AdaBoost, and RandomForest, were applied. The dataset was evaluated using 10-fold cross-validation, repeated 1,000 times. Accuracy, F-measure, Matthews Correlation Coefficient (MCC), receiver operating characteristic (ROC) area, and precision-recall curve (PRC) area were used as performance criteria.

RESULTS: Among the 395 patients, 52.9% were male, with a mean age of 37.3 ± 15.6 years. Histopathological examination confirmed acute appendicitis in 341 (86.3%) patients and negative appendectomy in 54 (13.7%) patients. The diagnostic accuracy of the Alvarado score at a cut-off value of ≥ 6 was 79.0%. Among the ML algorithms, the hybrid model achieved the best performance, with 92.9% accuracy, 93% F-measure, 70.4% MCC, 90.8% ROC area, and 93.4% PRC area. This model correctly predicted 95.6% of acute appendicitis cases and 75.9% of negative appendectomy cases.

CONCLUSION: The hybrid ML model demonstrated superior diagnostic accuracy compared to the Alvarado score for acute appendicitis. Integration of such models into clinical practice could reduce negative appendectomy rates and enhance patient management by enabling faster and more reliable diagnosis.

Keywords: Acute appendicitis; hybrid model; diagnostic accuracy; negative appendectomy; machine learning.

INTRODUCTION

Acute appendicitis is the most common diagnosis considered in patients presenting to the emergency department with right iliac fossa pain. Studies show that approximately 7% of people will experience this condition at some point in their lives.^[1] Although proper diagnosis is usually straightforward

in patients presenting with classical symptoms such as migratory abdominal pain and nausea, atypical presentations often lead to unnecessary tests and delays in treatment. The challenge of making a proper and timely diagnosis remains a significant risk for patients, leading to unnecessary surgical operations, prolonged hospital stays, and increased medical costs.^[2] Globally, the rate of negative acute appendicitis was

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previously reported to be between 15% and 30%, but it has fallen below 10% in recent years due to the increased availability of laparoscopy and advanced radiological tools.^[3-5]

Early recognition and interpretation of symptoms and signs in the emergency department are essential for optimizing the benefits of diagnostic imaging, reducing hospital stay, and preventing unnecessary surgical interventions. In this regard, clinical scoring systems, imaging techniques such as ultrasonography and computed tomography, diagnostic laparoscopy, and computer-aided diagnostic systems have been developed. Some researchers use only laboratory parameters in predictive scoring models, while others combine laboratory results with clinical signs and symptoms.^[6-8] The most commonly used clinical scoring system, the Alvarado score, is sensitive enough to rule out appendicitis but lacks specificity, leading to a significant rate of false-positive cases.^[8,9] The limitations of the Alvarado score and similar models include limited sensitivity in complex cases and a lack of universal applicability across different patient populations. In addition, there may be a lack of correlation between different diagnostic methods and clinical observations. Therefore, the need for a reliable, quick, and user-friendly scoring system to aid in the preoperative diagnosis of appendicitis still remains.

Artificial neural networks (ANN) and machine learning (ML) models have often outperformed the Alvarado scoring system in predicting acute appendicitis.^[10,11] Unlike appendicitis scoring systems based on summing scores for important clinical parameters, ML algorithms can process the complex, nonlinear correlations and interactions between factors. Apart from traditional statistical techniques, ML is a subfield of artificial intelligence aimed at making predictions about new observations by learning from existing data. However, a significant limitation of many ML models is the lack of transparency, interpretability, and explainability. To overcome these shortcomings, hybrid models have recently gained increased attention in clinical research. Our hypothesis is that an ML model can detect acute appendicitis in individuals with right iliac fossa pain with higher accuracy than the Alvarado scoring system.

MATERIALS AND METHODS

Patient Selection

In this study, patients who underwent appendectomy for suspected acute appendicitis at the Department of General Surgery, Ankara University Faculty of Medicine, between 2020 and 2024 were retrospectively evaluated. Ethical approval for the study was obtained from the Ankara University Human Research Ethical Committee (Approval No: İ03-225-25). All methods were conducted in accordance with relevant guidelines and regulations, including institutional ethical standards and the Declaration of Helsinki. As this was a retrospective study based on the analysis of patient data from institutional databases, the requirement for informed consent was waived.

Patients aged > 18 years with suspected acute appendicitis who

underwent emergency surgery were included in the study. Patients under 18 years of age, pregnant patients, those who underwent incidental appendectomy, and those whose histopathological results revealed neuroendocrine tumors or appendiceal mucinous neoplasms were excluded from the study.

Data Collection

Demographic characteristics (age and sex), symptom duration, presence of migratory pain to the right iliac fossa, anorexia, nausea/vomiting, tenderness in the right iliac fossa, rebound pain, elevated temperature (fever), leukocytosis, left shift (>75% neutrophils), Alvarado scores, laboratory parameters (total bilirubin, C-reactive protein [CRP], white blood cell [WBC] count, hemoglobin [Hb], lymphocyte count, platelet [PLT] count, red blood cell distribution width [RDW], neutrophil count, neutrophil percentage, platelet-to-neutrophil ratio [PNR], neutrophil-to-lymphocyte ratio [NLR], white cell nucleated region [WNR]), radiological findings including appendiceal diameter and periappendiceal fat stranding, and histopathological results were retrospectively evaluated. The Alvarado score was calculated based on eight parameters, with a total score ranging from 1 to 10 [7]. Radiological and pathological evaluations in this study were conducted independently by multiple specialists rather than a single observer, in accordance with the methodological design of the study.

Study Design

A total of 395 patients were included, of whom 150 (38%) underwent open appendectomy and 245 (62%) underwent laparoscopic appendectomy (three-port technique). Patients were divided into two groups (negative appendectomy and acute appendicitis) based on histological results. Negative appendectomy was defined as the absence of inflammatory cell infiltration. The aim of this study was to develop ML models to predict negative appendectomy and acute appendicitis (based on histological results) and to evaluate the performance of these models.

Statistical Analysis

SPSS Statistics for Windows, version 11.5 (IBM Corp., Armonk, NY, USA) was used for data analysis. Mean $\pm$ standard deviation (SD) for continuous variables and frequency (percentage) for categorical variables were used for descriptive statistical analysis. The Mann-Whitney U test was used to evaluate differences between continuous variables with two categories when normal distribution assumptions were not met. The chi-square test was used to examine relationships between two categorical variables. The receiver operating characteristic (ROC) curve was used to determine the cut-off value for the Alvarado score. Statistical significance was set at 0.05.

All ML analyses were conducted using the R programming language with the RWEka and e1071 packages. Variable importance was assessed using the InfoGain and GainRatioAttributeEval tests. ML classification methods, including NaiveBayes, MultilayerPerceptron, k-nearest neighbors (IBk), AdaBoost, RandomForest (RF), and a hybrid model (Na-

Table 1. Demographic characteristics of the study population (n=395)

Sex, n (%)	
Male	209 (52.9)
Female	186 (47.1)
Age, years	
Mean±SD	37.27±15.65
Symptom duration, n (%)	
<24 hours	183 (46.3)
24-48 hours	128 (32.4)
≥48 hours	84 (21.3)
Migration of pain to the right lower quadrant, n (%)	
Present	312 (79.0)
Absent	83 (21.0)
Anorexia, n (%)	
Present	234 (59.2)
Absent	161 (40.8)
Nausea/vomiting, n (%)	
Present	214 (54.2)
Absent	181 (45.8)
Right lower quadrant tenderness, n (%)	
Present	382 (96.7)
Absent	13 (3.3)
Rebound, n (%)	
Present	261 (66.1)
Absent	134 (33.9)
Fever (≥37.3°C), n (%)	
Present	22 (5.6)
Absent	373 (94.4)
Left shift (>75% neutrophils), n (%)	
Present	333 (84.3)
Absent	62 (15.7)
Alvarado score	
Mean±SD	6.87±1.75
Total bilirubin, mg/dL	
Mean±SD	0.83±1.06
CRP, mg/dL	
Mean±SD	57.06±74.43
WBC, 103/μl	
Mean±SD	13.70±4.79
Hb, g/dL	
Mean±SD	13.89±2.00
Lymphocyte count, 103/μl	
Mean±SD	1.91±0.88
PLT count, 103/μl	
Mean±SD	260.05±71.47

RDW	
Mean±SD	13.29±1.67
Neutrophil count, 103/μl	
Mean±SD	10.67±4.55
Neutrophil, %	
Mean±SD	76.96±18.41
PNR	
Mean±SD	30.06±19.06
NLR	
Mean±SD	7.32±5.88
WNR	
Mean±SD	1.37±0.40
Appendiceal diameter, mm	
Mean±SD	10.02±2.93
Periappendiceal fat stranding, n (%)	
Present	362 (91.6)
Absent	33 (8.4)
Histopathological diagnosis, n (%)	
Negative appendectomy	54 (13.7)
Acute appendicitis	341 (86.3)

CRP: C-reactive protein; WBC: White blood cell count; PLT: Platelet count; RDW: Red blood cell distribution width; PNR: Platelet-to-neutrophil ratio; NLR: Neutrophil-to-lymphocyte ratio; WNR: White cell nucleated ratio.

iveBayes + AdaBoost + RandomForest), were applied. The dataset was evaluated using 10-fold cross-validation, and all analyses were repeated 1,000 times. Performance metrics included accuracy, F-measure, Matthews correlation coefficient (MCC), ROC area, and precision-recall curve (PRC) area.

RESULTS

Of the 395 patients included in the study, 52.9% were male, with an average age of 37.27±15.65 years (range: 18–79). The duration of symptoms was less than 24 hours in 183 (46.3%) patients, between 24 and 48 hours in 128 (32.4%), and more than 48 hours in 84 (21.3%) patients. Migration of pain to the right lower quadrant was present in 79.0% of patients, anorexia in 59.2%, nausea/vomiting in 54.2%, tenderness in the right lower quadrant in 96.7%, rebound pain in 66.1%, fever in 5.6%, and left shift in 84.3%.

The mean Alvarado score was 6.87±1.75. The mean values for total bilirubin, CRP, WBC, Hb, lymphocyte count, PLT count, RDW, and neutrophil count were 0.83±1.06, 57.06±74.43, 13.70±4.79, 13.89±2.00, 1.91±0.88, 260.05±71.47, 13.29±1.67, and 10.67±4.55, respectively. The mean appendiceal diameter detected radiologically was 10.02±2.93 mm, and periappendiceal fat stranding was observed in 362 (91.6%) patients. Histopathological examination revealed inflammatory changes consistent with acute appendicitis in 341 (86.3%) patients, while 54 (13.7%) had normal appendi-

Table 2. Demographic, clinical, laboratory, and radiological characteristics of the study groups

	Negative Appendectomy (n=54,13.7%)	Acute Appendicitis (n=341,86.3%)	p value
Sex, n (%)			
Male	23 (11.0)	186 (89.0)	0.102 ^a
Female	31 (16.7)	155 (83.3)	
Age, years			
Mean±SD	35.00±14.59	37.63±15.80	0.247 ^c
Symptoms duration, n (%)			
<24 hours	20 (10.9)	163 (89.1)	0.278 ^a
24-48 hours	19 (14.8)	109 (85.2)	
>48 hours	15 (17.9)	69 (82.1)	
Migration of pain to the right lower quadrant, n (%)			
Present	38 (12.2)	274 (87.8)	0.094 ^a
Absent	16 (19.3)	67 (80.7)	
Anorexia, n (%)			
Present	27 (11.5)	207 (88.5)	0.137 ^a
Absent	27 (16.8)	134 (83.2)	
Nausea/vomiting, n (%)			
Present	24 (11.2)	190 (88.8)	0.122 ^a
Absent	30 (16.6)	151 (83.4)	
Right lower quadrant tenderness, n (%)			
Present	50 (13.1)	332 (86.9)	0.087 ^b
Absent	4 (30.8)	9 (69.2)	
Rebound, n (%)			
Present	28 (10.7)	233 (89.3)	0.017 ^a
Absent	26 (29.4)	108 (80.6)	
Fever (≥37.3°C), n (%)			
Present	2 (9.1)	20 (90.9)	0.520 ^a
Absent	52 (13.9)	321 (86.1)	
Left shift (>75% neutrophils), n (%)			
Present	32 (9.6)	301 (90.4)	<0.001 ^a
Absent	22 (35.5)	40 (64.5)	
Alvarado score			
Mean±SD	5.46±1.80	7.09±1.64	<0.001 ^c
Total bilirubin, mg/dL			
Mean±SD	0.57±0.51	0.87±1.12	<0.001 ^c
CRP, mg/dL			
Mean±SD	25.34±36.85	62.09±77.60	<0.001 ^c
WBC, 10 ³ /μl			
Mean±SD	10.33±4.33	14.23±4.65	<0.001 ^c
Hb, g/dL			
Mean±SD	13.46±2.16	13.96±1.97	0.124 ^c
Lymphocyte count, 10 ³ /μl			
Mean±SD	2.02±0.79	1.89±0.89	0.149 ^c

PLT, 10 ³ /µl			
Mean±SD	267.39±84.90	258.88±69.18	0.617 ^c
RDW			
Mean±SD	13.15±1.04	13.31±1.75	0.656 ^c
Neutrophil count, 10 ³ /µl			
Mean±SD	7.34±4.27	11.18±4.37	<0.001 ^c
Neutrophil, %			
Mean±SD	69.07±17.25	78.18±18.30	<0.001 ^c
PNR			
Mean±SD	45.12±21.93	27.72±17.48	<0.001 ^c
NLR			
Mean±SD	5.02±6.37	7.67±5.73	<0.001 ^c
WNR			
Mean±SD	1.54±0.40	1.35±0.40	<0.001 ^c
Appendiceal diameter, mm			
Mean±SD	8.43±2.53	10.27±2.91	<0.001 ^c
Periappendiceal fat stranding, n (%)			
Present	40 (11.0)	322 (89.0)	<0.001 ^b
Absent	14 (42.4)	19 (57.6)	

CRP: C-reactive protein; WBC: White blood cell count; PLT: Platelet count; RDW: Red blood cell distribution width; PNR: Platelet-to-neutrophil ratio; NLR: Neutrophil-to-lymphocyte ratio; WNR: White cell nucleated ratio; SD: Standard derivation. ^aChi-square test; ^bFishers's exact test; ^cMann-Whitney U test.

ceal tissue and were classified as the negative appendectomy group. The demographic characteristics of the study population are presented in Table 1.

Table 2 presents a comparison of demographic, clinical, laboratory, and radiological characteristics between the groups. No significant differences were observed between the groups in terms of age, sex, symptom duration, right-sided localized pain, anorexia, nausea/vomiting, tenderness in the right lower quadrant, and fever. Rebound was present in 10.7% of patients in the negative appendectomy group and 89.3% of those in the acute appendicitis group ($p=0.017$). A left shift was present in 9.6% of patients in the negative appendectomy group and 90.4% of those in the acute appendicitis group ($p<0.001$). The mean Alvarado score was significantly higher in the acute appendicitis group than in the negative appendectomy group (7.09 ± 1.64 vs. 5.46 ± 1.80 , respectively; $p<0.001$). Mean levels of total bilirubin, CRP, WBC, neutrophil count, neutrophil %, and NLR were significantly higher in the acute appendicitis group ($p<0.001$ for all). No significant differences were observed between the groups in laboratory parameters such as Hb, lymphocyte count, PLT count, and RDW. The mean appendiceal diameter was significantly larger in the acute appendicitis group compared to the negative appendectomy group (10.27 ± 2.91 vs. 8.43 ± 2.53 , respectively; $p<0.001$). The rate of periappendiceal fat stranding was 11% in the negative appendectomy group and 89% in the acute appendicitis group ($p<0.001$). The mean PNR and WNR values were significantly higher in the negative appendectomy group ($p<0.001$ for both).

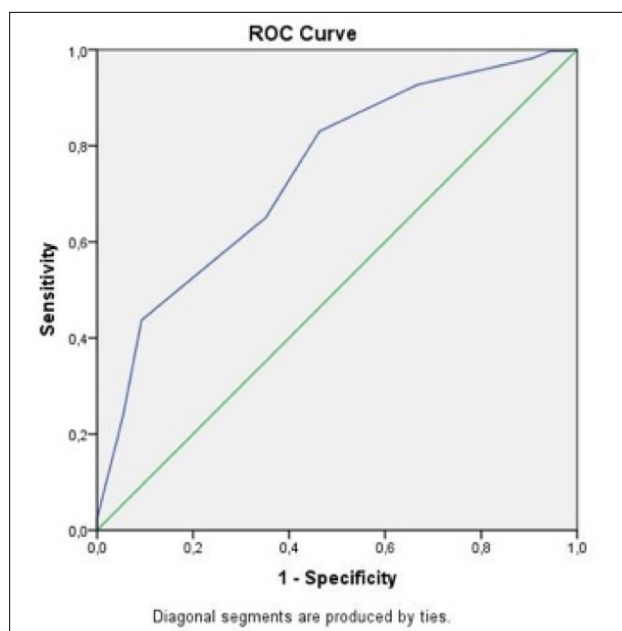


Figure 1. Receiver operating characteristic (ROC) curve of the Alvarado score for histopathological results.

In the ROC analysis of the Alvarado score for histopathological results, the area under the curve was 0.744, and the cut-off value for the Alvarado score was 6. The sensitivity and specificity values for this threshold were 0.830 and 0.537, respectively. The ROC curve is shown in Figure 1. For an Alvarado score ≥ 6 , the accuracy was 78.99%, with true-positive

and true-negative results of 283 (91.9%) and 29 (33.3%) respectively.

In the selection of variables for the ML model, the importance of variables and their effect on the outcome variable were evaluated using the InfoGain and GainRatioAttributeEval tests (Fig. 2). When variable importance and clinical relevance were evaluated in combination, the model consisted of the variables neutrophil count, WBC, NLR, PNR, appendiceal diameter, neutrophil percentage, WNR, total bilirubin, and CRP. As a result, 10 variables (nine independent variables and one dependent [pathology]) were included in the overall model, and ML analyses were performed using these variables.

NaiveBayes, MultilayerPerceptron, IBk, AdaBoost, and RandomForest methods were used to evaluate prediction performance. When the results of these methods were assessed, the accuracy for predicting acute appendicitis was high, whereas the accuracy for predicting negative appendectomy was low. To improve overall accuracy, a hybrid model approach (which has recently been introduced in the literature and involves

the combination of multiple methods) was applied, consisting of NaiveBayes, AdaBoost, and RandomForest (Table 3).

Among the ML models, the best performance was achieved using the hybrid model. When the performance criteria of the hybrid model were examined, the F-measure was 93%, the MCC was 70.4%, the ROC area was 90.8%, and the PRC area was 93.4%. Based on the hybrid model created, the overall accuracy was 92.9%. Additionally, this model correctly predicted 95.6% of patients diagnosed with acute appendicitis and 75.9% of patients with negative appendectomy (Table 3).

DISCUSSION

Our study aimed to evaluate the applicability of ML models for the diagnosis of acute appendicitis. In this study, the hybrid model consisting of NaiveBayes, AdaBoost, and RandomForest methods was found to predict acute appendicitis with high accuracy. This finding is consistent with previous studies in the literature, supporting the superior performance of hybrid models.^[12,13]

Table 3. Machine learning performance metrics for pathology prediction

	Accuracy	F-Measure	MCC	ROC Area	PRC Area
NaiveBayes					
Negative appendectomy	0.630	0.430	0.331	0.749	0.376
Acute appendicitis	0.795	0.858			0.926
Overall	0.772	0.799			0.851
MultilayerPerceptron					
Negative appendectomy	0.296	0.372	0.314	0.723	0.402
Acute appendicitis	0.953	0.923			0.929
Overall	0.863	0.848			0.857
IBk					
Negative appendectomy	0.352	0.342	0.235	0.650	0.227
Acute appendicitis	0.889	0.892			0.902
Overall	0.815	0.817			0.810
AdaBoost					
Negative appendectomy	0.278	0.375	0.340	0.779	0.450
Acute appendicitis	0.968	0.930			0.947
Overall	0.873	0.854			0.879
RandomForest					
Negative appendectomy	0.278	0.375	0.340	0.779	0.450
Acute appendicitis	0.968	0.930			0.947
Overall	0.873	0.854			0.879
Hybrid Model					
Negative appendectomy	0.759	0.745	0.704	0.908	0.763
Acute appendicitis	0.956	0.959			0.961
Overall	0.929	0.930			0.934

MCC: Matthews correlation coefficient; PRC: Precision-recall curve.

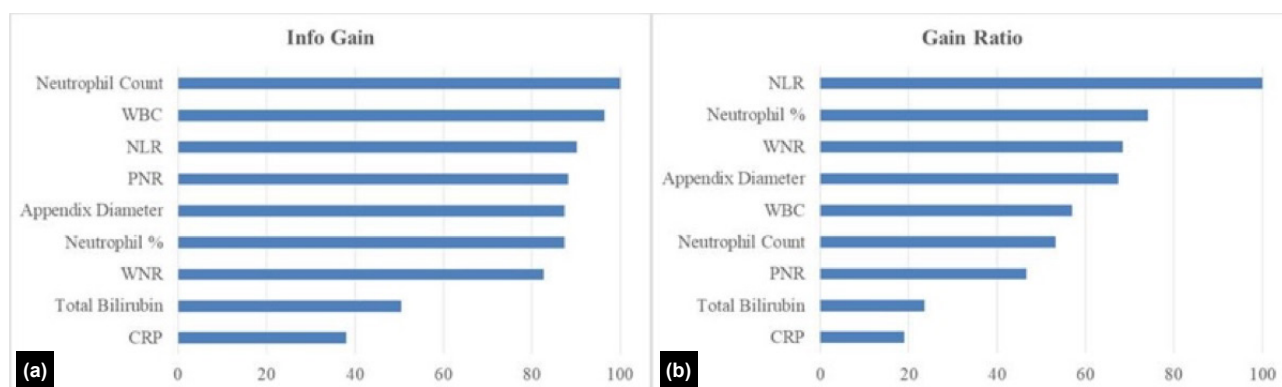


Figure 2. Feature importance results for the pathology groups. (a) InfoGainAttributeEval; (b) GainRatioAttributeEval.

Due to the lack of consistent international guidelines, the diagnosis and treatment of appendicitis are primarily based on clinical findings, standard laboratory tests, and radiological imaging modalities. The persistence of negative appendectomy rates indicates that the clinical diagnosis of acute appendicitis remains a significant challenge. The use of laparoscopy has been shown to reduce negative appendectomy rates.^[14,15] This reduction may be achieved by leaving the appendix in situ in cases where pathologies mimicking appendicitis are identified or when a macroscopically normal-appearing appendix is observed. With the increasing use of laparoscopy, the laparoscopic appendicitis score has been employed to help surgeons standardize macroscopic evaluation and has been reported to be effective in reducing the rate of negative appendectomy without missing acute appendicitis.^[4] To address these diagnostic challenges, various scoring systems have been developed to support accurate diagnosis of acute appendicitis. Nevertheless, considerable variability has been reported across studies in terms of diagnostic sensitivity and accuracy.^[16-18]

The Alvarado score is considered an effective tool in the diagnosis of acute appendicitis.^[7,8] However, it is influenced by physical examination findings, which depend on the experience of the attending physician, and its sensitivity is lower in women. False-positive and false-negative results may lead to unnecessary medical procedures and wasted resources. In this context, integrating laboratory parameters, as well as clinical and radiological findings, into ML models has improved diagnostic accuracy. A systematic review by Issaiy et al.^[10] reported that ANN and ML models demonstrate high performance in diagnosing acute appendicitis. Males et al.^[19] showed that their ML model spared 17% of pediatric patients from unnecessary surgery while missing required surgery in only 0.3% of cases. Similarly, Akbulut et al.^[20] used CatBoost with SHAP to accurately distinguish between perforated and non-perforated appendicitis in a large adult population. In another study, Navaei et al.^[21] achieved 94.5% accuracy using a Random Forest model that integrated clinical, laboratory, and imaging variables in pediatric cohorts. These findings are consistent with our results and highlight the benefit of combining

diverse clinical features with interpretable machine learning frameworks. Incorporating tools such as SHAP or LIME could further enhance model transparency and facilitate physician acceptance, which remains a critical barrier to the clinical adoption of AI-supported decision-making tools.

Studies using ML models provide an essential foundation for future research. However, the performance and generalizability of these models depend on the quality and diversity of the datasets used. Therefore, future studies should aim to include larger and more heterogeneous patient populations, explore different ML algorithms, and integrate additional variables, such as time-series changes or serial laboratory trends, to further enhance model performance. Variable selection in ML models significantly affects model success. For example, in a study by Schipper et al.,^[22] an ML model based on vital signs, physical examination, and patient history achieved an area under the ROC curve (AUROC) of 0.919, which increased to 0.923 when laboratory data were included. In this study, we found that parameters such as neutrophil count, WBC, NLR, PNR, appendiceal diameter, neutrophil percentage, WNR, total bilirubin, and CRP played a crucial role in the model's performance (Fig. 2).

The performance of various ML models, including NaiveBayes, MultilayerPerceptron, IBk, AdaBoost, and RandomForest, was evaluated. Most ML models demonstrated high accuracy, particularly in the diagnosis of acute appendicitis, except for the NaiveBayes model. The fact that the prediction results for patients diagnosed with negative appendectomy were lower than expected indicates that current models need improvement. The hybrid model leverages the strengths of different ML algorithms, resulting in more balanced and accurate results. Based on accuracy, F-measure, and MCC values, the best-performing ML model was the hybrid model consisting of NaiveBayes, AdaBoost, and RandomForest. In our study, the hybrid model achieved a pathology prediction accuracy of 92.9%. These findings highlight the potential of ML algorithms in medical diagnostics. Such models can facilitate accurate and rapid diagnoses, thereby reducing negative appendectomy rates and improving patient outcomes.

ML models have been shown to provide higher accuracy and reliability than traditional methods in the diagnosis of acute appendicitis. Hsieh et al. demonstrated that ML and artificial intelligence (ANN) achieved higher accuracy than the Alvarado score (accuracy of RF, ANN, and Alvarado score was 96%, 91%, and 80%, respectively).^[23] In a study using a decision tree model, Kang et al.^[24] showed that the ML model had a higher diagnostic value than the Alvarado score (area under the curve [AUC]: 0.850 vs. 0.695). This finding demonstrates that the Alvarado score is a clinically useful tool in the diagnosis of acute appendicitis. ROC analysis of the Alvarado score revealed an AUC of 0.744 and a cutoff value of 6. At this cut-off, sensitivity, specificity, and accuracy were 83%, 53.7%, and 78.99%, respectively. As the specificity was not satisfactory, it is evident that the Alvarado scoring system has shortcomings and requires additional diagnostic methods to improve its accuracy. ML models offer a novel approach that can compensate for the shortcomings of existing scoring systems. In our study, ML methods such as NaiveBayes, MultilayerPerceptron, IBk, AdaBoost, and RandomForest were used. Accuracy above 80% was achieved with the MultilayerPerceptron, IBk, AdaBoost, and RandomForest models. However, it was observed that these models could not predict patients diagnosed with negative appendectomy with high accuracy. The NaiveBayes model achieved more accurate predictions for patients with negative appendectomy compared to the other models. The highest diagnostic accuracy for both acute appendicitis and negative appendectomy was achieved with the hybrid model. Notably, 75.9% of patients with negative appendectomy were correctly predicted using the hybrid model consisting of NaiveBayes, AdaBoost, and RandomForest. In this study, the hybrid model achieved a high accuracy of 92.9%. Our results show that a hybrid ML model can be used to reduce negative appendectomy rates.

Nevertheless, this study has several limitations. The relatively small sample size of 395 patients may limit the representativeness of the findings, and the retrospective design may introduce bias due to incomplete or inconsistent clinical documentation. In addition, the single-center nature of the study restricts generalizability. It should also be noted that radiological and pathological assessments were not performed by a single reviewer. Instead, multiple specialists independently conducted the evaluations, reflecting routine multidisciplinary clinical practice. Although this approach may introduce some interobserver variability, it enhances the generalizability of the findings by more closely mirroring real-world conditions. Future studies employing standardized and blinded assessments by designated reviewers may further reduce variability and improve diagnostic consistency. In our study, we focused on comparing the hybrid learning model specifically with the Alvarado score as a widely used reference. In future research, comparing machine learning models with existing diagnostic scoring systems for acute appendicitis may further improve diagnostic accuracy and support clinical decision-making processes.

CONCLUSION

This study evaluated the effectiveness of ML models for diagnosing acute appendicitis. Our findings demonstrate that the ML model developed using the hybrid approach provides higher diagnostic accuracy for acute appendicitis. The accuracy (92.9%) of the hybrid model was higher than that of the traditional Alvarado scoring system (78.99%). These results indicate that the hybrid model significantly contributes to reducing negative appendectomy rates. Integrating ML models into clinical practice has the potential to improve patient management by enabling faster and more accurate diagnoses, particularly in time-sensitive conditions such as acute appendicitis.

Ethics Committee Approval: This study was approved by the Ankara University Human Research Ethics Committee (Date: 18.03.2025, Decision No: İ03-225-25).

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ORİJİNAL ÇALIŞMA - ÖZ

Akut apandisit tanısında tanısal doğruluğu artırmaya yönelik hibrit makine öğrenmesi yaklaşımı

AMAÇ: Akut apandisit, acil serviste sağ alt kadranda ağrısı ile başvuran hastalarda en sık değerlendirilen tanıdır. Ancak atipik bulgular tanısal güçlükler yaratmakta, gereksiz operasyonlara ve maliyet artışına yol açabilmektedir. Bu çalışmanın amacı, hibrit makine öğrenmesi (ML) modeli kullanılarak akut apandisit tanısında doğruluğun artırılmasıdır.

GEREÇ VE YÖNTEM: 2020-2024 yılları arasında Ankara Üniversitesi Tıp Fakültesi Genel Cerrahi Anabilim Dalı'nda akut apandisit ön tanısı ile opere edilen 395 hasta retrospektif olarak incelendi. Demografik, klinik, laboratuvar ve radyolojik veriler değerlendirildi. NaiveBayes, MultilayerPerceptron, lBk, AdaBoost, RandomForest ve bu modellerin kombinasyonundan oluşturulan Hibrit Model uygulandı. Veriler 10-kat çapraz doğrulama ile analiz edildi. Doğruluk, F-measure, Matthews Korelasyon Katsayısı (MCC), ROC ve PRC alanı performans kriteri olarak kullanıldı.

BULGULAR: Çalışmaya dahil edilen hastaların %52.9'u erkek olup ortalama yaş 37.3 ± 15.6 yıl idi. Histopatolojik incelemede 341 (%86.3) olgu akut apandisit, 54 (%13.7) olgu negatif apandektomi olarak raporlandı. Alvarado skoru ≥ 6 için tanısal doğruluk %79.0 bulundu. ML algoritmaları içinde en iyi sonuç Hibrit Model ile elde edildi. Bu model %92.9 doğruluk oranı, %93 F-measure, %70.4 MCC, %90.8 ROC ve %93.4 PRC alanı sağladı. Ayrıca, akut apandisitli olguların %95.6'sı ve negatif apandektomi grubunun %75.9'u doğru tahmin edildi.

SONUÇ: Hibrit ML modeli, akut apandisit tanısında Alvarado skoruna kıyasla daha yüksek doğruluk sunmaktadır. Bu yaklaşımın klinik kullanıma entegrasyonu, negatif apandektomi oranlarını azaltarak hasta yönetimini iyileştirebilir.

Anahtar sözcükler: Akut apandisit; hibrit model; makine öğrenimi; negatif apandektomi; tanısal doğruluk.

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Prognostic role of systemic inflammatory indices in predicting the severity of acute calculous cholecystitis

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ABSTRACT

BACKGROUND: Acute calculous cholecystitis (ACC) is one of the most common conditions encountered in emergency medicine and surgical practice. Delayed recognition of severe cases can lead to complications such as empyema, gangrene, or perforation, resulting in high morbidity and mortality. While the Tokyo Guidelines provide standardized diagnostic and severity grading criteria, the availability and reliability of imaging may be limited in certain settings. Therefore, there is growing interest in simple and cost-effective biomarkers. This study aimed to evaluate the diagnostic and prognostic value of complete blood count-derived (CBC-derived) systemic inflammatory indices, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte $\times$ platelet ratio (NLPR), systemic immune-inflammation index (SII), and multiple inflammatory index (MII), in predicting disease severity in patients with ACC.

METHODS: A total of 160 patients diagnosed with ACC in the emergency department between January 2020 and May 2024 were retrospectively analyzed. Patients with acalculous cholecystitis, cholangitis, choledocholithiasis, incomplete data, or age younger than 18 years were excluded. Demographic, clinical, and laboratory findings were reviewed. Receiver operating characteristic (ROC) curve analysis was used to determine optimal cut-off values.

RESULTS: The strongest predictive performance was observed for MII (cut-off=250.011; sensitivity 76.9%; specificity 78.9%; area under the curve [AUC]=0.770). NLR (cut-off=8.45) showed 76.9% sensitivity and 68.0% specificity (AUC=0.755). NLPR (cut-off=0.027) had 76.9% sensitivity and 54.4% specificity, while SII (cut-off=2414) achieved 69.2% sensitivity and 72.1% specificity (all $p<0.05$). All indices were significant predictors of severe ACC.

CONCLUSION: CBC-derived systemic inflammatory indices, particularly MII and NLR, are effective, accessible, and inexpensive markers for predicting the severity of ACC. These parameters may complement clinical assessment and assist in decision-making, especially in situations where imaging is unavailable or inconclusive.

Keywords: Severe acute cholecystitis; gallstones; systemic immune-inflammation index; emergency medicine.

INTRODUCTION

Acute calculous cholecystitis (ACC) is among the most common causes of acute abdominal pain and a major indication for urgent surgical intervention worldwide.^[1] Despite advances in imaging, delayed diagnosis or misjudgment of disease severity can result in complications such as empyema, gangrene, or perforation, which substantially increase morbidity and mortality.^[2]

The Tokyo Guidelines (TG13/18) provide standardized diagnostic and severity grading criteria by integrating clinical, laboratory, and imaging findings.^[3,4] They recommend early cholecystectomy for Grade I and II cases, whereas Grade III cases with organ dysfunction require urgent drainage followed by delayed surgery.^[5] However, reliance on imaging reduces applicability in resource-limited settings, and up to 28% of patients—particularly older adults—may present without classical signs such as fever or leukocytosis.^[6]

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Recently, systemic inflammatory indices such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte-platelet ratio (NLPR), and systemic immune-inflammation index (SII) have been proposed as cost-effective and widely available biomarkers for disease severity in ACC.^[7-9] Derived from routine complete blood counts, these indices reflect the balance between immune activation and systemic inflammation, and their prognostic value has also been emphasized in emergency medicine more broadly.^[10] Nevertheless, their clinical utility and optimal cut-off values remain uncertain, particularly in patients with ACC.^[9]

This study aimed to evaluate the prognostic performance of systemic inflammatory indices in predicting ACC severity, determine their optimal cut-off values, and explore their potential role in clinical risk stratification.

MATERIALS AND METHODS

A retrospective study was conducted on patients admitted to the Emergency Department of Balıkesir University Health Practice and Research Hospital with acute cholecystitis between January 1, 2020 and May 31, 2024. Data were collected from hospital archives and electronic patient records. All patients aged 18 years or older who were admitted with a diagnosis of acute calculous cholecystitis and subsequently evaluated by the General Surgery Department were included in the statistical analysis. Initially, 276 patients were identified; however, 116 patients with acute acalculous cholecystitis, cholangitis, or choledocholithiasis, and 20 patients with incomplete data were excluded from the analysis. Consequently, 160 patients with acute calculous cholecystitis were included in the final analysis.

Ultrasonography (US) and abdominal computed tomography (CT) were used to detect stones, measure gallbladder wall thickness, identify signs of pericholecystitis, and evaluate both local and systemic inflammatory indicators. For all patients, demographic and clinical data—including age, comorbidities, symptom onset time, and clinical signs—were recorded. Laboratory tests included complete blood count (CBC), hepatic transaminases, bilirubin, urea, creatinine, albumin, international normalized ratio (INR), and C-reactive protein (CRP) at the time of admission.

Patients were classified according to the TG13/18 guidelines into three severity grades: Grade I (mild), Grade II (moderate), and Grade III (severe) acute cholecystitis. Systemic inflammatory biomarkers were calculated from neutrophil (N), platelet (P), and lymphocyte (L) counts obtained from the same blood sample. Based on these values, NLR, PLR, NLPR, SII, and MII (multiple inflammatory index) were calculated as follows: NLR (neutrophil-to-lymphocyte ratio), PLR (platelet-to-lymphocyte ratio), NLPR (neutrophil / (lymphocyte × platelet) ratio), SII ((neutrophils × platelets) / lymphocytes), and MII (SII × CRP).

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval was obtained from the Balıkesir University Clinical Research Ethics Committee (Approval Number: 2024/124, Date: 06.08.2024). Written informed consent was waived due to the retrospective nature of the study.

Statistical Analysis

All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences, version 28.0). The normality of numerical data was tested using the Shapiro-Wilk test. Descriptive statistics for numerical data are presented as means ± standard deviations or medians (Q1-Q3). Frequencies (n) and percentages (%) are provided for categorical data. Group comparisons were performed using the Chi-square test for categorical variables and the Kruskal-Wallis H test for numerical variables. Receiver Operating Characteristic (ROC) curve analysis was employed to identify optimal cut-off points by maximizing sensitivity and specificity based on the Youden J index.

RESULTS

A total of 160 patients diagnosed with ACC were included in the study, with a mean age of 56.7 ± 17.5 years (range, 18–92). The majority were classified as moderate cases (Grade II, $n=96$, 60%), followed by mild (Grade I, $n=51$, 31.9%) and severe (Grade III, $n=13$, 8.1%). Female patients accounted for 51.2% of the cohort. Patients with severe ACC (Grade III) were significantly older (68.8 ± 12.9 years, $p=0.018$) compared to those with Grades I and II, and male patients were more common in Grades II and III. Hypertension (26.9%), diabetes mellitus (12.5%), and coronary artery disease (9.4%) were the most frequent comorbidities, with coronary artery disease significantly more prevalent in Grade III cases ($p=0.032$). Most patients were admitted more than 72 hours after symptom onset (40.6%). The majority required hospitalization (88.8%), and 61.2% did not undergo surgical intervention (Table 1).

Laboratory analyses revealed significantly higher values in severe cases for leukocyte count ($p=0.033$), neutrophil count ($p=0.015$), lymphocyte count ($p=0.010$), CRP ($p=0.001$), NLR ($p=0.001$), PLR ($p=0.046$), NLPR ($p=0.004$), SII ($p=0.004$), and MII ($p=0.001$). No significant differences were observed for platelet counts, aspartate aminotransferase (AST), or alanine aminotransferase (ALT) levels. Median CRP levels increased progressively with disease severity, ranging from 6.7 mg/L in Grade I to 122.2 mg/L in Grade III ($p<0.001$). Similarly, NLR increased from 3.5 in mild cases to 11.0 in severe cases ($p<0.001$). Complete laboratory comparisons are presented in Table 2.

ROC curve analysis demonstrated that NLR, NLPR, CRP, SII, and MII had moderate predictive accuracy for severe ACC (area under the curve [AUC]=0.70–0.88), while PLR and white blood cell count (WBC) showed lower accuracy

Table 1. Comparison of demographic and clinical characteristics of patients categorized according to the TGI3/18 severity grades of acute calculous cholecystitis

	GRADE I	GRADE II	GRADE III	TOTAL	p
Age, mean±SD	53.43±16.15	56.82±18.14	68.77±12.89	56.71±17.51	0.018 ^{1*}
Female, N, %	32	45	5	82 (51.2%)	0.117 ²
Male, N, %	19	51	8	78 (48.8%)	
US, N, %	42	70	9	121 (75.6%)	0.369 ²
CT, N, %	31	61	8	100 (62.5%)	0.945 ²
Comorbidities					
Hypertension	11	27	5	43 (26.9%)	0.435 ²
Diabetes mellitus	5	13	2	20 (12.5%)	0.760 ²
Coronary artery disease	2	9	4	15 (9.4%)	0.032 ²
Chronic respiratory disease	2	3	0	5 (3.1%)	0.630 ²
Complaint initiation period					
<24 h, N	18	23	1	42 (26.3%)	0.121 ²
24-72 h, N	18	31	4	53 (33.1%)	
>72 h, N	15	42	8	65 (40.6%)	
Hospitalization					
Discharged, N	8	1	0	9 (5.6%)	0.0222 ³
Hospitalized, N	40	90	12	142 (88.8%)	
Transfer, N	2	4	1	7 (4.4%)	
Treatment rejection	1	1	0	2 (1.3%)	
Length of hospitalization, days, mean±SD	4.38±1.78	5.17±2.36	6.58±3.18	5.06±2.35	0.119 ¹
Surgery					
Non-surgical management	28	63	7	98 (61.20%)	0.601 ²
<30 days surgery	15	18	3	36 (22.50%)	
>30 days surgery	8	15	3	26 (16.25%)	
TOTAL	51 (31.9%)	96 (60%)	13 (8.1%)	160 (100%)	

¹ANOVA; ²Pearson chi-square or Fisher's exact test. Data are presented as mean±standard deviation or number (percentage). *P<0.05. SD: Standard deviation; US: Ultrasonography; CT: Computed tomography; ACC: Acute calculous cholecystitis.

(AUC=0.54–0.69). The optimal cut-off values were: NLR 8.45 (sensitivity 76.9%, specificity 68.0%), PLR 219.2 (sensitivity 69.2%, specificity 68.7%), NLPR 0.027 (sensitivity 76.9%, specificity 54.4%), CRP 78.45 mg/L (sensitivity 76.9%, specificity 66.0%), SII 2414 (sensitivity 69.2%, specificity 72.1%), and MII 250,011 (sensitivity 76.9%, specificity 78.9%). Among these, MII (AUC=0.770) and NLR (AUC=0.755) were the strongest predictors of severe ACC, whereas WBC had poor discriminative performance (AUC=0.541, p=0.628). Detailed results are summarized in Table 3 and illustrated in Figure 1.

DISCUSSION

Cholelithiasis and cholecystitis remain among the most common causes of abdominal pain requiring emergency department (ED) evaluation, often leading to hospital admission and urgent surgical intervention. Accurate early recognition

of severe cases is crucial because delayed treatment can result in complications such as empyema, gangrene, or perforation, which substantially increase morbidity and mortality. Although the Tokyo Guidelines (TG18) offer a standardized framework for diagnosis and severity grading, they depend primarily on imaging modalities, which may not be consistently available in resource-limited environments and are subject to interobserver variability.^[11] Therefore, there is growing interest in cost-effective biomarkers that are widely available, reproducible, and capable of supporting clinical decision-making in the ED.

Systemic inflammatory indices have been extensively studied in recent years as prognostic markers in a range of acute and chronic diseases.^[12] These indices, including the neutrophil-to-lymphocyte ratio, neutrophil-to-lymphocyte-platelet ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation

Table 2. Laboratory findings of patients with acute calculous cholecystitis, stratified by severity

	Mean±SD	Q1	Q3	P
Hemoglobin, g/dL	12.9±1.82	11.72	14.1	0.958
White blood cells, /mm ³	12.41±5.14	9.03	14.83	0.033*
Neutrophils, ×10 ³ /mm ³	9.89±5.04	6.7	12.2	0.015*
Lymphocytes, ×10 ³ /mm ³	1.59±0.95	1	1.9	0.01*
Platelets, ×10 ³ /mm ³	263.52±80.66	209.5	304	0.508
BUN, mg/dL	15.78±7.99	10.4	19.04	0.016*
Urea, mg/dL	33.77±17.08	22.25	40.75	0.019*
Creatinine, mg/dL	0.94±0.34	0.71	1.07	0.007*
AST, IU/L	67.21±108.92	18	61.75	0.447
ALT, IU/L	69.22±116.86	14	56	0.419
GGT, IU/L	109.15±176.45	22	88.5	0.921
ALP, IU/L	104.58±94.43	61.25	109.5	0.327
Total bilirubin, mg/dL	1.23±1.17	0.56	1.42	0.005*
Direct bilirubin, mg/dL	0.46±0.76	0.11	0.46	0.006*
Indirect bilirubin, mg/dL	0.77±0.55	0.41	0.96	0.037*
INR (sec)	1.08±0.13	1	1.14	0.001*
CRP, mg/dL	69.43±72.32	6.73	122.25	0.001*
Albumin, g/dL	36.28±5.12	33	40	0.001*
NLR	9.1±8.97	3.46	11.05	0.001*
PLR	217.25±157.28	132.09	256.6	0.046*
NLPR	0.04±0.05	0.01	0.05	0.004*
SII	2329.27±2511	905.87	2661.67	0.004*
MII	215,183.86±371,341	8711.5	251,233.5	0.001*

*P<0.05. BUN: Blood urea nitrogen; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; ALP: Alkaline phosphatase; INR: International normalized ratio; CRP: C-reactive protein; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; NLPR: Neutrophil-to-lymphocyte-platelet ratio; SII: Systemic immune-inflammation index; MII: Multiple inflammatory index.

Table 3. Receiver operating characteristic (ROC) curve analysis of systemic inflammatory indices for predicting severe acute calculous cholecystitis

	AUC	Cut-off	Youden J Index	P value	Sensitivity (%)	Specificity (%)
NLR	0.755 (0.609-0.90)	8.45	0.450	0.002*	76.92	68.03
PLR	0.696 (0.514-0.878)	219.2	0.379	0.019*	69.23	68.71
NLPR	0.735 (0.544-0.866)	0.027	0.313	0.015*	76.92	54.42
WBC	0.541 (0.365-0.716)	11.35	0.119	0.628	61.54	50.34
CRP	0.728 (0.585-0.872)	78.45	0.429	0.006*	76.90	66.00
SII	0.717 (0.558-0.877)	2414	0.413	0.009*	69.23	72.11
MII	0.770 (0.625-0.916)	250,011	0.558	0.001*	76.90	78.90

AUC: Area under the curve; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; NLPR: Neutrophil-to-lymphocyte-platelet ratio; WBC: White blood cell count; CRP: C-reactive protein; SII: Systemic immune-inflammation index; MII: Multiple inflammatory index.

index, and multiple inflammatory index, are derived from routine complete blood count parameters. They reflect the interplay between immune activation and systemic inflamma-

tion. In acute calculous cholecystitis, gallbladder obstruction and bacterial invasion activate innate immunity, triggering neutrophil proliferation, lymphocyte apoptosis, and platelet-

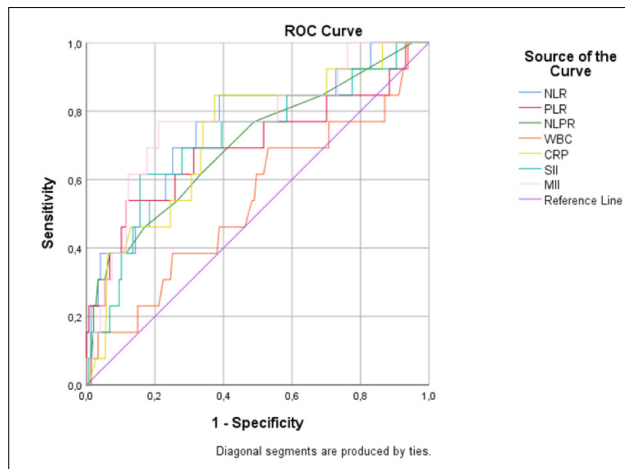


Figure 1. ROC curve analysis of systemic inflammatory indices (NLR, PLR, NLPR, WBC, CRP, SII, and MII) for predicting severe acute calculous cholecystitis. ROC: Receiver operating characteristic; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; NLPR: Neutrophil-to-lymphocyte-platelet ratio; WBC: White blood cell count; CRP: C-reactive protein; SII: Systemic immune-inflammation index; MII: Multiple inflammatory index.

mediated microvascular injury. Pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) play a central role in this cascade. IL-6 amplifies inflammatory signaling through NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) pathways and induces hepatic synthesis of C-reactive protein, while TNF- α promotes neutrophil recruitment and vascular injury.^[13,14] Elevated levels of IL-6 and TNF- α have been reported in patients with ACC, where they correlate with disease severity and complications.^[15] Moreover, clinical and meta-analytic studies confirm the prognostic value of these cytokines in acute inflammatory diseases.^[16,17] This mechanistic background explains why indices such as NLR, NLPR, and SII increase with greater disease severity.

In the present cohort, cut-off values were determined for NLR (8.45), PLR (219.2), NLPR (0.027), CRP (78.45 mg/L), SII (2414), and MII (250,011). Patients exceeding these thresholds were more likely to develop complications such as gangrenous cholecystitis or perforation. Elevated NLR reflects disproportionate neutrophil activation relative to lymphocyte suppression, while high MII captures the combined influence of SII and CRP, integrating both cellular and humoral aspects of the inflammatory process. This study is consistent with Efgan et al.^[7] (2025), who demonstrated that inflammatory indices, particularly NLR and SII, are reliable predictors of complications in ACC. However, this study is the first to define and propose a specific MII cut-off, thereby extending the clinical applicability of these indices in severity assessment. This finding is also consistent with Afzal et al.^[18] (2025), who reported elevated NLPR values in patients requiring conversion to open cholecystectomy due to severe inflammation. Similarly, Özkan et al.^[19] (2024) demonstrated the diagnostic utility of NLPR in acute appendicitis, with excellent discrimi-

natory performance (AUC=0.94). These findings suggest that such indices may serve as early warning markers of clinical deterioration, potentially preceding radiological evidence of severe disease.

Our results align with previous studies. Efgan et al.^[7] (2025) demonstrated that elevated NLR and SII were predictive of complications and extended hospitalization. Turhan et al.^[20] (2022) similarly reported significantly higher NLR and PLR levels in complicated ACC, supporting the role of systemic inflammation in disease progression. The systemic inflammation response index (SIRI) has also been proposed as a marker of chronic inflammatory processes contributing to gallstone pathogenesis rather than acute exacerbations.^[20] Meng and Liu (2023) observed a significant correlation between higher SII levels and gallstone formation in younger adults, suggesting that inflammatory indices may also play a role in early biliary pathology.^[21,22] Collectively, these findings highlight the broader utility of systemic indices across the spectrum of gallbladder disease.

Molecular and biochemical markers provide additional insight. Shan et al.^[17] (2024) reported that combining IL-6 with procalcitonin (PCT) and neutrophil count achieved excellent discriminatory power (AUC $\approx$ 0.90) for severe ACC, underscoring IL-6 as a central mediator of the inflammatory cascade. Chen et al.^[4] (2024) identified lower cut-off values for NLR, PLR, SII, and NLPR than those observed in the present cohort, yet confirmed the same trend: higher values were consistently associated with disease severity. Variations may reflect differences in patient populations and the timing of laboratory testing. In elderly patients, Xia et al.^[5] (2023) reported NLR thresholds of 5–7 for distinguishing purulent or gangrenous cholecystitis, while Prabhu et al.^[23] (2024) prospectively demonstrated that NLR >10 effectively distinguished severe forms, with high sensitivity and specificity.

Additional evidence also supports the clinical utility of these indices. Prakash and Hasan (2022) demonstrated that NLR was strongly associated with CT findings such as gallbladder distension, increased pericholecystic fat, and pericholecystic fluid collection, highlighting its ability to reflect radiological severity.^[24] Li et al.^[22] (2024) evaluated biomarkers including NLR, PLR, SII, and the Prognostic Nutrition Index (PNI) in acute cholangitis, reporting significantly higher NLR and SII levels in severe cases, which they attributed to systemic inflammation and immune dysregulation. Similarly, Kler et al.^[25] (2022) found that NLR was significantly higher in patients with acute cholecystitis compared with non-acute cholecystitis (non-AC) controls, and notably higher in severe compared to uncomplicated cases, supporting its role as an independent predictor.

Other emerging biomarkers may further enhance prognostic accuracy. Yodying et al.^[26] (2025) demonstrated that the neutrophil percentage-to-albumin ratio (NPAR) >21.5 had excellent predictive performance (AUC=0.906) for conser-

vative treatment failure, outperforming NLR and PLR. Likewise, Güneş et al.^[27] (2024) reported that both the C-reactive protein-to-albumin ratio (CAR >1.86) and systemic immune-inflammation index (SII >1327.69) were independent predictors of severe ACC and perioperative complications. These findings underscore the value of combining inflammatory and nutritional indices to refine risk stratification in ACC.

From a clinical perspective, incorporating these indices into ED workflows may enhance triage and treatment planning. For example, patients presenting with NLR >8.5 or CRP >78 mg/L could be prioritized for early surgical consultation and closer monitoring, even when imaging findings are inconclusive. Integrating systemic indices with TG18 severity grading may provide a more objective framework for risk stratification, improving decision-making in both high-volume tertiary centers and resource-limited hospitals. Such strategies could reduce delays, lower complication rates, and optimize resource utilization.

This research has several limitations. It was retrospective and single-centered, with a relatively small cohort size, which may restrict generalizability. Laboratory parameters were obtained only at admission; serial evaluations could yield additional prognostic insight. Nonetheless, the findings provide preliminary cut-off values for systemic inflammatory indices in ACC and demonstrate their potential association with disease severity.

These results may serve as a reference point for future investigations. In particular, prospective multicenter studies and analyses integrating inflammatory indices with established clinical scores or molecular biomarkers could clarify their role in risk stratification and guide the development of more comprehensive prognostic models.

CONCLUSION

Acute calculous cholecystitis can be assessed rapidly and cost-effectively using systemic inflammatory markers such as NLR, PLR, NLPR, SII, and MII, which are derived from routine complete blood counts. These indices are inexpensive, widely available, and can be integrated into standard diagnostic protocols without additional resource burden, offering a practical alternative in settings where advanced imaging is limited. Early identification of severe cases through these markers may facilitate timely surgical intervention, reduce complication rates, and optimize hospital outcomes. Future multicenter studies are warranted to confirm optimal cut-off values and validate their utility across diverse populations.

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ORİJİNAL ÇALIŞMA - ÖZ

Akut taşlı kolesistitin ciddiyetini tahmin etmede sistemik inflamatuvar indekslerin prognostik rolü

AMAÇ: Akut kolesistit, acil tıp ve cerrahi kliniklerinde en sık karşılaşılan ve tedavi edilen acil durumlardan biridir. Akut taşlı kolesistit (ATK) olgularında inflamasyonun şiddetini ve kapsamını öngörmeye kullanılabilecek sistemik inflamatuvar parametreleri değerlendiren çalışmalar sınırlıdır. Bu çalışmanın amacı, nötrofil/lenfosit oranı (NLR), trombosit/lenfosit oranı (PLR), nötrofil/lenfosit × trombosit oranı (NLPR), sistemik immün-inflamasyon indeksi (SII) ve çoklu inflamasyon indeksi (MII) gibi tam kan sayımı (TKS) kaynaklı parametrelerin ATK'nın ayırıcı tanısı ve şiddetinin belirlenmesindeki tanılal değerini araştırmaktır.

GEREÇ VE YÖNTEM: Çalışmaya 1 Ocak 2020-31 Mayıs 2024 tarihleri arasında acil servise başvuran ve genel cerrahi tarafından ATK tanısı doğrulan 160 hasta dahil edildi. Akut akalkülöz kolesistit, kolanjit, koledokolitiazis tanısı alan, eksik verisi bulunan ve 18 yaş altı hastalar çalışma dışı bırakıldı. Hastaların demografik, klinik, laboratuvar ve görüntüleme bulguları incelendi; NLR, PLR, NLPR, SII ve MII hesaplandı. Parametrelerin şiddet öngörüsündeki etkinliği ROC analizi ile değerlendirildi.

BULGULAR: En yüksek prediktif değer MII'de saptandı (kesme değeri=250.011; duyarlılık %76.9; özgüllük %78.9; AUC=0.770). NLR için 8.45 kesme değeri %76.9 duyarlılık ve %68,0 özgüllük gösterdi. NLPR (cut-off=0.027) %76.9 duyarlılık ve %54.4 özgüllük; SII (cut-off=2414) ise %69.2 duyarlılık ve %72.1 özgüllük sağladı (tümü p<0.05).

SONUÇ: Sistemik inflamasyon indeksleri, özellikle MII ve NLR, ATK şiddetinin değerlendirilmesinde etkili, ucuz ve erişilebilir biyobelirteçlerdir. Bu parametreler, özellikle görüntüleme yöntemlerinin sınırlı olduğu durumlarda klinik karar sürecine önemli katkı sağlayabilir.

Anahtar sözcükler: Acil tıp; safra taşı; sistemik immün-inflamasyon indeksi; şiddetli akut kolesistit.

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The role of the C-reactive protein to lymphocyte ratio in the diagnosis of complicated acute appendicitis

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ABSTRACT

BACKGROUND: To assess the diagnostic value of the C-reactive protein to lymphocyte ratio (CLR) and other inflammatory markers in distinguishing complicated from uncomplicated acute appendicitis (AA) to support timely surgical intervention.

METHODS: This retrospective study included 682 patients who underwent appendectomy between January 2018 and January 2021. Based on the histopathological American Association for the Surgery of Trauma (AAST) AA grading system, patients were classified as complicated AA (grades 3–5; n=144) or uncomplicated AA (grades 1–2; n=538). Preoperative laboratory values—white blood cell (WBC) count, neutrophil count, C-reactive protein (CRP), sodium (Na), CLR, neutrophil-to-lymphocyte ratio (NLR), and CRP/Na—were analyzed. Diagnostic performance was assessed using receiver operating characteristic (ROC) analysis.

RESULTS: Complicated AA cases were significantly older (37.5 ± 17.6 vs. 30.0 ± 12.8 years; $p < 0.001$). CRP (7.17 ± 6.78 vs. 2.98 ± 4.52 mg/dL), WBC, neutrophils, and CLR (5.66 ± 9.13 vs. 1.89 ± 3.94) were significantly elevated in the complicated group ($p < 0.001$). CLR showed moderate diagnostic accuracy (AUC=0.712), with a cutoff of ≥ 2.82 yielding 53.5% sensitivity and 82.7% specificity (OR=5.49, 95% CI: 3.69–8.16). Hyponatremia and elevated NLR/PLR also correlated with complications.

CONCLUSION: CLR is a moderately accurate, highly specific, and accessible biomarker for identifying complicated AA. Its integration with clinical evaluation may enhance preoperative risk stratification, especially in resource-limited settings.

Keywords: Acute; appendicitis; biomarkers; c-reactive protein; inflammation mediators; lymphocyte count.

INTRODUCTION

Acute appendicitis (AA) is a prevalent surgical emergency that often necessitates urgent intervention and is a primary cause of abdominal pain presenting in emergency department settings.^[1,2] The lifetime incidence of acute appendicitis is estimated to be 8.6% in men and 6.9% in women.^[3] Timely diagnosis and intervention are crucial in preventing the onset of complications.^[4] Mortality risk in patients with AA is 0.3%; however, this risk increases to 0.6% in cases of perforation.^[5,6]

Determining whether a patient has complicated AA is crucial when planning treatment. Complicated AA can be identified in the presence of gangrene, perforation, or abscess formation.^[7,8] In recent years, it has been suggested that uncomplicated AA may be treated solely with antibiotics.^[9,10] However, despite being effective and safe, non-operative treatment carries a risk of recurrent AA of up to 40% within five years.^[11] On the other hand, patients with complicated AA should not be treated with antibiotics alone because they may have

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perforated AA. Guidelines recommend that patients with complicated AA should undergo surgery as soon as possible, or at least within 8 hours of diagnosis.^[12]

Computed tomography (CT) is frequently utilized in clinical practice to assess the severity of AA. However, considering the radiation exposure and the loss of radiologist workload, a practical laboratory test capable of predicting this condition is still being sought. Among systemic inflammatory parameters, studies have demonstrated an association between the severity of AA and laboratory parameters such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-eosinophil ratio (MER), and C-reactive protein (CRP).^[13,14] Additionally, the CRP-to-lymphocyte ratio (CLR) is a promising marker for detecting complicated AA.^[15,16]

The objective of our study is to identify laboratory markers that can effectively distinguish between complicated and uncomplicated AA in patients presenting to the emergency department with a preliminary diagnosis of AA.

MATERIALS AND METHODS

This study was performed as a retrospective analysis of patients diagnosed with AA who underwent surgical intervention in the Department of General Surgery between January 2018 and January 2021.

Historical records of patients were evaluated retrospectively from a prospectively recorded database. Patients younger than the age of 18 years, patients with a history of ongoing inflammatory diseases such as arthritis, inflammatory bowel disease, and familial Mediterranean fever were excluded. Additionally, patients who underwent appendectomy alongside another surgical procedure or for stump appendicitis were not included.

Demographic data (age, gender), type of surgery, intraoperative findings, preoperative hemogram and biochemical parameters, and physical examination findings were recorded. All patients were arranged for follow-up appointments one week and one month after surgery, on an outpatient basis.

Pathology reports were reviewed and categorized according to the American Association for the Surgery of Trauma (AAST) AA grading system. The AAST classification grades AA severity from 1 to 5: Grade 1 – acutely inflamed, intact appendix; Grade 2 – intact, gangrenous appendix; Grade 3 – perforated appendix with localized contamination; Grade 4 – perforated appendix with periappendiceal phlegmon or abscess; and Grade 5 – perforated appendix with generalized peritonitis.^[17] Patients with grades 1–2 were classified as having uncomplicated AA, while those with grades 3–5 were categorized as having complicated AA.

All procedures followed the ethical guidelines set forth in the 1964 Helsinki Declaration and its later revisions. Approval from the Institutional Review Board (IRB) was granted [IRB number: 2023/0814], and informed consent was obtained

from all participants.

Descriptive statistics were presented as counts (percentages) for categorical variables and as mean $\pm$ standard deviation, median (range) for continuous variables. The normality of continuous variables was assessed both analytically using the Kolmogorov-Smirnov test and visually through graphical methods. Differences in patient characteristics and preoperative laboratory values between the complicated and uncomplicated AA groups were compared using Pearson's chi-squared test for categorical variables, and either the Independent Sample t-test or the Mann-Whitney U test for continuous variables. Standardized effect sizes (Cohen's d) for group differences in laboratory data were calculated based on the respective z-test statistic values.

The diagnostic performance of laboratory parameters with significant p-values from group comparisons was evaluated through receiver operating characteristic (ROC) curves and the area under the curve (AUC). The optimal cutoff values for potential biomarkers were determined using the Youden Index, and sensitivity, specificity, along with their 95% confidence intervals (CI), were calculated. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS, Version 11.5, SPSS Inc., Chicago, IL), and a p-value of less than 0.05 was considered indicative of statistical significance.

RESULTS

The study group consisted of 682 surgically treated AA cases. The mean age of patients in the complicated AA group (n=144) was 37.5 ± 17.59 [median: 37.5 (18-90)] years, while the mean age of patients in the uncomplicated AA group (n=538) was 30.0 ± 12.76 [median: 30.0 (18-88)] years. The age of patients in the complicated AA group was significantly higher than in the uncomplicated group ($p < 0.001$) (Table 1).

Regarding gender distribution, 62 women (43.1%) and 82 men (56.9%) were in the complicated AA group, while 186 women (34.6%) and 352 men (65.4%) were in the uncomplicated group. The difference in gender distribution was not statistically significant ($p = 0.06$).

The distribution of surgical procedures was evaluated, and it was found that 130 patients (90.3%) in the complicated AA group were treated with laparoscopic surgery, 6 patients (4.2%) underwent conversion to open surgery, and 8 patients (5.6%) were treated with conventional open surgery. In the uncomplicated group, these rates were 505 patients (93.9%), 12 patients (2.2%), and 21 patients (3.9%), respectively. No statistically significant difference was observed between the groups regarding the type of surgery performed ($p = 0.287$) (Table 1).

According to the intraoperative grading of appendicitis, 33 cases were inflamed (22.9%), 59 cases were phlegmonous (41.0%), 34 cases were perforated with localized free fluid (23.6%), 13 cases were perforated with regional abscess

Table 1. Evaluation of the age, gender, type of surgery, and perioperative findings of patients between the groups

		Complicated (n=144)	Non-complicated (n=538)	P
Gender				
Female	n (%)	62 (43.1)	186 (34.6)	0.06
Male	n (%)	82 (56.9)	352 (65.4)	
Age (years)	Mean±SD	37.5±17.59	30.0±12.76	<0.001
	Median (min-max)	37.5 (18-90)	30.0 (18-88)	
Operation type				
Laparoscopic	n (%)	130 (90.3)	505 (93.9)	0.287
Conversion to open surgery	n (%)	6 (4.2)	12 (2.2)	
Conventional	n (%)	8 (5.6)	21 (3.9)	
Intraoperative grade				
Inflamed	n (%)	33 (22.9)	290 (53.9)	<0.001
Phlegmonous	n (%)	59 (41.0)	207 (38.5)	
Perforated with localized free fluid	n (%)	34 (23.6)	30 (5.6)	
Perforated with regional abscess formation	n (%)	13 (9.0)	9 (1.7)	
Perforated with diffuse peritonitis	n (%)	5 (3.5)	2 (0.4)	

Pearson's chi-squared test, Mann-Whitney U test.

(9.0%), and 5 cases were perforated with diffuse peritonitis (3.5%) in the complicated AA group. In the uncomplicated group, these rates were 290 cases (53.9%), 207 cases (38.5%), 30 cases (5.6%), 9 cases (1.7%), and 2 cases (0.4%), respectively. In the complicated AA group, inflamed cases were at a lower rate, while perforated cases were significantly higher ($p<0.001$) (Table 1).

The laboratory parameters are summarized in Table 2. In the complicated AA group, the mean WBC count was $15.26\pm4.09 \times 10^3/\mu\text{L}$ [median: 14.8 (5.1-31.3)], the mean neutrophil count was $12.66\pm3.83 \times 10^3/\mu\text{L}$ [median: 12.4 (2.9-25.8)], and the mean neutrophil percentage was $82.25\pm6.7\%$ [median: 83.6% (57.2%–94.7%)]. In the uncomplicated group, these values were $14.08\pm4.2 \times 10^3/\mu\text{L}$ [median: 13.5 (3.4-36.9)], $11.37\pm6.1 \times 10^3/\mu\text{L}$ [median: 10.7 (1.8-31.2)], and $76.8\pm10.43\%$ [median: 76.9% (42.4%-95.3%)], respectively. In the complicated AA group, WBC, neutrophil, and neutrophil percentage values were significantly higher ($p<0.001$).

The CRP level was found to be $7.17\pm6.78 \text{ mg/L}$ [median: 5.53 (0.2-29.5)] in the complicated group and $2.98\pm4.52 \text{ mg/L}$ [median: 1.5 (0.1-45.7)] in the uncomplicated group, being significantly higher in the complicated group ($p<0.001$). The sodium (Na) level was $136.14\pm2.49 \text{ mmol/L}$ [median: 136 (126-141)] in the complicated group and $137.14\pm2.21 \text{ mmol/L}$ [median: 137 (124-143)] in the uncomplicated group. According to these results, Na levels were significantly higher in the uncomplicated group ($p<0.001$).

The CRP/neutrophil percentage, CRP/neutrophil, CRP/Na, and CLR ratios were calculated as 0.086 ± 0.08 [median 0.063

(0.001-0.39)], 0.625 ± 0.645 [median: 0.484 (0.008-3.68)], 0.051 ± 0.05 [median: 0.041 (0.002-0.29)], and 5.66 ± 9.126 [median: 3.19 (0.2-77.5)], respectively, in the complicated group. In the uncomplicated group, these ratios were 0.039 ± 0.057 [median: 0.024 (0.001-0.7)], 0.33 ± 0.565 [median: 0.162 (0.006-7.76)], 0.022 ± 0.033 [median: 0.013 (0.001-0.47)], and 1.89 ± 3.942 [median: 0.92 (0.05-41.8)], respectively. These ratios were significantly higher in the complicated AA group ($p<0.001$). Lymphocyte counts were calculated as $1.89\pm1.47 \times 10^3/\mu\text{L}$ [median: 1.56 (0.2-7.8)] in the complicated group and $2.18\pm1.23 \times 10^3/\mu\text{L}$ [median: 2.0 (0.1-10.8)] in the uncomplicated group. The lymphocyte levels were significantly higher in the uncomplicated group ($p<0.001$).

The ROC analysis of laboratory parameters is summarized in Table 3 and Figure 1. According to these findings, CRP (AUC: 0.710), CRP/lymphocyte ratio (AUC: 0.712), and CRP/Na ratio (AUC: 0.712) had high diagnostic accuracy. CRP showed 52.1% sensitivity and 81.8% specificity at a cutoff value of ≥ 5.11 , and CRP/Na ratio showed 52.1% sensitivity and 80.3% specificity at a cutoff value of ≥ 0.035 .

At a CLR cutoff value of ≥ 2.82 , sensitivity was 53.5% and specificity was 82.7%. The odds ratio (OR) of the CLR was calculated as 5.487 (95% CI: 3.691-8.156); the positive predictive value was 45.3%, and the negative predictive value was 86.9% (Table 4).

DISCUSSION

Acute appendicitis is a disease characterized by a rapidly developing inflammatory response and variable clinical severity.

Table 2. Distribution of laboratory data of patients by groups

	Complicated (n=144)	Non-complicated (n=538)	P
WBC, ($\times 10^3/\mu\text{L}$)			
Mean $\pm$ SD	15.26 $\pm$ 4.09	14.08 $\pm$ 4.20	0.001
Median (min–max)	15.25 (4.40–26.90)	13.60 (4.20–27.80)	
Neutrophil, ($\times 10^3/\mu\text{L}$)			
Mean $\pm$ SD	12.66 $\pm$ 3.83	11.37 $\pm$ 6.10	<0.001
Median (min–max)	12.42 (3.56–23.09)	10.63 (2.25–87.50)	
Neutrophil percentage			
Mean $\pm$ SD	82.25 $\pm$ 6.70	76.8 $\pm$ 10.43	<0.001
Median (min–max)	83.25 (63.10–94.70)	78.30 (9.23–94.70)	
CRP, (mg/L)			
Mean $\pm$ SD	7.17 $\pm$ 6.78	2.98 $\pm$ 4.52	<0.001
Median (min–max)	5.50 (0.10–28.17)	1.17 (0.10–32.30)	
Sodium, (mmol/L)			
Mean $\pm$ SD	136.14 $\pm$ 2.49	137.14 $\pm$ 2.21	<0.001
Median (min–max)	136.00 (127.00–141.00)	137.00 (129.00–144.00)	
CRP/ Neutrophil percentage			
Mean $\pm$ SD	0.086 $\pm$ 0.08	0.039 $\pm$ 0.06	<0.001
Median (min–max)	0.06 (0.00–0.33)	0.02 (0.00–0.38)	
CRP/Neutrophil			
Mean $\pm$ SD	0.625 $\pm$ 0.65	0.33 $\pm$ 0.57	<0.001
Median (min–max)	0.41 (0.00–2.89)	0.12 (0.00–4.31)	
CRP/Sodium			
Mean $\pm$ SD	0.051 $\pm$ 0.05	0.022 $\pm$ 0.033	<0.001
Median (min–max)	0.04 (0.00–0.21)	0.01 (0.00–0.24)	
CRP/Lymphocyte			
Mean $\pm$ SD	5.66 $\pm$ 9.13	1.89 $\pm$ 3.94	<0.001
Median (min–max)	3.13 (0.00–83.80)	0.63 (0.02–40.37)	
Lymphocyte, ($\times 10^3/\mu\text{L}$)			
Mean $\pm$ SD	1.89 $\pm$ 1.47	2.18 $\pm$ 1.23	<0.001
Median (min–max)	1.70 (0.30–16.00)	2.00 (0.40–22.10)	
Platelets, ($\times 10^3/\mu\text{L}$)			
Mean $\pm$ SD	247.38 $\pm$ 65.03	247.63 $\pm$ 62.33	0.732
Median (min–max)	238.50 (102.00–499.00)	245.00 (44.00–705.00)	
Neutrophil/Lymphocyte			
Mean $\pm$ SD	9.07 $\pm$ 6.21	6.71 $\pm$ 5.82	<0.001
Median (min–max)	7.37 (0.88–50.63)	5.16 (0.69–67.31)	
Platelets/Lymphocyte			
Mean $\pm$ SD	172.20 $\pm$ 103.50	138.31 $\pm$ 83.11	<0.001
Median (min–max)	154.03 (19.75–780.00)	120.53 (13.26–980.00)	

Mann-Whitney U test, CRP: C-Reactive Protein, WBC: White Blood Cell.

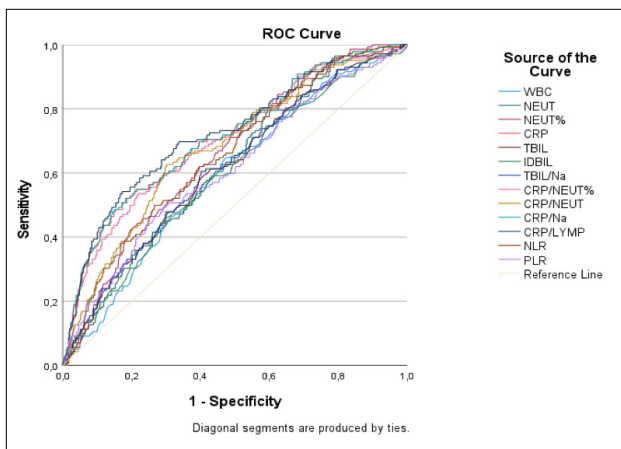
[18] Laboratory parameters play an important role in the differentiation of complicated and uncomplicated cases. Recent studies have shown that inflammatory markers such as CRP, neutrophil-to-lymphocyte ratio (NLR), and CRP-to-lympho-

cyte ratio (CLR) can be strong indicators for predicting the severity of the disease.[19] The diagnostic accuracy of CRP and NLR is particularly notable in the early detection of complications and the optimization of clinical interventions.[20]

Table 3. Receiver Operating Characteristic analysis results of laboratory parameters

Variables	AUC	Cutoff	P Value	Sensitivity (%)	Specificity (%)
WBC	0.595	≥ 13.85	0.001	64.80	52.70
Neutrophil	0.617	≥ 9.62	<0.001	79.60	40.60
CRP	0.710	≥ 5.11	<0.001	52.10	81.80
CRP/Neutrophil	0.676	≥ 0.29	<0.001	61.80	69.60
CRP/Sodium	0.712	≥ 0.035	<0.001	52.10	80.30
CRP/Lymphocyte	0.712	≥ 2.82	<0.001	53.50	82.70
Neutrophil/Lymphocyte	0.654	≥ 7.77	<0.001	50.00	73.40
Platelets/Lymphocyte	0.611	≥ 153.36	<0.001	50.00	70.40
Sodium	0.619	≤ 135.50	<0.001	36.80	80.60
Lymphocyte	0.619	≤ 1.65	<0.001	49.30	69.30

AUC: Area Under the Curve, CRP: C-Reactive Protein, WBC: White Blood Cell. AUC, cutoff, sensitivity, and specificity values were calculated using ROC curve analysis and the Youden Index.

**Figure 1.** Receiver Operating Characteristic curve analysis of laboratory parameters.**Table 4.** Receiver Operating Characteristic analysis of C-reactive protein to lymphocyte ratio

	Value	Lower	Upper
Sensitivity	0.535	0.500	0.618
Specificity	0.827	0.792	0.858
Positive Predictive Value	0.453	0.395	0.513
Negative Predictive Value	0.869	0.847	0.888
Positive Likelihood Ratio	3.09	2.43	3.92
Negative Likelihood Ratio	0.56	0.47	0.67

Values calculated via Receiver Operating Characteristic (ROC) analysis with 95% confidence intervals.

Furthermore, CLR appears to have potential as a sensitive biomarker that can assist in surgical decision-making.^[21] The findings of this study may shed light on how the combination of inflammatory parameters can be used to improve clinical management in cases of AA.

Advanced age is an important factor that increases the risk of complicated AA.^[22] Xu et al.^[23] reported that older patients had a higher risk of perforation in their study. In the present study, the mean age of patients in the complicated AA group was 37.5 ± 17.59 [median: 37.5 (18-90)] years, which is significantly higher than the mean age of 30.0 ± 12.76 [median: 30.0 (18-88)] years in the uncomplicated group ($p < 0.001$).

The effect of gender on AA complications remains unclear. Doğan et al.^[24] reported that the effect of gender on the development of complications was limited and did not make a significant difference in determining the severity of AA. In our study group, the proportion of female and male patients in the complicated AA group was 25% and 18.9%, respectively. In the uncomplicated group, the proportion of women was 75% and men 81.1%. However, this difference was not statistically significant ($p > 0.05$).

As expected, complicated AA cases present greater challenges for surgeons. Higher rates of conversion from laparoscopic to open surgery are observed in complicated cases.^[25] In our study, 90.3% of patients in the complicated group underwent laparoscopic surgery, 4.2% underwent conversion to open surgery, and 5.6% underwent conventional surgery. On the other hand, in the uncomplicated group, laparoscopic surgery was performed in 93.9% of cases. Although the conversion and conventional surgery rates were lower in the uncomplicated group, these differences did not reach statistical significance ($p > 0.05$).

Perforation is more common in complicated AA cases, and early surgical intervention is required. Similarly, the presence of perforation has been shown to be an important predictive factor for the severity of complicated AA cases.^[26] When intraoperative appendicitis grading results were analyzed, inflamed appendicitis was found in 33 (22.9%) of the complicated AA cases, while patients with perforation consisted of 34 (23.6%) cases with the presence of localized free fluid, 13 (9.0%) cases with regional abscess formation, and 5 (3.5%) cases with diffuse peritonitis. In contrast, the rate of inflamed cases in the uncomplicated group was as high as 53.9%, while perforation rates were 5.6% for the presence of localized free fluid, 1.7% for regional abscess formation, and only 0.4% for diffuse peritonitis. As expected, intraoperative findings were associated with a higher rate of perforated cases in the complicated AA group ($p<0.001$).

Neutrophil count, WBC, and CRP are the most frequently used inflammatory parameters in daily clinical practice. Güngör et al. reported that CRP and neutrophil counts were reliable diagnostic markers for complicated AA.^[27] In our study, the CRP level was 7.17 ± 6.78 mg/dL, WBC was $15.26\pm4.09 \times 10^3/\mu\text{L}$, and neutrophil count was $12.66\pm3.83 \times 10^3/\mu\text{L}$ in the complicated group. These values in the uncomplicated group were 2.98 ± 4.52 mg/dL, $14.08\pm4.2 \times 10^3/\mu\text{L}$, and $11.37\pm6.1 \times 10^3/\mu\text{L}$, respectively. All these differences were statistically significant ($p<0.001$).

Another important parameter indicating the severity of the inflammatory response is NLR, which has been reported to have high predictive value for detecting complicated AA cases.^[15] In the present study, NLR was also found to be significantly higher in the complicated AA group ($p<0.001$).

Recent studies have reported that CLR was effective in determining the severity of AA and has high diagnostic accuracy.^[21,28] In our study, CLR was found to be 5.66 ± 9.126 in the complicated group and 1.89 ± 3.942 in the uncomplicated group ($p<0.001$). Accordingly, CLR with a cutoff value of ≥ 2.82 exhibited a sensitivity of 53.5% and a specificity of 82.7%, indicating that this parameter was a reliable biomarker for distinguishing complicated AA cases ($\text{OR}=5.487$; 95% $\text{CI}=3.691-8.156$, $p<0.001$). These findings support that CLR was a strong biochemical indicator for predicting the risk of complications in clinical practice, as the risk of complicated AA was found to be approximately sixfold higher in cases with a CLR value equal to or above 2.82.

The pathophysiology of hyponatremia, a known complication in inflammatory conditions, is still under investigation. It has been suggested that this condition is related to immunoneuroendocrine pathways and is due to the effect of interleukin-6 level alterations on vasopressin.^[29] Low Na levels are more common in complicated cases and are associated with the severity of inflammation.^[30] In our study, Na levels were significantly lower in the complicated AA group ($p<0.001$). These findings suggest that hyponatremia could also be used

as a marker in determining complicated AA cases and was associated with the severity of the inflammatory process.

Oymaci et al.^[31] reported that PLR was an effective marker in distinguishing complicated AA cases. PLR was found to be 172.20 ± 103.50 in the complicated group and 138.31 ± 83.11 in the uncomplicated group ($p<0.001$). These findings indicate that elevated PLR could be considered a potential indicator in the clinical management of AA patients as well.

This study has several limitations. Firstly, the retrospective design restricted the findings to the data that were available. Furthermore, the study was carried out at a single center, which may limit the generalizability of the results. Additionally, the inflammatory parameters were measured only at admission preoperatively, which may not adequately reflect the dynamic changes of the inflammatory response.

CONCLUSION

In conclusion, the findings of our study demonstrated that CLR was an important biomarker for the early detection of complicated AA cases. Inflammatory markers such as CRP, NLR, and CLR play a significant role in clinical and surgical decision-making. Especially, the high specificity and sensitivity values of CLR emphasize this parameter as an independent prognostic factor. The findings of this study suggest that CLR can be widely used in clinical practice and may be an important tool, particularly when access to imaging methods is limited, as this inflammatory biomarker is simple to measure and calculate.

Ethics Committee Approval: This study was approved by the Göztepe Prof. Dr. Süleyman Yalçın Research and Training Hospital Ethics Committee (Date: 29.11.2023, Decision No: 2023/0814).

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ORİJİNAL ÇALIŞMA - ÖZ

Komplike akut apandisit tanısında C-reaktif protein/lenfosit oranının rolü

AMAÇ: Bu çalışmanın amacı, komplike ve komplike olmayan akut apandisit (AA) olgularını ayırt etmede C-reaktif protein/lenfosit oranı (CLR) ile diğer inflamatuvar belirteçlerin tanısai değerini değerlendirmek ve zamanında cerrahi müdahaleye katkı sağlamaktır.

GEREÇ VE YÖNTEM: Ocak 2018-Ocak 2021 tarihleri arasında apendektomi uygulanan 682 hasta retrospektif olarak incelendi. Hastalar, Amerikan Travma Cerrahisi Derneği (AAST) akut apandisit histopatolojik evreleme sistemine göre komplike AA (evre 3–5; n=144) ve komplike olmayan AA (evre 1–2; n=538) olarak sınıflandırıldı. Preoperatif beyaz küre (WBC), nötrofil sayısı, C-reaktif protein (CRP), sodyum (Na), CLR, nötrofil/lenfosit oranı (NLR) ve CRP/Na düzeyleri analiz edildi. Tanısai performans, ROC analizi ile değerlendirildi.

BULGULAR: Komplike AA olguları anlamlı şekilde daha ileri yaş grubundaydı (37.5 ± 17.6 vs. 3.0 ± 12.8 yıl; $p < 0.001$). CRP (7.17 ± 6.78 vs. 2.98 ± 4.52 mg/dL), WBC, nötrofil ve CLR (5.66 ± 9.13 vs. 1.89 ± 3.94) düzeyleri komplike grupta anlamlı derecede yüksekti ($p < 0.001$). CLR, AUC=0.712 ile orta düzeyde tanısai doğruluk gösterdi; ≥ 2.82 eşik değeriyle %53.5 sensitivite ve %82.7 spesifiteye ulaşıldı (OR=5.49, %95 GA: 3.69-8.16). Hiponatremi ve artmış NLR/PLR de komplikasyonlarla ilişkili bulundu.

SONUÇ: CLR, komplike akut apandisit tanısında orta derecede duyarlı, yüksek özgüllüğe sahip ve kolay erişilebilir bir biyobelirteçtir. Klinik değerlendirme ile birlikte kullanıldığında, özellikle kaynakların kısıtlı olduğu ortamlarda preoperatif risk sınıflandırmasını destekleyebilir.

Anahtar sözcükler: Apandisit; biyobelirteçler; c-reaktif protein; inflamasyon; lenfosit sayısı.

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The effect of blood urea nitrogen (BUN)/albumin ratio in evaluating mortality in pediatric burn patients with 20% or greater total body surface area involvement

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ABSTRACT

BACKGROUND: This study aims to evaluate the predictive value of the blood urea nitrogen (BUN)/albumin ratio for in-hospital mortality in pediatric burn patients with a total body surface area (TBSA) of 20% or greater and to compare its performance with established scoring systems, namely the Abbreviated Burn Severity Index (ABSI) and the Pediatric Baux Score (P-Baux).

METHODS: Patients hospitalized with burns involving 20% or greater TBSA in our pediatric burn unit between 2018 and 2023 were reviewed retrospectively. Patients were analyzed for demographic information, basic clinical data, cause of burn, operative interventions, ABSI and P-Baux scores and the follow-up period. The BUN/albumin ratio was calculated using BUN and albumin values measured at the time of index hospital admission. Data were evaluated for in-hospital mortality.

RESULTS: A total of 212 patients were included in the study. Patients were divided into two groups: survivors and non-survivors. The non-survivor group had significantly higher TBSA involvement, full-thickness burns, inhalation injuries, and operative requirements ($p<0.001$). The overall mortality rate was 4.5%. Receiver operating characteristic (ROC) analysis demonstrated that the BUN/albumin ratio is a strong predictor of in-hospital mortality, with predictive power similar to that of the ABSI and P-Baux scores. The cut-off value for mortality prediction using the BUN/albumin ratio was >5.24 .

CONCLUSION: The BUN/albumin ratio is a simple and easily accessible marker that demonstrates strong statistical value in predicting in-hospital mortality in pediatric patients with burns covering 20% or more of the body. Given its availability from routine blood tests, we believe it may serve as a practical and helpful tool for clinicians caring for pediatric burn patients.

Keywords: Pediatric burn; blood urea nitrogen (BUN); albumin; mortality; Abbreviated Burn Severity Index (ABSI); Pediatric Baux Score (P-Baux).

INTRODUCTION

Burn injuries are most commonly seen in males younger than 2 years of age and most frequently occur as scald burns.^[1] Despite significant advances in burn care, burn injuries continue to represent a major and preventable cause of mortality and morbidity among the pediatric population worldwide.

^[2] Several mortality-predictive classifications exist for adult burn patients.^[3] However, there is no classification specifically designed for children. The Abbreviated Burn Severity Index (ABSI) is one of the most commonly used scoring systems for adult patients and is also applied to pediatric burn patients. Another mortality prediction score for burn patients is the Baux score. For pediatric patients, a modified version of the

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Revised Baux Score, known as the P-Baux score, has been defined.^[4]

Therefore, it is important to identify useful and easily available prognostic parameters for predicting mortality in pediatric burn patients to ensure appropriate treatment through proper triage.

ABSI Score

This scoring system, first defined in 1982, is based on age, gender, total body surface area (TBSA), inhalation injury, and full-thickness burn parameters, and it has been widely used since its introduction.^[5]

In children, second-degree burns with a total burned surface area of 10% or greater, third-degree burns greater than 5%, inhalation injuries, electrical burns, chemical burns, accompanying traumatic injuries, and facial and genital burns are classified as severe burns and require close follow-up and hospital admission to a burn center due to the high risk of mortality. As the percentage of TBSA burned increases, the risk of mortality also increases.

P-Baux Score

In adult patients, the Baux score was developed using TBSA and patient age to predict mortality in severe burn cases. However, the importance of inhalation injury led the literature to revise the scoring system to include this parameter, resulting in the Revised Baux (R-Baux) score. The revised score is calculated using the formula: R-Baux score = (TBSA + age + [17 × R]), where R=1 if the patient has an inhalation injury and R=0 if not. For pediatric patients, the P-Baux score has been defined and calculated as the Pediatric Baux score = (TBSA – age + [18 × R]) or pBAUX score = TBSA + (3 × Age) [6]. BAUX >100, rBAUX >105, and pBAUX >80 indicate a very high risk of mortality. Although the increase in score is not linear, the risk of mortality rises as the score increases (low, moderate, high, and very high risk).^[7]

Researchers have defined many biochemical parameters that predict mortality in adult and critically ill patients.^[8] The relationship between mortality and parameters such as white blood cell count (WBC), blood lactate level, serum creatinine, and blood urea nitrogen (BUN) has been demonstrated in previous studies.^[9,10] Albumin, synthesized by the liver, is a protein that serves as a negative acute-phase reactant and reflects the patient's nutritional status.^[8] Hypoalbuminemia is associated with increased mortality in severe conditions such as shock and sepsis.^[11] Blood urea nitrogen levels increase due to dehydration and inflammation during physiological stress,^[12] and elevated BUN levels indicate a poor prognosis.^[8]

Studies conducted with the hypothesis that the BUN/albumin ratio could predict mortality have shown that this ratio has predictive value, based on observations of low albumin levels and high BUN levels in intensive care patients.^[13]

As a tertiary care center with a high volume of pediatric burn admissions, we recognized the need for a rapid and easily

accessible marker to predict in-hospital mortality. The potential utility of the BUN/albumin ratio as a practical and reliable predictor of mortality is also highlighted, particularly in peripheral or resource-limited settings where accurate estimation of TBSA—required for scoring systems such as ABSI and P-Baux—may be difficult to achieve. This study aimed to evaluate the prognostic value of the BUN/albumin ratio in predicting in-hospital mortality among pediatric burn patients and to compare its predictive performance with that of the widely used ABSI and P-Baux scoring systems.

MATERIALS AND METHODS

This study was approved by the Institutional Ethics Committee (Date: 25/05/2023, No: 822) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Due to the retrospective design of the study, signed informed consent from the patients was not required.

Data from 219 burn patients with TBSA involvement of 20% or greater who were admitted to our pediatric burn center between 2018 and 2023 were retrospectively analyzed. Patients who continued treatment at another hospital, left the hospital before completing treatment, had age-appropriate low body mass index (BMI), showed signs of malnutrition, or had additional comorbid illnesses were excluded from the study. Patient age, gender, TBSA, cause of burn, burn depth, presence of inhalation injury, BUN and albumin levels obtained from index admission blood tests, operative intervention, need for mechanical ventilation, length of hospital stay, and ABSI and P-Baux scores were analyzed. Patients were divided into two groups: survivors and non-survivors.

Although we defined BUN and albumin levels as those measured after initial resuscitation, it should be noted that the exact timing of blood sampling varied slightly among patients due to logistical factors during admission. However, all patients were evaluated and treated according to the standardized early burn care protocol at our center, which includes immediate intravenous fluid resuscitation based on the Parkland formula using lactated Ringer's solution, clinical stabilization, and initial laboratory workup within the first 1–2 hours after admission. Since all patients were admitted within the first 8 hours post-injury and stabilized before blood sampling, we believe that the BUN/albumin ratio reflects a comparable physiological window across patients. In future prospective studies, standardized sampling time points after burn injury and more detailed fluid balance monitoring will be implemented to further improve precision.

A history of burns, burned nasal hair, coarse voice, and carbonaceous deposits in the oral cavity, as well as airway bronchoscopy findings, were evaluated to determine the presence of inhalation injury. TBSA was calculated according to the Lund-Browder diagram.^[14]

Statistical Analysis

Data were analyzed using IBM SPSS Statistics Standard Concurrent User version 26 (IBM Corp., Armonk, New York, USA). Descriptive statistics were presented as number of cases (n), percentage (%), and mean $\pm$ standard deviation values. The normal distribution of numerical variables was assessed using the Shapiro-Wilk normality test. For comparisons between two groups, the independent samples t-test was used for normally distributed data, and the Mann-Whitney U test was used when the data were not normally distributed. Relationships between categorical variables were evaluated using Pearson's chi-square test and Fisher's exact test. A p-value of <0.05 was considered statistically significant. Receiver operating characteristic (ROC) analysis was performed to determine the predictive power of BUN, albumin, and BUN/albumin ratio levels, as well as ABSI and P-Baux scores, for in-hospital mortality.

Post hoc power for ROC area under the curve (AUC) was calculated using the Hanley-McNeil variance with $\alpha=0.05$, based on class sizes (non-survivors $n=10$; survivors $n=202$). For each model, power to reject H_0 : AUC=0.5 was evaluated. The minimal detectable AUC at 80% power was also determined.

RESULTS

The study included 212 pediatric burn patients who met the

inclusion criteria. The mean age of the patients was 5.41 years (range: 1–16 years), and 62% were male. The majority of patients sustained scald burns (79.7%). The median TBSA was 27% (20–80%). A total of 40.6% of patients required surgical intervention (debridement and grafting). The requirement for mechanical ventilation was higher in the non-survivor group ($p<0.05$). The median length of hospital stay was 28 days (5–131) (Table 1).

No significant differences were observed between the two groups in terms of age, gender, or cause of burn. Statistically significant differences were found between the groups regarding TBSA (%), presence of inhalation injury, burn depth, escharotomy, and need for mechanical ventilation ($p<0.05$). The remaining variables were similar between the two groups ($p>0.05$) (Table 1).

The mean BUN levels in survivors and non-survivors were 12.54 ± 4.57 mg/dL (2–28.7) and 15.22 ± 11.38 mg/dL (2–42), respectively ($p>0.05$). The mean albumin level in non-survivors was lower than in survivors (2.33 ± 0.7 g/dL [1.4–3.5] vs. 3.88 ± 2.33 g/dL [1.9–35.8], respectively; $p<0.05$). The mean BUN/albumin ratio was higher in non-survivors than in survivors (7.6 ± 7.5 [0.71–26.25] vs. 3.41 ± 1.32 [0.44–7.83] respectively; $p<0.05$) (Table 2). The overall in-hospital mortality rate was 4.5%. Both ABSI and P-Baux scores showed statistically significant differences between the groups ($p<0.05$) (Table 2).

The receiver operating characteristic analysis results for the

Table 1. Demographic and clinical characteristics of pediatric burn patients according to survival status

	Total	Survivors	Non-survivors	p-value
Age (years)	5.41 $\pm$ 4.51 (1–16)	5.32 $\pm$ 4.51 (1–16)	7.36 $\pm$ 4.28 (1–12)	0.152
Male sex	129 (62)	121 (61.1)	8 (80)	0.324
Burn type (%)				
Electrical	4 (1.9)	4 (2)	0 (0)	0.061
Flame	37 (17.5)	32 (15.8)	5 (50)	
Scald	169 (79.7)	164 (81.2)	5 (50)	
Other	2 (0.9)	2 (1)	0 (0)	
TBSA (%)*	27.49 $\pm$ 10.27 (20–80)	26.46 $\pm$ 8.2 (20–65)	48.2 $\pm$ 21.71 (20–80)	0.002
Inhalation injury (%)	26 (12.3)	19 (9.4)	7 (70)	<0.001
Burn depth (%)				
Partial thickness	178 (84)	174 (86.1)	4 (40)	0.001
Full thickness	34 (16)	28 (13.9)	6 (60)	
Operation (%)	86 (40.6)	79 (39.1)	7 (70)	0.094
Escharotomy	38 (17.9)	33 (16.3)	5 (50)	0.018
Grafting	76 (35.8)	72 (35.6)	4 (40)	0.748
Mechanical ventilation (%)	0.22 $\pm$ 1.5 (0–16)	0.03 $\pm$ 0.49 (0–7)	4 $\pm$ 5.52 (0–16)	<0.001
Length of hospital stay (days)	28.08 $\pm$ 19.6 (5–131)	28.32 $\pm$ 19.26 (5–131)	23.1 $\pm$ 26.26 (10–69)	0.146

Non-survivors had significantly larger TBSA involvement, a higher frequency of full-thickness burns, inhalation injury, escharotomy, and a greater need for mechanical ventilation compared with survivors ($p<0.05$). Fisher's exact test, Mann-Whitney U test. Abbreviations: TBSA: Total body surface area.

Table 2. Distribution of blood urea nitrogen (BUN), albumin, BUN/albumin ratio, Abbreviated Burn Severity Index (ABSI), and Pediatric Baux (P-Baux) scores according to survival status

	Total	Survivors	Non-survivors	p-value
BUN	12.65±5.02 (2-42)	12.54±4.57 (2-28.7)	15.22±11.38 (2-42)	0.571
Albumin	3.81±2.3 (1.4-35.8)	3.88±2.33 (1.9-35.8)	2.33±0.7 (1.4-3.5)	<0.001
BUN/Albumin Ratio	3.59±2.13 (0.44-26.25)	3.41±1.32 (0.44-7.83)	7.6±7.5 (0.71-26.25)	0.009
ABSI Score	4.63±1.54 (3-11)	4.48±1.34 (3-10)	7.6±2.32 (5-11)	<0.001
P-Baux Score	33.6±15.19 (20.4-101)	32.09±12.89 (20.4-82)	64.08±24.83 (30.8-101)	<0.001

Non-survivors showed significantly lower albumin levels and higher BUN/albumin ratios, ABSI scores, and P-Baux scores compared to survivors ($p<0.05$). Mann-Whitney U test. Abbreviations: BUN: Blood urea nitrogen; ABSI: Abbreviated Burn Severity Index; P-Baux: Pediatric Baux score.

Table 3. Receiver operating characteristic (ROC) analysis of blood urea nitrogen/albumin ratio (BUN/albumin ratio), Abbreviated Burn Severity Index (ABSI), and Pediatric Baux (P-Baux) score for predicting in-hospital mortality

	BUN/Albumin Ratio	ABSI Score	P-Baux Score
Cut-off	>5.24	>4	>41
Sensitivity	66.67	100	80.0
95% CI	29.9-92.5	69.2-100.0	44.4-97.5
Specificity	90.1	63.37	81.19
95% CI	85.1-93.8	56.3-70.0	75.1-86.3
+LR	6.73	2.73	4.25
95% CI	3.6-12.5	2.3-3.3	1.8-6.5
-LR	0.37	0	0.25
95% CI	0.1-0.9		0.007-0.90
+PV	23.1	11.9	17.4
95% CI	9.0-43.6	5.9-20.8	7.8-31.4
-PV	98.4	100	98.8
95% CI	95.3-99.7	97.2-100.0	95.7-99.9
AUC	0.759	0.897	0.890
95% CI	0.696-0.815	0.848-0.934	0.840-0.929
P-value	0.019	0.0011	<0.0001

The BUN/albumin ratio cut-off value of >5.24 yielded high specificity (90.1%) but moderate sensitivity (66.7%). ABSI and P-Baux scores demonstrated higher overall predictive accuracy, with AUCs of 0.897 and 0.890, respectively. ROC: Receiver operating characteristic; AUC: Area under the curve; BUN: Blood urea nitrogen; ABSI: Abbreviated Burn Severity Index; P-Baux: Pediatric Baux score; CI: Confidence interval; +LR: Positive likelihood ratio; -LR: Negative likelihood ratio; +PV: Positive predictive value; -PV: Negative predictive value.

BUN/albumin ratio, ABSI, and P-Baux scores in predicting in-hospital mortality among pediatric burn patients are shown in Table 3. Among the three parameters, the ABSI score demonstrated the highest sensitivity (100%; 95% confidence interval [CI]: 69.2–100.0) and an excellent AUC (0.897; 95% CI: 0.848–0.934), indicating strong predictive performance. The P-Baux score also showed a high AUC (0.890; 95% CI: 0.840–0.929), with a sensitivity of 80.0% and a specificity of 81.19%. The BUN/albumin ratio, with a cutoff value >5.24,

demonstrated a statistically significant AUC of 0.759 (95% CI: 0.696–0.815; $p=0.019$), suggesting moderate discriminative ability. It showed high specificity (90.1%; 95% CI: 85.1–93.8), supporting its potential role as a valuable rule-in parameter. Its positive likelihood ratio (+LR) of 6.73 and negative predictive value (NPV) of 98.4% also indicate clinical utility in excluding low-risk patients (Table 3, Figure 1).

Cox regression analysis did not show a statistically significant effect of BUN values alone on mortality ($p>0.05$). However,

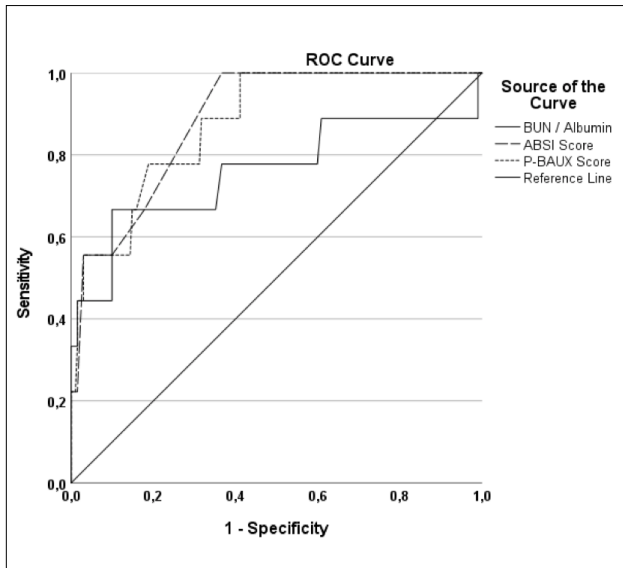


Figure 1. ROC curves of BUN/Albumin ratio and ABSI and P-BAUX score

er, the BUN/albumin ratio, ABSI, P-Baux score values were found to be statistically significant predictors of mortality ($p<0.05$) (Table 4).

Post hoc power calculations were performed to evaluate the adequacy of the study sample. With 10 non-survivors and 202 survivors, the observed AUC of the BUN/albumin ratio (0.759) corresponded to approximately 82% power to reject the null hypothesis of no discrimination ($AUC=0.5$) at a two-sided $\alpha=0.05$. The minimal detectable AUC for 80% power in this cohort was ~ 0.754 , indicating that only moderate-to-large effect sizes could be reliably detected. Both ABSI ($AUC=0.897$) and P-Baux ($AUC=0.890$) achieved near-complete power ($>99\%$). These findings suggest that although the number of events was limited, the study was sufficiently powered to support the main inference that the BUN/albumin ratio predicts mortality better than chance; however, direct comparisons between models should be interpreted with caution.

DISCUSSION

In adult burn patients, several scoring systems have been developed to predict mortality, including ABSI, R-Baux, FLAMES score (Fatality by Longevity, APACHE II score, Measured Extent of burn, and Sex), and others.^[5-15-16] Studies have shown that ABSI scoring is the most valid among adults compared to other classifications.^[3] There is no classification specifically designed to predict mortality in pediatric burn patients. Although ABSI and P-Baux scoring maintain their validity in pediatric burn patients, they typically require comprehensive clinical assessment and specialized burn care knowledge, which can limit their practicality for prompt use in emergency department settings. Our study addresses this gap by demonstrating that routine blood tests, specifically the BUN/albumin ratio, can predict mortality at the time of hospital admission.

To the best of our knowledge, this ratio represents a novel, easily obtainable marker derived from routine admission laboratory tests, potentially enhancing early mortality risk stratification and clinical decision-making in pediatric burn care, with predictive strength comparable to that of ABSI and P-Baux.

An epidemiological study of pediatric burns showed that 35.4% of patients were between aged 1–4 years, and boys were twice as many as girls (71,2%).^[17] In our study, similar to the literature, male predominance was observed, and the mean age was 5.41 years.

As demonstrated in adult studies, older age, higher total body surface area, flame burns, presence of inhalation injury, third-degree burns, need for mechanical ventilation, and operative requirements have been identified as poor prognostic factors for survival in burn patients.^[18]

A recent study demonstrated that the gender parameter in ABSI scoring does not influence mortality prediction, while the validity of the other parameters of the scoring system remains intact.^[19] Female gender is considered a poor prognostic factor for mortality in ABSI scoring. In our study, the overall mortality rate was 4.5% (10 patients), with males accounting for 80% of the deceased patients. While no statistically significant difference was observed, in light of these find-

Table 4. Multivariate logistic regression analysis for predictors of in-hospital mortality

	B	SE	Wald	p-value	Exp(B)	95% CI
BUN	-0.003	0.050	0.003	0.959	0.997	0.904-1.101
BUN/Albumin Ratio	0.206	0.046	19.836	<0.001	1.229	1.122-1.346
ABSI Score	0.667	0.179	13.948	<0.001	1.949	1.373-2.766
P-Baux Score	0.082	0.018	21.025	<0.001	1.086	1.048-1.125

BUN/Albumin ratio, ABSI score, and P-Baux score were independent predictors of mortality ($p<0.001$), whereas BUN alone was not statistically significant. BUN: Blood urea nitrogen; ABSI: Abbreviated Burn Severity Index; P-Baux: Pediatric Baux score; SE: Standard error; Exp(B): Exponentiated coefficient; CI: Confidence interval.

ings, the validity of modified ABSI scoring in pediatric patients should be investigated in future studies.^[19]

Albumin is a protein synthesized by the liver that maintains intravascular oncotic pressure. Researchers have used blood albumin levels to monitor patients' nutritional status and as a negative acute-phase reactant.^[11] Hypoalbuminemia is associated with increased morbidity and mortality in critically ill patients.^[20]

Poor nutrition and inflammation lead to decreased albumin synthesis. As albumin is also a negative acute-phase reactant, obtaining initial values upon admission (before initiating intravenous hydration and nutritional support) is important for reliable results.^[21]

In acute physiological stress, blood urea nitrogen levels increase secondary to dehydration and inflammation. Previous studies have shown that elevated BUN levels are indicators of poor prognosis in such patients.^[22] In our study, deceased patients had higher BUN levels and lower albumin levels than survivors.

Burn injuries induce a hypermetabolic state, leading to nutritional derangement. Due to factors such as hypermetabolism and increased susceptibility to infection in pediatric burn patients, accurately predicting prognosis is essential to guide appropriate treatment and clinical decision-making.^[13]

The BUN/albumin ratio enables evaluation of renal function, degree of inflammation, and nutritional status. Recent studies have shown that a high BUN/albumin ratio is associated with increased mortality in critically ill adult patients in intensive care units.^[8]

In summary, both ROC and regression analysis demonstrated that index admission values of ABSI, P-Baux score, and the BUN/albumin ratio are predictors of survival in pediatric patients with severe burns. The BUN/albumin ratio is an independent marker for predicting mortality, without being affected by factors that influence scoring systems, such as age, gender, TBSA, burn depth, and presence of inhalation injury.

Limitations

This study has several limitations that should be considered. First, it was conducted in a single-center setting, which may limit the generalizability of the findings to institutions with different patient populations, care protocols, or resource availability. Second, the retrospective design introduces potential challenges such as incomplete data documentation, selection bias, and unmeasured confounding variables. Third, although BUN and albumin levels were obtained at index admission, the exact timing of laboratory testing relative to the burn injury varied among patients. This temporal variation may have influenced the reliability of the BUN/albumin ratio in accurately reflecting physiological stress and nutritional status. Lastly, the study did not evaluate dynamic changes in BUN or albumin levels during the clinical course, which may provide more precise prognostic information than single time-point measurements.

Future prospective, multicenter studies with larger sample sizes and serial biomarker monitoring are warranted to validate and expand upon these findings.

CONCLUSION

In conclusion, this study highlights the need for rapid and readily available parameters to assess survival in pediatric burn patients. While established scoring systems such as ABSI and P-Baux remain valuable, identifying the BUN/albumin ratio as a significant predictor of mortality offers a simpler and more practical alternative.

Ethics Committee Approval: This study was approved by the Dr. Behcet Uz Pediatric Diseases and Surgery Training and Research Hospital Ethics Committee (Date: 25.05.2023, Decision No: 822).

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Authorship Contributions: Concept: A.D.P., A.E.B.; Design: A.D.P., A.E.B.; Supervision: A.O.; Resource: A.D.P., A.E.B.; Materials: A.D.P.; Data collection and/or processing: A.D.P., A.E.B.; Analysis and/or interpretation: A.D.P., A.E.B.; Literature review: A.D.P., A.E.B.; Writing: A.E.B.; Critical review: A.O.

Conflict of Interest: None declared.

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ORJİNAL ÇALIŞMA - ÖZ

%20 ve üzeri yanık alanı olan pediatrik hastalarda mortaliteyi değerlendirmede bun/ albümin oranının etkisi

AMAÇ: Bu çalışmanın amacı, %20 ve üzeri toplam vücut yüzey alanı (TVYA) yanığı olan pediatrik hastalarda kan üre azotu (BUN)/Albümin oranının hastane içi mortaliteyi öngörmedeki etkinliğini değerlendirmek ve Abbreviated Burn Severity Index (ABSI) ile Pediatrik BAUX (P-BAUX) skorları ile karşılaştırılmasını değerlendirmektir.

GEREÇ VE YÖNTEM: Yanık ünitemizde 2018-2023 yılları arasında, %20 ve üzeri TVYA yanığı ile yatırılan 212 pediatrik hastanın verileri retrospektif olarak incelendi. Hastaların demografik bilgileri, temel klinik verileri, yanık nedeni, operasyon ihtiyacı, ABSI ile P-BAUX skorları ve takip süreçleri analiz edildi. BUN/Albümin oranı, hastaneye ilk başvuru sırasında ölçülen BUN ve albümin değerleriyle hesaplandı. Veriler hastane içi mortalite ile ilişkilendirilerek değerlendirildi.

BULGULAR: Hastaların %37'si kız, %63'ü erkekti ve medyan yaş 4 yıldır. Genel mortalite oranı %4,5 olarak saptandı. ROC analizi, hem ABSI ve P-BAUX skorunun hem de BUN/Albümin oranının mortaliteyi öngörmeye benzer düzeyde anlamlı olduğu gösterildi. BUN/Albümin oranı için mortaliteyi öngören eşik değeri >5,24 olarak belirlendi. Eksitus olan hastaların medyan BUN/Albümin oranı, sağ kalan hastalara kıyasla anlamlı derecede daha yüksekti (5,27; 3,41 p = 0,009).

SONUÇ: BUN/Albümin oranının, özellikle %20 ve üzeri toplam yanık yüzey alanına sahip pediatrik hastalarda, hastane içi mortaliteyi öngörmeye istatistiksel olarak anlamlı, hızlı, kolay erişilebilir ve uygulanabilir bir biyokimyasal belirteç olduğu ortaya konmuştur. Bu bulgu, söz konusu oranın pediatrik yanık hastalarında erken dönem risk sınıflandırması amacıyla klinik uygulamalarda kullanılabilecek değerli bir prognostik araç olabileceğini düşündürmektedir.

Anahtar sözcükler: ABSI; albümin; BUN; mortalite; P-BAUX; pediatrik yanık.

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Early risk stratification in traumatic brain injury: An analysis of MEWS and rSIG scores in patients with isolated head trauma

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ABSTRACT

BACKGROUND: Traumatic brain injury (TBI) is a major cause of trauma-related morbidity and mortality worldwide. Early identification of patients at risk of clinical deterioration is essential for optimizing emergency management. The Modified Early Warning Score (MEWS) and the reverse Shock Index multiplied by the Glasgow Coma Scale (rSIG) are simple, rapidly calculable tools that may assist clinicians in early prognostic assessment. This study aimed to evaluate the prognostic performance of MEWS and rSIG in predicting poor outcomes among patients with isolated head trauma.

METHODS: This retrospective observational study included patients presenting to the emergency department of Manisa Celal Bayar University Hospital between June 2021 and June 2024 with isolated head trauma. Demographic, clinical, and laboratory data were retrieved from the hospital information system. MEWS, Shock Index (SI), reverse Shock Index (rSI), and rSIG values were calculated for each patient. Group comparisons were performed using nonparametric tests. Correlations were analyzed using Spearman coefficients. Receiver operating characteristic (ROC) curves were constructed to assess discriminative power, and binary logistic regression was used to identify independent predictors of poor outcomes, defined as intensive care unit admission and/or in-hospital mortality.

RESULTS: A total of 705 patients (65.7% male; mean age 37.2±27.0 years) were analyzed. Pathological cranial CT findings were present in 24.7%, and the overall mortality rate was 2.7%. Patients with poor outcomes exhibited significantly higher MEWS and SI values, whereas GCS, rSI, and rSIG were markedly lower (all $p < 0.001$). ROC analysis showed moderate predictive ability for rSIG (AUC=0.701) and limited discriminative power for MEWS (AUC=0.610), with optimal cut-offs of ≤ 21.35 and ≥ 0.5 , respectively. In multivariate analyses, MEWS and rSIG demonstrated independent prognostic significance for poor outcomes in separate models, with rSIG remaining significant in models excluding GCS. MEWS correlated positively with hospital stay ($r=0.385$, $p<0.001$), while rSIG showed a negative correlation ($r=-0.252$, $p<0.001$).

CONCLUSION: MEWS and rSIG are practical bedside tools that may support early risk stratification in patients with isolated head trauma. MEWS reflects early physiological deterioration, while rSIG provides complementary hemodynamic-neurological information and should be interpreted as an adjunct rather than a standalone triage instrument. Routine use of these scores may support early clinical decision-making and patient monitoring in the emergency setting when interpreted as adjuncts to standard clinical assessment.

Keywords: Traumatic Brain Injury, Head Trauma, Modified Early Warning Score (MEWS), Reverse Shock Index multiplied by GCS (rSIG), Shock Index.

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INTRODUCTION

Head trauma occurs when mechanical forces, either direct or indirect, cause injury to the cranial region.^[1] The rising prevalence of motor vehicle use, urban development, and industrialization has led to a marked increase in head trauma cases, which now constitute a leading cause of trauma-related deaths in many developed countries.^[2] Traumatic brain injury (TBI) continues to be a significant public health challenge globally, contributing heavily to mortality and long-term disability, particularly among patients experiencing multiple trauma.^[3] Falls and traffic accidents are the most common causes of TBI, whereas assaults, firearm injuries, and blunt trauma to the head are less frequent but clinically relevant etiologies.^[4] In Türkiye, traffic accidents account for 60–68% of multiple trauma cases, and head injuries rank third among trauma-related fatalities.^[5,6]

The Glasgow Coma Scale (GCS) remains the standard tool for assessing head injury severity. According to the GCS, injuries are classified as mild (14–15), moderate (9–13), or severe (≤ 8).^[7] Approximately 80% of TBI cases are mild, 10% moderate, and the remainder severe, with moderate and severe injuries carrying a significantly higher risk of long-term disability and death.^[8,9]

While GCS provides critical information about consciousness, it does not fully capture systemic physiological changes following trauma. Consequently, scoring systems such as the Modified Early Warning Score (MEWS), Revised Trauma Score (RTS), quick Sequential Organ Failure Assessment (qSOFA), and Shock Index (SI) have been developed. Among these, MEWS has shown strong predictive performance for mortality, ICU admission, and early death in TBI patients.^[10]

The Shock Index (SI), calculated as the ratio of heart rate (HR) to systolic blood pressure (SBP), is a simple tool for evaluating hypovolemic shock severity.^[11] SI values above 0.9 have been associated with increased mortality.^[12] Recognizing that hemodynamic instability may result from low SBP as well as elevated HR, the reverse Shock Index (rSI = SBP/HR) was introduced. Values of rSI below 1 have been linked to adverse outcomes, even in the absence of hypotension.^[13–15]

Given the strong correlation between GCS and mortality,^[16,17] a composite score, rSIG (rSI $\times$ GCS), has been proposed. While this measure has been reported to demonstrate high discriminative ability in predicting in-hospital mortality in broad trauma populations,^[18] its specific prognostic value in isolated head trauma remains to be further validated, as these patients may present with unique physiological challenges where neurological deterioration can occur independently of systemic hemodynamic changes.

This study aimed to evaluate the prognostic performance of MEWS and rSIG in patients presenting with isolated head trauma. Furthermore, we examined whether these scores can serve as rapid, reliable, and practical tools for early risk stratification in emergency care, acknowledging their potential role alongside established clinical assessments.

MATERIALS AND METHODS

Study Design and Ethical Approval

This retrospective descriptive study received approval from the Ethics Committee (Approval No: 20.478.486/2589, Date: September 4, 2024). This study was conducted in accordance with the Declaration of Helsinki and relevant institutional regulations. Patient data were collected from the hospital information management system (HIMS) and archived records of the Emergency Department of Manisa Celal Bayar University Faculty of Medicine, Hafsa Sultan Hospital. All personal data were anonymized to ensure confidentiality.

Study Period

Patients presenting with isolated head trauma between June 1, 2021, and June 1, 2024, were included. The study analysis was conducted between September 1, 2024, and September 1, 2025.

Inclusion Criteria

- Confirmed isolated head trauma
- No pre-existing organ dysfunction
- No systemic infection or sepsis prior to trauma

Exclusion Criteria

- Incomplete clinical or laboratory data

Data Collection

Demographic data (age, gender), vital signs (systolic and diastolic blood pressure, heart rate), laboratory values (glucose, phosphorus, glucose/phosphorus ratio), imaging results, and triage codes were recorded. The glucose/phosphorus ratio was calculated by dividing serum glucose by serum phosphorus at admission.

MEWS, SI, rSI, and rSIG scores were calculated for each patient using standard formulas.

Variables

The main parameters evaluated in the study are:

- Independent variables: Age, gender, vital signs, laboratory parameters, MEWS, GCS, SI, rSI, rSIG scores.
- Dependent variables: Brain CT result, intubation status, triage category, hospital stay, and clinical outcome (discharge, ward/ICU admission, mortality).
- Poor outcome was defined as admission to the intensive care unit and/or in-hospital mortality.

Statistical Analysis

All analyses were performed using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics included:

- Categorical variables as n (%)
- Continuous variables as mean $\pm$ SD or median (min–max)

Normality was tested using the Kolmogorov–Smirnov meth-

od. Group comparisons were conducted with the Mann–Whitney U or Kruskal–Wallis tests as appropriate. Spearman correlation evaluated relationships between continuous variables. Receiver operating characteristic (ROC) curve analysis was conducted to assess the discriminatory power of MEWS, rSIG, and biochemical parameters for predicting poor outcomes. The Youden index was used to determine optimal cut-off values, sensitivity, and specificity. Variables with statistical significance in univariate analyses were included in a binary logistic regression model to identify independent predictors of intensive care unit admission and in-hospital mortality. Considering the substantial overlap between GCS and rSIG, separate multivariate logistic regression models were constructed to prevent multicollinearity. The model's fit was evaluated using the Hosmer–Lemeshow test and Nagelkerke R^2 . A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 705 patients who presented to the emergency department with isolated head trauma between June 1, 2021, and June 1, 2024, were included in the study. Of the participants, 65.7% (n=463) were male, and 34.3% (n=242) were female. The mean age was 37.2 ± 27.0 (range, 1–98) years (Table 1).

The proportion of patients with trauma-related pathology detected on brain CT was 24.7% (n=174). The intubation rate was 4.0% (n=28). 16.3% (n=115) of patients received a red triage code, and 83.7% (n=590) received a yellow triage code. Based on outcome, 74.6% (n=526) of patients were discharged, 13.9% (n=98) were admitted to the ward, 8.8% (n=62) were admitted to the intensive care unit, and 2.7% (n=19) died (Figure 1).

In patients with trauma-related pathological findings on brain

CT, diastolic blood pressure ($p=0.033$), pulse ($p<0.001$), MEWS ($p<0.001$), shock index ($p<0.001$), and length of stay ($p<0.001$) were significantly higher, while GCS ($p<0.001$), reverse shock index ($p<0.001$), and rSIG ($p<0.001$) values were significantly lower (Table 2).

In patients who underwent intubation, diastolic blood pres-

Table 1. Patients' Sociodemographic Characteristics, Some Health Data, and Trauma Scores

Variables	n	%
Sex		
Female	242	34.3
Male	463	65.7
	Mean±SD	Median (Min- Max)
Age	37.2 ± 27.0	31 (1-98)
Systolic Blood Pressure	126.2 ± 19.7	124 (85-200)
Diastolic Blood Pressure	67.7 ± 11.3	67 (43-138)
Heart Rate	93.9 ± 20.9	90 (49-164)
Glucose	125.2 ± 51.3	111 (32-493)
Phosphate	3.4 ± 1.1	3.3 (0.7-11.6)
Glucose/Phosphate Ratio	41.3 ± 25.5	35.1 (7.7-295.0)
Scores		
GCS	14.6 ± 1.8	15 (2-15)
MEWS	1.0 ± 1.5	0 (0-8)
Shock Index (SI)	0.7 ± 0.2	0.7 (0.3-1.6)
Reverse Shock Index (rSI)	1.4 ± 0.4	1.4 (0.1-3.1)
rSIG	20.6 ± 6.0	20.9 (1.5-46.7)

Table 2. Comparison of patients' brain CT results with vitals, glucose/phosphorus ratio, scores, and length of stay

	Brain CT Results		p*
	Presence of pathology (n=174)	No pathology (n=531)	
	Mean±SD	Mean±SD	
Systolic Blood Pressure	127.0 ± 22.1	125.9 ± 18.8	0.956
Diastolic Blood Pressure	69.9 ± 13.4	67.0 ± 13.4	0.033
Pulse Rate	103.3 ± 23.8	90.9 ± 18.9	<0.001
Glucose/Phosphorus Ratio	43.3 ± 23.7	40.7 ± 26.0	0.098
GCS	13.6 ± 3.3	15.0 ± 0.3	<0.001
MEWS	1.9 ± 2.0	0.7 ± 1.2	<0.001
Shock Index	0.8 ± 0.3	0.7 ± 0.2	<0.001
Reverse Shock Index	1.3 ± 0.4	1.4 ± 0.4	<0.001
rSIG	17.6 ± 7.0	21.6 ± 5.3	<0.001
Length of Stay	6.2 ± 3.1	4.2 ± 1.5	<0.001

* Mann-Whitney U Test

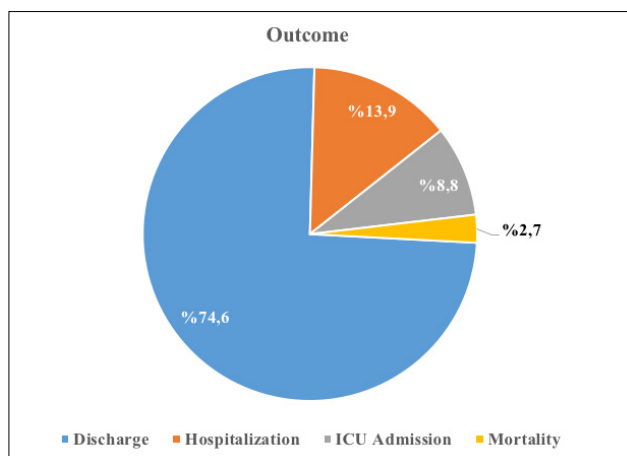


Figure 1. Outcome Distributions of Patients.

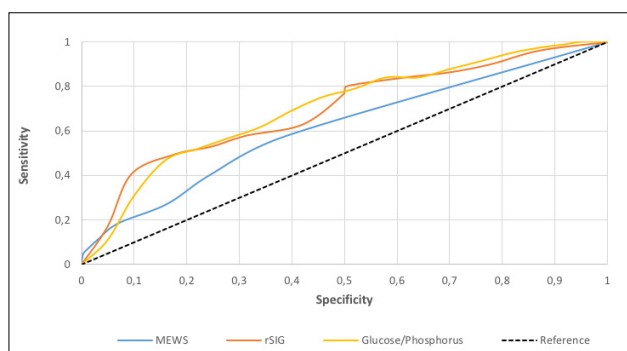


Figure 2. ROC curves of MEWS, rSIG, and glucose/phosphorus ratio for predicting poor outcomes in isolated head trauma.

sure ($p<0.001$), pulse rate ($p=0.045$), glucose/phosphorus ratio ($p<0.001$), and MEWS ($p=0.002$) were higher, whereas GCS ($p<0.001$) and rSIG ($p<0.001$) were lower (Table 3).

Patients in the red triage group exhibited significantly higher diastolic blood pressure ($p=0.001$), heart rate ($p<0.001$), glucose/phosphate ratio ($p<0.001$), MEWS ($p<0.001$), shock index ($p=0.005$), and length of hospital stay ($p<0.001$). In contrast, GCS ($p<0.001$), reverse shock index ($p=0.010$), and rSIG ($p<0.001$) were significantly lower (Table 4).

Analysis according to patient outcomes revealed that GCS ($p<0.001$) and rSIG ($p<0.001$) were highest in discharged patients and lowest in those who died. In contrast, MEWS, shock index, glucose/phosphate ratio, and length of stay were significantly elevated in patients with a fatal course ($p<0.001$, Table 5).

ROC analysis was performed to evaluate the discriminative performance of MEWS, rSIG, and the glucose/phosphorus ratio in predicting poor clinical outcomes, defined as intensive care unit admission and/or in-hospital mortality (Figure 2). The area under the curve (AUC) for MEWS was 0.610 (95% CI: 0.542–0.679; $p=0.001$), indicating limited discriminative ability. The AUC for rSIG was 0.701 (95% CI: 0.636–0.767; $p<0.001$), reflecting moderate discriminative performance. The glucose/phosphorus ratio demonstrated a statistically significant but limited discriminative ability, with an AUC of 0.697 (95% CI: 0.637–0.757; $p=0.031$). Optimal cut-off values were determined using the Youden index. The optimal threshold for MEWS was ≥ 0.5 (sensitivity: 58.0%, specificity: 60.9%), while the optimal cut-off for rSIG was ≤ 21.35 (sensitivity: 80.2%, specificity: 49.5%).

Table 3. Association of intubation status with vital signs, glucose/phosphate ratio, clinical scores, and hospital stay

	Intubation		p*
	Present (n=28) Mean±SD	Absent (n=677) Mean±SD	
Systolic Blood Pressure	137.5±28.8	125.7±19.1	0.068
Diastolic Blood Pressure	79.1±18.9	67.2±10.6	<0.001
Pulse Rate	102.3±23.1	93.6±20.7	0.045
Glucose/Phosphorus Ratio	58.8±22.3	40.6±25.3	<0.001
GCS	7.0±4.0	14.9±0.4	<0.001
MEWS	2.0±2.1	1.0±1.5	0.002
Shock Index	0.8±0.3	0.7±0.2	0.975
Reverse Shock Index	1.4±0.4	1.4±0.4	0.952
rSIG	10.2±6.4	21.0±5.6	<0.001
Length of Stay	4.3±1.8	4.7±2.2	0.373

* Mann-Whitney U Test.

Table 4. Comparison of patients' triage status with vitals, glucose/phosphorus ratio, scores, and length of stay

	Triage		p*
	Red (n=115) Mean±SD	Yellow (n=590) Mean±SD	
Systolic Blood Pressure	128.2±22.8	125.8±19.0	0.667
Diastolic Blood Pressure	71.4±13.6	69.0±10.6	0.001
Pulse Rate	102.8±23.8	92.2±19.8	<0.001
Glucose/Phosphorus Ratio	48.9±25.1	39.8±25.3	<0.001
GCS	12.8±3.9	15.0±0.2	<0.001
MEWS	1.8±2.0	0.9±1.4	<0.001
Shock Index	0.8±0.3	0.7±0.2	0.005
Reverse Shock Index	1.3±0.4	1.4±0.4	0.010
rSIG	16.8±7.2	21.3±5.5	<0.001
Length of Stay	6.1±3.1	4.4±1.9	<0.001

* Mann-Whitney U Test.

Table 5. Comparison of patients' outcomes with vital signs, glucose/phosphate ratio, clinical scores, and length of stay

	Outcome				p*
	Discharge Mean±SD	Hospitalization Mean±SD	ICU Admission Mean±SD	Mortality Mean±SD	
Systolic Blood Pressure	125.9±18.8	125.2±20.1	130.8±24.3	124.3±24.9	0.608
Diastolic Blood Pressure	67.0±10.4 ^a	67.0±10.7 ^{a,b}	73.5±16.7 ^b	71.8±10.3 ^{a,b}	0.006
Pulse Rate	90.6±18.7 ^a	105.6±24.1 ^b	101.9±21.8 ^b	98.3±28.4 ^{a,b}	<0.001
Glucose/Phosphorus Ratio	40.8±26.1 ^a	34.7±19.0 ^b	52.2±23.3 ^c	55.0±30.5 ^c	<0.001
GCS	15.0±0.2 ^a	14.9±0.5 ^a	12.3±4.2 ^b	10.7±4.8 ^c	<0.001
MEWS	0.7±1.2 ^a	2.0±2.0 ^b	1.5±1.9 ^b	2.4±2.4 ^b	<0.001
Shock Index	0.7±0.2 ^a	0.9±0.3 ^b	0.8±0.3 ^{a,b}	0.8±0.3 ^{a,b}	<0.001
Reverse Shock Index	1.4±0.4 ^a	1.2±0.4 ^b	1.3±0.4 ^{a,b}	1.3±0.5 ^{a,b}	<0.001
rSIG	21.6±5.3 ^a	18.8±6.4 ^b	16.4±7.1 ^b	15.0±8.2 ^b	<0.001
Length of Stay	4.2±1.5 ^a	6.8±3.2 ^b	5.1±2.4 ^{a,c}	6.4±3.4 ^{b,c}	<0.001

*Kruskal Wallis Test.

In multivariate logistic regression analyses performed to identify independent predictors of intensive care unit admission and/or in-hospital mortality, two separate models were constructed to avoid multicollinearity between GCS and rSIG. In Model 1, which included GCS, MEWS, and age, lower GCS values and higher MEWS values were independently associated with an increased risk of poor outcome, whereas age was not a significant predictor. This model demonstrated higher explanatory power (Nagelkerke $R^2=0.372$) and acceptable calibration (Hosmer–Lemeshow $p=0.209$). In Model 2, which included rSIG, MEWS, and age, lower rSIG values were independently associated with poor outcome,

whereas MEWS and age were not independently associated. Compared to Model 1, this model showed lower explanatory power (Nagelkerke $R^2=0.179$) with acceptable model fit (Hosmer–Lemeshow $p=0.097$) (Table 6).

Correlation analysis between length of stay and scoring systems revealed a moderate positive correlation with MEWS ($r=0.385$; $p<0.001$) and a weak positive correlation with shock index ($r=0.238$; $p<0.001$). In contrast, rSIG ($r=-0.252$; $p<0.001$) and reverse shock index ($r=-0.240$; $p<0.001$) showed a weak negative correlation with length of stay. Notably, although GCS scores significantly differed between patients with and without CT pathologies (as shown in Table 2,

Table 6. Multivariate logistic regression models for predicting poor outcome

Variable	Model 1 (GCS-based) OR (95% CI)	p*	Model 2 (rSIG-based) OR (95% CI)	p*
Age	1.005 (0.983-1.028)	0.664	1.028 (1.014-1.043)	<0.001
MEWS	1.279 (1.056-1.550)	0.012	1.004 (0.897-1.124)	0.943
GCS	0.304 (0.187-0.494)	<0.001	—	—
rSIG	—	—	0.825 (0.775-0.878)	<0.001

Model characteristics: Model 1-Nagelkerke $R^2=0.372$, Hosmer–Lemeshow $p=0.209$; Model 2-Nagelkerke $R^2=0.179$, Hosmer–Lemeshow $p=0.097$. Statistical significance was set at $p<0.05$. Due to the substantial overlap between GCS and rSIG, these variables were not included in the same model to avoid multicollinearity and the potential masking effect of GCS on rSIG.

Table 7. Correlation between patients' length of stay and clinical scores

	Length of Stay	
	r	p*
GCS	-0,067	0,076
MEWS	0,385	<0,001
Shock Index	0,238	<0,001
Reverse Shock Index	-0,240	<0,001
rSIG	-0,252	<0,001

*Spearman Correlation Test.

$p<0.001$), GCS did not demonstrate a significant linear correlation with the length of hospital stay ($r=-0.067$; $p=0.076$) (Table 7).

DISCUSSION

This study assessed the prognostic utility of the Modified Early Warning Score (MEWS) and the reverse Shock Index multiplied by Glasgow Coma Scale (rSIG) for predicting poor outcomes, defined as intensive care unit admission and/or in-hospital mortality in patients presenting to the Emergency Department with isolated head injuries.

Our results demonstrated that patients with unfavorable or fatal outcomes exhibited higher MEWS and shock index, while lower GCS, reverse shock index, and rSIG scores were associated with poor outcomes. The glucose/phosphate ratio was also higher in patients with adverse outcomes.

Traumatic brain injury (TBI) remains a major contributor to trauma-related death and long-term disability. Early risk stratification in patients with head trauma is essential for guiding treatment and monitoring strategies.^[3] Although the Glasgow Coma Scale (GCS) is widely used to evaluate consciousness, it does not fully account for hemodynamic instability or systemic physiological alterations. Therefore, integrating physiological early warning scores with GCS has become increas-

ingly valuable in recent years.^[18]

Our findings align with prior studies. Dündar et al.^[10] (2016) reported that MEWS effectively predicts mortality in trauma patients and can identify elderly patients who may require intensive care. Similarly, Gardner-Thorpe et al. found that $MEWS \geq 4$ was linked to significantly higher mortality.^[19] In our cohort, MEWS was higher among patients with pathological findings on brain CT and in those with fatal outcomes, supporting its prognostic relevance in head trauma.

The rSIG score, which combines hemodynamic and neurological assessment, has emerged as a novel tool in trauma care. Using data from the Japan Trauma Data Bank, Kimura and Tanaka demonstrated that rSIG outperforms SI or GCS alone in mortality prediction in broad trauma populations.^[18] Lai et al.^[14] also showed that patients with $rSIG < 10$ had markedly increased mortality. In our cohort, rSIG had a moderately high discriminative ability in univariate ROC analysis ($AUC=0.701$), indicating a statistically significant but moderate discriminative performance. This finding aligns with the understanding that in isolated head trauma, neurological status can deteriorate independently of systemic physiological changes. Therefore, while rSIG provides valuable clinical context, it should be interpreted as an auxiliary tool rather than a definitive triage instrument.

Shock index (SI) and reverse shock index (rSI) also showed prognostic significance. Literature suggests that $SI \geq 0.9$ correlates with higher mortality,^[12] which aligns with our results. Patients with lower rSI and consequently lower rSIG scores demonstrated closer associations with poor outcomes, highlighting the advantage of combining hemodynamic and neurological evaluation for more precise risk stratification.

While comprehensive models such as IMPACT and CRASH can predict long-term outcomes, they require advanced imaging and laboratory data, limiting rapid clinical decision-making.^[20] In contrast, MEWS and rSIG rely on readily available vital signs and GCS, allowing early bedside risk assessment. Our comparison of MEWS and rSIG indicates that MEWS may reflect overall clinical trajectory, including length of stay and morbidity, whereas rSIG provides additional discriminatory information for poor outcomes.

These findings are consistent with previous literature. Kim et al.^[21] found that MEWS predicted in-hospital mortality in head trauma patients, and Kimura et al.^[18] reported that rSIG surpassed GCS and SI in mortality prediction. Wan-Ting et al.^[22] demonstrated an AUC of 0.76 for rSIG, supporting its role in trauma risk stratification. In our cohort, rSIG had the highest discriminative ability in univariate ROC analysis (AUC=0.701), indicating a moderate but statistically significant discriminative performance. Conversely, although the glucose/phosphate ratio demonstrated a statistically significant AUC (0.697) in univariate ROC analysis, this finding reflects a limited discriminative ability and should be interpreted with caution, as the parameter was not incorporated into multivariate prognostic models.

Logistic regression analyses demonstrated that lower Glasgow Coma Scale (GCS) scores and higher Modified Early Warning Score (MEWS) values were independently associated with poor outcomes, underscoring the combined prognostic impact of neurological status and early physiological deterioration.^[23] When rSIG was evaluated in multivariate analyses excluding GCS, it showed independent prognostic significance, supporting its role as a composite parameter integrating hemodynamic and neurological information. However, when GCS and rSIG were considered simultaneously, the well-established prognostic value of GCS in traumatic brain injury appeared to attenuate the independent contribution of rSIG. This finding suggests that rSIG should not be viewed as an alternative to GCS, but rather as a complementary tool that may provide additional clinical context, particularly in patients with preserved consciousness but concomitant hemodynamic instability.

Elevated glucose/phosphate ratios in patients with severe or fatal courses may reflect systemic metabolic stress following TBI. Mechanisms such as catecholamine surge, cortisol increase, insulin resistance, intracellular phosphate depletion, and renal phosphate excretion may contribute to elevated ratios, reflecting tissue energy imbalance. Prior studies also link high glucose/phosphate ratios to worse neurological outcomes.^[24] However, in the present study, the glucose/phosphate ratio demonstrated limited discriminative performance and did not show independent prognostic value. Therefore, this parameter should be interpreted with caution in the context of early risk stratification.

This study has limitations due to its retrospective, single-center design. Data from archived records may be incomplete or inaccurate. Chronic or systemic comorbidities affecting outcomes were not included. Glucose and phosphate were measured only at admission, without longitudinal follow-up. Long-term neurological recovery was not assessed. The study focused solely on isolated head trauma, which may limit generalizability. Nevertheless, the relatively large sample size and the combined evaluation of MEWS and rSIG strengthen the descriptive findings of this study, and future multicenter prospective studies are needed to further validate these results.

CONCLUSION

In conclusion, MEWS and rSIG demonstrated statistically significant but moderate prognostic performance for predicting intensive care unit admission and/or in-hospital mortality in patients with isolated head trauma. MEWS appears to reflect overall physiological deterioration, whereas rSIG should be regarded as a complementary parameter rather than an alternative to the Glasgow Coma Scale. In contrast, the glucose/phosphate ratio showed limited discriminative ability and did not demonstrate robust prognostic value in this cohort. Therefore, these parameters should be considered adjunctive tools to support early clinical assessment rather than stand-alone triage instruments. Further prospective studies are warranted to clarify their role in emergency care.

Ethics Committee Approval: This study was approved by the Manisa Celal Bayar University Ethics Committee (Date: 04.09.2024, Decision No: 20.478.486/2589).

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ORİJİNAL ÇALIŞMA - ÖZ

Travmatik beyin hasarında erken risk sınıflandırması: izole kafa travmalı hastalarda MEWS ve rSIG skorlarının analizi

AMAÇ: Travmatik beyin hasarı (TBH), dünya genelinde travmaya bağlı morbidite ve mortalitenin başlıca nedenlerinden biridir. Klinik kötüleşme riski taşıyan hastaların erken dönemde tanınması, acil yönetimin optimize edilmesi açısından kritik öneme sahiptir. Modifiye Erken Uyarı Skoru (MEWS) ve Glasgow Koma Skalası ile çarpılmış ters Şok İndeksi (rSIG), erken prognostik değerlendirmede klinisyenlere yardımcı olabilecek, basit ve hızlı hesaplanabilen araçlardır. Bu çalışmanın amacı, izole kafa travması olan hastalarda MEWS ve rSIG'nin kötü sonlanımı öngörmedeki prognostik performansını değerlendirmektir.

GEREÇ VE YÖNTEM: Bu retrospektif gözlemsel çalışmaya, Haziran 2021-Haziran 2024 tarihleri arasında Manisa Celal Bayar Üniversitesi Hastanesi Acil Servisi'ne izole kafa travması ile başvuran hastalar dâhil edildi. Demografik, klinik ve laboratuvar verileri hastane bilgi yönetim sisteminden elde edildi. Tüm hastalar için MEWS, Şok İndeksi (SI), ters Şok İndeksi (rSI) ve rSIG değerleri hesaplandı. Grup karşılaştırmaları parametrik olmayan testlerle yapıldı. Korelasyonlar Spearman katsayıları kullanılarak analiz edildi. Skorların ayırt edici gücünü değerlendirmek amacıyla alıcı işletim karakteristiği (ROC) eğrileri oluşturuldu ve kötü sonlanımın (yoğun bakım yatışı ve/veya hastane içi mortalite) bağımsız belirleyicilerini saptamak için ikili lojistik regresyon analizi uygulandı.

BULGULAR: Toplam 705 hasta (%65.7 erkek; ortalama yaş 37.2±27.0 yıl) analiz edildi. Hastaların %24.7'sinde kraniyal BT'de patolojik bulgu saptandı ve genel mortalite oranı %2.7 idi. Kötü sonlanımı olan hastalarda MEWS ve SI değerleri anlamlı olarak daha yüksek bulunurken; GKS, rSI ve rSIG değerleri belirlenim şeklinde daha düşüktü (tümü için p<0.001). ROC analizinde rSIG için orta düzeyde ayırt edici performans (AUC=0.701), MEWS için ise sınırlı ayırt edici güç (AUC=0.610) saptandı; optimal kesme değerleri sırasıyla ≤21.35 ve ≥0.5 idi. Çok değişkenli analizlerde, MEWS ve rSIG kötü sonlanımı öngörmede ayrı modellerde bağımsız prognostik anlamlılık gösterdi; GKS'nin dışlandığı modellerde rSIG anlamlılığını korudu. MEWS, hastanede kalış süresi ile pozitif yönde korelasyon gösterirken (r=0.385; p<0.001), rSIG ile negatif yönde korelasyon saptandı (r=-0.252; p<0.001).

SONUÇ: MEWS ve rSIG, izole kafa travması olan hastalarda erken risk sınıflamasını destekleyebilecek pratik yatak başı araçlardır. MEWS erken fizyolojik bozulmayı yansıtırken, rSIG tamamlayıcı hemodinamik-nörolojik bilgi sağlamaktadır ve tek başına bir triyaj aracı olarak değil, destekleyici bir parametre olarak yorumlanmalıdır. Bu skorların rutin kullanımı, standart klinik değerlendirmeye ek olarak acil serviste erken klinik karar verme ve hasta izlemine katkı sağlayabilir.

Anahtar sözcükler: Glasgow koma skoru ile çarpılmış ters şok indeksi (rSIG); kafa travması; modifiye erken uyarı skoru (MEWS); şok indeksi; travmatik beyin hasarı.

Impact of discrepancies in radiological interpretation on forensic report outcomes: A retrospective study

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ABSTRACT

BACKGROUND: In the evaluation of forensic cases, misinterpretations of radiological imaging can directly affect not only patients' diagnostic and therapeutic processes but also judicial proceedings. This retrospective study aimed to investigate the impact of radiological re-evaluations on forensic report outcomes.

METHODS: Between July 2023 and March 2025, a total of 365 forensic cases that underwent radiological evaluation were retrospectively reviewed. For radiological examinations performed in the emergency department (plain radiography or computed tomography), interpretations made by our radiology specialist and the corresponding forensic reports were reviewed retrospectively. X-ray images requested in the emergency department that lacked a radiologist report and were evaluated by emergency physicians were subsequently interpreted by our radiology specialist; this cohort was defined as an "X-ray interpretation" group. Computed tomography (CT) images requested in the emergency department that were initially reported via teleradiology were subsequently reinterpreted by our radiology specialist; this cohort was defined as the "CT interpretation" group.

RESULTS: Following interpretations performed by our radiologist, changes in the conclusion section of forensic reports were observed in 35.3% of cases. The rate of changes in forensic report conclusions was statistically significantly higher in the "CT interpretation" group (47.8%) than in the "X-ray interpretation" group (34.2%). The likelihood of modifications in forensic report outcomes was significantly greater in cases involving three or more injury sites. The most frequent cause of error was the misinterpretation of bone fractures (84.5%), predominantly affecting the craniofacial and upper extremity regions. In fracture assessment, false-positive findings were more commonly identified on plain radiographs (73.8%), whereas false-negative findings were more frequently encountered on computed tomography scans (59.5%).

CONCLUSION: These findings demonstrate that radiological misinterpretations, particularly in the assessment of bone fractures, can significantly influence forensic report outcomes and, consequently, judicial processes. This study underscores the necessity of involving trauma-experienced radiologists in forensic imaging and highlights the importance of effective interdisciplinary collaboration between radiology and forensic medicine.

Keywords: Forensic imaging; forensic reports; forensic medicine; diagnostic errors; fracture misinterpretation.

INTRODUCTION

Any incident that results in the deterioration of an individual's physical or mental health, injury, or death due to intent, negligence, or lack of precaution is defined as a forensic case.

Traffic accidents, firearm injuries, stab wounds, falls, burns, electric shocks, and sexual assaults constitute the main types of forensic cases.^[1,2] The initial evaluation and medical documentation of forensic cases are most commonly performed in emergency departments. By nature, emergency departments

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are fast-paced, stressful, and among the busiest units in hospitals. General practitioners and emergency medicine specialists working in emergency departments frequently make use of diagnostic radiological imaging, particularly in the assessment of trauma patients. These imaging studies (especially plain radiography) are interpreted by emergency department physicians, emergency medicine specialists, or radiology residents to obtain rapid results, often due to the unavailability of radiologists, particularly outside regular working hours.^[3,4] Differences may occasionally be observed between diagnoses based on the evaluation of these images and the final radiology reports. Studies have indicated that there is a discrepancy of up to approximately 9% between the evaluations of emergency department physicians and radiology specialists.^[5] In fact, even when the same images are evaluated by multiple radiologists, different reports may be produced.^[6]

In Türkiye, according to Article 280 of the Turkish Penal Code, it is mandatory for physicians and healthcare personnel to report forensic cases they encounter to judicial authorities.^[7] Since emergency departments are the settings in which forensic cases are most frequently encountered, these notifications are often made by general practitioners or emergency medicine specialists.^[2] Emergency physicians prepare the necessary forensic documents based on anamnesis, physical examination, laboratory tests, and radiological examinations. Therefore, emergency medicine physicians and specialists must demonstrate appropriate care and attention during examinations. Unfortunately, numerous studies have shown that these prepared medical documents and forensic reports are often incorrect or incomplete for various reasons.^[8-10]

Incorrect evaluations in radiological examinations not only lead to errors in the diagnosis and treatment processes of patients in the emergency department but also result in forensic medical documents prepared in emergency settings being inaccurate or incomplete. The significance of these errors can range from a minor condition (e.g., a phalanx fracture) to a potentially life-threatening situation (e.g., pneumothorax). Modern legal systems focus on the harm inflicted on the victim and establish legal sanctions accordingly to remedy victimization and protect public safety.^[11] The role of forensic medicine specialists is to assess the impact of injuries on victims based on scientific principles, thereby supporting the legal process. Errors occurring during radiological evaluation can lead to the misclassification of injuries—such as categorizing a simple injury as serious, or vice versa—depending on the criminal laws of each country. Therefore, accurate and complete interpretation of radiological imaging is critically important for ensuring the accuracy of forensic reports, determining the perpetrator's responsibility, and restoring justice within the social order disrupted by the commission of a crime.

In this study, by retrospectively reviewing cases interpreted by our radiologist for the preparation of forensic medicine reports, we aimed to identify the characteristics of the inci-

dents, discrepancies between radiology reports, the impact of newly prepared radiology reports on forensic medicine reports, and the false-negative and false-positive diagnoses responsible for these impacts.

MATERIALS AND METHODS

Study Design and Data Source

This retrospective study was conducted at a tertiary-level university hospital. Patients who were reported as forensic cases to official authorities, had their documents prepared in the emergency department of our hospital, and were subsequently referred by official authorities to the forensic medicine outpatient clinic for the preparation of forensic reports between 15/07/2023 and 15/03/2025 were retrospectively reviewed. Cases included in the study were those in which radiological evaluations (X-ray or computed tomography [CT]) were performed by the department of radiology on images obtained in the emergency department. Cases containing uncertain expressions such as “suspicious” or “?” in emergency department reports, which did not allow for comparison, were excluded from the study.

Data were obtained from the hospital information management system, emergency department records, and official forensic report forms completed in the emergency department. For each case, the following information was recorded: patient age at the time of the incident, gender, type of incident, number of injured body regions, radiological interpretation results reported by the radiologist, the impact of these evaluations on the conclusion section of the forensic report, the injured region in which misinterpretation occurred, the incorrectly evaluated pathologies, and pathologies classified as false positive or false negative.

Definitions

In our institution, plain radiographs requested in the emergency department are initially interpreted by emergency medicine practitioners or specialists, who are responsible for the diagnostic and therapeutic management of patients. These radiographs are not routinely reported by a radiologist unless a consultation is requested by the emergency department. Computed tomography images requested in the emergency department are reported within a maximum of two hours by an external provider offering teleradiology services (outsourced outside the hospital).

In this study, X-ray images requested in the emergency department that had no radiologist report and were evaluated by emergency physicians were subsequently interpreted by a radiology specialist at our institution. The group consisting of these cases was defined as the “X-ray interpretation” group. CT images requested in the emergency department that were initially reported via teleradiology were subsequently reinterpreted by our radiology specialist; these cases were defined as the “CT interpretation” group. For the “X-

ray interpretation" group, the interpretations of emergency physicians were compared with those of our radiologist. For the "CT interpretation" group, teleradiology interpretations were compared with those of our radiologist, and the impact of these comparisons on forensic report outcomes was evaluated. Evaluations at our hospital's department of radiology were performed by an academic radiologist with expertise in trauma imaging and without time constraints.

False positivity was defined as pathologies reported during the initial assessment (by emergency physicians or via teleradiology) that were not confirmed upon interpretation by our radiologist. False negativity was defined as pathologies not detected during the initial assessment (by emergency physicians or via teleradiology) but identified upon interpretation by our radiologist. In this study, the effects of inconsistencies in radiological interpretation on forensic medicine report outcomes were analyzed.

Legal and Regulatory Framework

Forensic medicine practices vary across countries globally. In Türkiye, in addition to postmortem examinations, forensic medicine specialists prepare forensic reports for individuals reported as forensic cases in emergency departments upon the request of prosecutors or courts. The degree of injury is determined within the framework of the guideline entitled Evaluation of Criminal Injuries Defined in the Turkish Penal Code in Terms of Forensic Medicine and is submitted to the court.^[12] Articles 86 to 89 of the Turkish Penal Code define crimes committed against bodily integrity.^[7] According to these articles, injury evaluations are primarily requested with respect to two main points, on the basis of which judicial sentences are determined. The first point involves assessing whether the injury can be treated with simple medical intervention (SMI). Soft tissue traumas, such as ecchymosis and abrasions, are classified as injuries that can be treated with SMI. In contrast, pathologies such as extremity or facial (viscerocranium) bone fractures, penetrating or cutting injuries extending into muscle tissue, and isolated rib fractures (without accompanying pneumothorax or hemothorax) are classified as injuries that cannot be treated with SMI (i.e., non-SMI). The second point concerns whether the injury causes a life-threatening condition (LTC), which constitutes the most severe injury group (12). Pathologies such as skull (neurocranium) bone fractures, pneumothorax, penetrating injuries to the abdominal or thoracic cavities, liver lacerations, and lung parenchymal contusions are classified within this group. Forensic medicine specialists evaluate forensic cases using emergency department examination notes, preliminary forensic reports prepared in the emergency department, laboratory findings, and radiological imaging. Based on these medicolegal evaluations, their reports specify whether the injury is classified as "SMI or non-SMI" and "LTC or non-LTC."

Ethical Approval

Ethical approval for the study was obtained from the Institutional Non-Interventional Research Ethics Committee (decision dated 26.03.2025; No. 2025/437). All stages of the research were conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as means and standard deviations for continuous variables, and as frequencies and percentages for categorical variables. The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to assess the normality of data distribution. For comparisons between two independent groups, the independent samples t-test was used for normally distributed data. Categorical variables were compared using the Chi-square and Fisher's exact tests. A p-value of <0.05 was considered statistically significant.

RESULTS

In this study, radiological evaluation was performed in an initial total of 365 cases. Interpretations were based on X-ray images in 56.2% of cases (n=205) and CT images in 43.8% (n=160). When compared with forensic report outcomes based on emergency department medical records, our X-ray or CT interpretations resulted in changes affecting the forensic report outcome in 35.3% of cases (n=129), while no change was observed in 53.4% (n=195). In 11.2% of cases (n=41), the initial evaluation was described as "suspicious," making it unclear whether a change had occurred. Cases

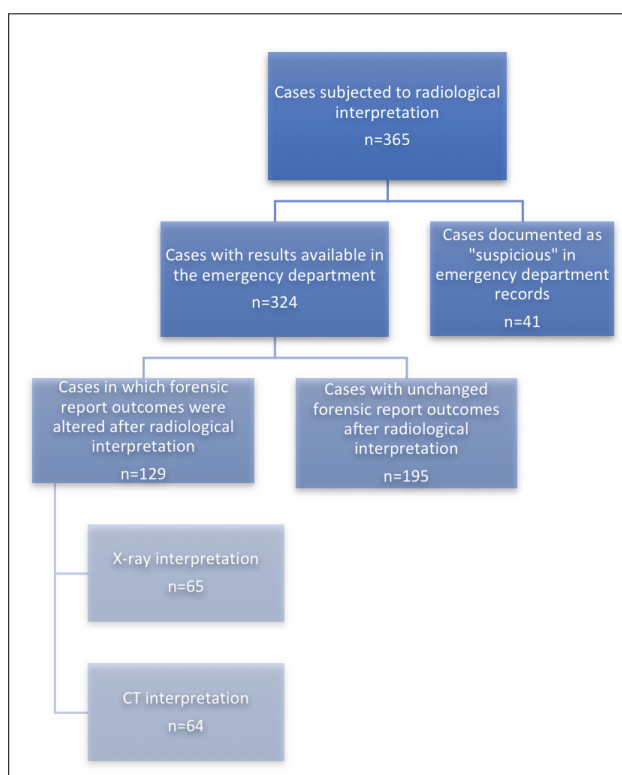


Figure 1. Flowchart of case distribution.

marked as “suspicious” were excluded from the study, and the analysis was continued with 324 cases (Fig. 1).

The characteristics of both groups, stratified according to whether a change occurred in the forensic report outcome, are presented in Table 1. Changes in forensic report outcomes occurred in 34.2% of the “X-ray interpretation” group (n=65/190) and in 47.8% of the “CT interpretation” group (n=64/134), with a statistically significant difference between the groups (p=0.014) (Table 2). The evaluations affected the determination of whether the injury was classified as “SMI or non-SMI” in 86.8% of cases (n=112) and as “LTC or non-LTC” in 13.2% of cases (n=17). The most common pathology leading to a change in the forensic report outcome was the

misinterpretation of bone fractures, accounting for 84.5% of cases (n=109). This was followed by the misinterpretation of penetrating injuries involving muscle and fascia in 7% of cases (n=9) (Fig. 2). The most frequently affected injury regions were the head-face region in 31% of cases (n=40) and the upper extremity in 25.6% of cases (n=33) (Fig. 3).

Among the most frequently misinterpreted bone fracture cases, 61.5% (n=67) were false-positive evaluations. Within this group, the most common false positives were nasal bone fractures (25.4%, n=17), metacarpal fractures (16.4%, n=11), and radius fractures (11.9%, n=8). False-negative evaluations accounted for 38.5% of cases (n=42), most frequently involving nasal bone fractures (31.0%, n=13), followed by rib

Table 1. Comparison of characteristics between study groups

Variable	All Cases (n=324) n (%)	Cases With Changes in Report Outcome (n=129) n (%)	Cases With Unchanged Report Outcome (n=195) n (%)	P value*
Sex				
Male	246 (75.9)	101 (78.3)	145 (74.4)	0.417§
Female	78 (24.1)	28 (21.7)	50 (25.6)	
Age (years)				
<18	29 (8.95)	14 (10.9)	15 (7.7)	0.621#
18-64	272 (83.95)	106 (82.1)	166 (85.1)	
≥65	23 (7.1)	9 (7)	14 (7.2)	
Type of injury				
Assault	190 (58.6)	67 (51.9)	123 (63.1)	0.129#
Traffic accident	97 (29.9)	44 (34.1)	53 (27.2)	
Other ^μ	37 (11.5)	18 (14.0)	19 (9.7)	
Number of injured areas				
Mean±SD ¹	3.01±2.01	3.4±2.1	2.7±1.8	0.003 ¹
<3	165 (50.9)	53 (41.1)	112 (57.4)	0.004§
3≥	159 (49.1)	76 (58.9)	83 (42.6)	

*p<0.05 was considered statistically significant. § χ^2 test. #Fisher's exact test. ^μIncludes falls, firearm injuries, and stab/cut injuries. ¹Independent samples t-test.

Table 2. Rates of changes in forensic report outcomes

	All Cases (n=324) n (%)	Cases With Changed Report Outcomes (n=129) n (%)	Cases With Unchanged Report Outcomes (n=195) n (%)	OR	95% CI	P value*
Type of Evaluation						
X-ray interpretation	190 (58.6)	65 (50.4)	125 (64.1)	1.758	1.118-2.764	0.014
CT interpretation	134 (41.4)	64 (49.6)	70 (35.9)			
Total	324 (100)	129 (100)	195 (100)			

*p<0.05 was considered statistically significant.

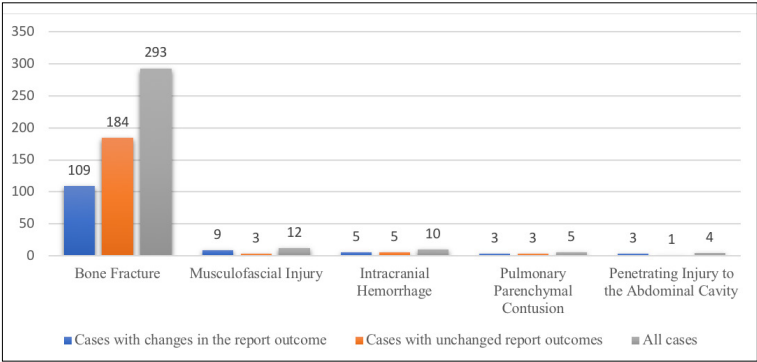


Figure 2. Distribution of injury types among the study groups.

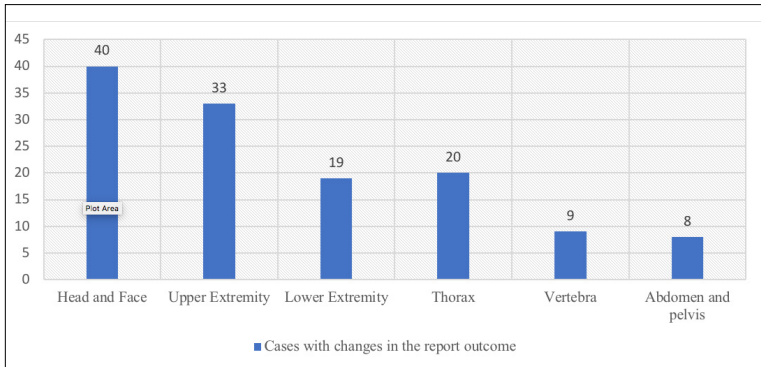


Figure 3. Distribution of cases with changes in forensic report outcomes according to injury regions.

Table 3. Distribution of false-negative and false-positive bone fracture evaluations

False-Negative Interpretations (n=42)			False-Positive Interpretations (n=67)		
	n	%		n	%
Nasal bone	13	31.0	Nasal bone	17	25.4
Rib	11	26.1	Metacarpal	11	16.4
Vertebra	5	11.9	Radius	8	11.8
Metacarpal	3	7.1	Phalanx	7	10.4
Metatarsal	3	7.1	Rib	4	6.0
Skull	2	4.8	Metatarsal	4	6.0
Phalanx	1	2.4	Vertebra	3	4.5
Calcaneus	1	2.4	Skull	3	4.5
Coccyx	1	2.4	Talus	2	3
Scaphoid	1	2.4	Calcaneus	2	3
Sacrum	1	2.4	Humerus	1	1.5
			Coccyx	1	1.5
			Sacrum	1	1.5
			Tibia	1	1.5
			Patella	1	1.5
			Scaphoid	1	1.5
Total	42	100	Total	67	100

Table 4. Distribution of bone fracture interpretations

	All Cases (n=109) n (%)	False-Positive Interpretations (n=67) n (%)	False-Negative Interpretations (n=42) n (%)	OR	95% CI	P value*
Type of Evaluation						
X-ray interpretation	65 (59.6)	48 (71.6)	17 (40.5)	3.715	1.647-8.381	0.001*
CT interpretation	44 (40.4)	19 (28.4)	25 (59.5)			
Total	109 (100)	67 (100)	195 (100)			

*p<0.05 was considered statistically significant.

fractures (23.8%, n=10) and vertebral fractures (9.5%, n=4) (Table 3).

It was determined that 73.8% of false-positive bone fracture assessments (n=48/67) occurred in the X-ray interpretation group. In contrast, 59.5% of false-negative assessments (n=25/42) occurred in the CT interpretation group, and this difference between the groups was statistically significant (p=0.001) (Table 4).

DISCUSSION

The number of radiological examinations performed worldwide is increasing steadily. This increase has led to a growing workload for radiologists.^[13,14] Increased workload, an insufficient number of radiology specialists, the lack of radiologist interpretation of radiographs in emergency departments—particularly outside regular working hours—and the interpretation of CT scans by radiologists outside the hospital with insufficient clinical information about the patient (such as in teleradiology) result in errors and incomplete assessments in radiology reports. Such errors not only affect patient diagnosis and treatment, but, in forensic cases, also influence the forensic documentation prepared for the individual.^[15,16] Errors that affect the determination of injury severity may result in either a loss of rights for the victim or unjust gain, thereby altering the judicial process of the forensic case.^[17]

A review of the literature shows that evaluations of medico-legal errors occurring in clinical cases remain limited. Most studies have focused on radiological diagnostic and clinical management errors made by emergency departments, clinical specialties, and radiology residents. Mattsson et al.^[18] reported a discrepancy rate of 20.35% between initial and final radiological evaluations. Nogueira et al.^[19] found a 27% discrepancy in their study of trauma patients, the majority of whom underwent thoracic CT scans. Robinson et al.^[20] reported a discordance rate of 35.3% in CT imaging of patients referred to the emergency department, while Eurin et al.^[21] identified a 47% rate of missed diagnoses in CT scans among trauma patients. Other studies have reported error rates below 20%.^[22-24] Most studies state that incorrect or

incomplete evaluations have a low clinical impact on patients or do not significantly affect patient mortality or morbidity.^[25,26] However, it is observed that the error rates reported in these studies are inconsistent with each other. Differences in the specialties compared, the inclusion of non-trauma patients in some studies, the use of different radiological imaging techniques, the exclusion of overdiagnoses in certain studies, and heterogeneity in professional experience have led us to believe that these factors may account for the inconsistent results. However, forensic cases need to be evaluated separately from clinical effects. In forensic cases, the severity of the injury sustained by an individual is of significant importance. For example, if a non-displaced phalangeal or metacarpal bone fracture that was not diagnosed in the emergency department results in splinting and immobilization of the patient's finger or hand, with orthopedic outpatient follow-up recommended, no issues would typically arise regarding clinical management. Nevertheless, the presence or absence of a bone fracture constitutes a pathological condition that must be clearly established from a medicolegal perspective, as it directly influences the assessment of injury severity. In this study, the impact rate of radiological interpretations on forensic report outcomes was found to be 35.3%. Although this rate approaches the upper limit of misdiagnosis rates reported in the literature, it is markedly higher than the reported impact of erroneous radiology reports on patients' clinical management. Therefore, these findings demonstrate that, in forensic cases, radiological examinations should always be evaluated by radiology specialists with expertise in trauma to ensure the accurate administration of justice.

One important aspect of our study that should not be overlooked is the impact of teleradiology. In the CT interpretation group, the initial reports used for comparison were teleradiology reports. Although studies in the literature have reported discrepancy rates of up to approximately 6% between teleradiology interpretations and those of in-hospital radiologists,^[27] Vendrell et al.^[28] reported a discrepancy rate of 21.4% in their double-reading study. In the CT interpretation group of our study, misinterpretations affecting the forensic report outcome were identified in 47.7% of cases.

This high rate suggests that, in forensic cases, interpretations performed by in-hospital radiologists—who are more likely to work in close coordination with clinicians, have access to complete emergency department records, and engage in direct consultation with clinicians when necessary—would ensure a more accurate and appropriate workflow.

When examining factors influencing forensic report outcomes in our study, age, gender, and type of incident were found to have no significant effect. Consistent with our findings, several studies have reported that gender is not a contributing factor to radiological assessment errors.^[29,30] However, there is no clear consensus regarding the impact of age. While our results align with some studies,^[29,30] Banaste et al.^[22] reported that age over 30 years, and Mattsson et al.^[18] reported that age over 65 years, were significant factors associated with radiological diagnostic errors. With respect to the type of incident, Şener et al.^[29] similarly reported no statistically significant difference, in line with the findings of our study.

In this study, the number of injured regions was significantly higher in the group in which the forensic report outcome was affected. Similarly, Banaste et al.^[22] reported that having more than two injured body regions was a contributing factor to missed diagnoses. In addition, studies that evaluated the Injury Severity Score (ISS) have shown significantly higher ISS values in groups with missed or misinterpreted diagnoses.^[21,31,32]

Although the ISS was not calculated in our study, the significantly higher number of injured regions demonstrates a similar pattern. This finding suggests that factors such as physicians prioritizing severe injuries requiring urgent treatment, thereby overlooking moderate or minor injuries, or the presence of multiple injured regions diverting the physician's attention may have contributed to this outcome.

Previous studies have indicated that radiological errors occur more frequently in the evaluation of CT images. Gergenti et al.^[33] reported that the most frequent radiological inconsistencies were observed in CT images (59.8%), followed by radiography (25.3%). Mattsson et al.^[18] identified inconsistencies in 17.91% of radiographic images and 25.29% of CT images, while Tomich et al.^[34] reported that 58% of errors occurred in CT images and 39% in radiographic images. Although other radiological evaluations (such as ultrasonography and magnetic resonance imaging [MRI]) were not included in our study, the error rate in CT evaluations was found to be significantly higher. Multislice radiological imaging modalities such as CT appear to be associated with more frequent misinterpretations than radiography due to anatomical coverage, greater anatomical complexity, motion artifacts, and image distortion caused by prior surgical materials.

In this study, the anatomical regions most commonly associated with diagnostic errors were the head-face region and the upper extremity, respectively. Kim et al.^[35] reported that diagnostic errors most frequently occurred in the extremities,

whereas Selçuk et al.^[36] identified thoracic CT images as the most common site, and Yang et al.^[37] reported the extremity and pelvic regions as the most frequently affected areas. Taken together, the lack of a consistent pattern suggests that the use of heterogeneous study populations and different imaging techniques contributes to variability in reported results.

In emergency departments, fracture detection using radiography is a commonly employed method in trauma patients with either high- or low-energy mechanisms of injury, particularly in cases involving the extremities.^[38] CT examinations, on the other hand, are more frequently used for injuries involving the skull, thorax, or pelvis.^[36] According to the literature, approximately 80% of diagnostic errors in emergency departments are attributable to failures in diagnosing fractures.^[39] Similarly, missed fractures on radiographs are considered the most common cause of diagnostic discrepancies between initial interpretations by emergency department personnel or radiology residents and final interpretations by radiologists.^[21,33,39] In a large-scale teleradiology study, bone fractures and dislocations were identified as the most common traumatic interpretation errors.^[40] Consistent with these findings, the most frequent misdiagnosis affecting forensic report outcomes in our study involved bone fractures. In parallel with these bone fracture misinterpretations, the forensic medicine specialists' decisions regarding whether the injury involved SMI were the most frequently subject to change.

With respect to diagnostic errors related to bone fractures, the literature presents varying results. While some studies report no clear predominance of a specific anatomical region,^[30] others indicate that the upper extremity,^[3] lower extremity,^[41] or facial bones^[33] are more frequently subject to misinterpretation. When examining which bone fractures were most commonly misinterpreted, Geyer et al.^[42] reported that missed fractures most frequently involved the ribs, vertebrae, and nasal bones. Tomich et al.^[34] stated that, on radiographs, hand bone fractures were the most commonly misinterpreted, whereas on CT scans, craniofacial fractures were most frequently misinterpreted. In the present study, the most frequently misinterpreted fracture involved the nasal bone, followed by the ribs and metacarpal bones. The anatomical regions or bones involved vary across studies, and one factor influencing this variability appears to be the distribution of case types within each study. Studies with a higher prevalence of assault cases are more likely to evaluate the nasal region or hand bones, whereas studies with a higher incidence of motorcycle or non-vehicle traffic accidents more frequently assess lower extremity bones due to the nature of the injury mechanisms. This may cause certain bones to be more prominent in misinterpretation analyses. Another contributing factor is the type of radiological imaging used. In the cases included in this study, plain radiography was predominantly used for evaluating the nasal region and extremities. According to the literature, although nasal bone assessments are frequently performed using CT, nasal radiographs are still

used to a considerable extent.^[43] The limited number of views available in plain radiography can be misleading for inexperienced physicians. Therefore, this study demonstrates the need for emergency department personnel to enhance their knowledge and experience in interpreting direct radiographs, as well as for forensic medicine specialists to collaborate with radiologists in the evaluation of such cases. Moreover, artificial intelligence (AI) technology offers an alternative approach. Previous studies have shown that AI-based systems used in the evaluation of bone fractures provide highly sensitive and specific results.^[44,45] Such systems may offer additional support for emergency physicians, particularly in situations where a radiologist is not readily available.

In CT image interpretation, radiologists may focus on clinically more significant findings, such as epidural or subdural hemorrhage or hemothorax, which can result in missed diagnoses of relatively minor findings, including non-displaced nasal bone fractures or rib fractures located away from the suspected area of bleeding. Consistent with this observation, our study identified a false-negative interpretation rate of 56.8% in the CT interpretation group. Similarly, Nogueira et al.^[19] reported a false-negative rate of 59.9% in CT imaging, and McCreddie et al.^[46] found that 61% of CT interpretation errors were due to false-negative findings. These rates are similar in CT image evaluations.

In contrast to CT, 73.8% of the errors in plain radiographs that affected forensic report outcomes in our study were attributable to false-positive interpretations. The literature reports substantial variability in false-positive rates for plain radiography, with some studies identifying predominantly false-positive errors,^[3] while others report a higher prevalence of false-negative errors.^[24,30] Kinnersley et al.^[47] found that emergency department personnel interpreting plain radiographs made 47% false-positive and 53% false-negative errors. The high rate of false-positive interpretations observed in our study suggests that this finding may be related to a tendency among younger and less experienced emergency department physicians to overdiagnose, possibly due to concerns about missing injuries or facing potential malpractice allegations. If these patients present to outpatient clinics (such as orthopedics or neurosurgery) after their emergency department visit, the correct diagnosis can be clarified. However, if no follow-up care is sought, the only means of determining the actual diagnosis is through the medical documentation and radiology reports prepared in the emergency department. This underscores the critical importance of accurate radiological evaluation. The false-positive interpretations of bone fractures on plain radiographs observed in this study may be attributable to the misinterpretation of normal anatomical variants or prior surgical procedures (such as suture lines and previous rhinoplasty in the nasal region, as well as unfused epiphyseal plates or old fractures in the extremities). These images, when combined with physicians' fear of missing a diagnosis, appear as misleading findings. Şener et al.^[29]

reported that emergency department physicians missed nasal bone fractures at a rate of 1.9% while producing false-positive interpretations at a rate of 24.5%. These findings support our perspective by indicating that overdiagnosis occurs at a rate approximately 12 times higher, particularly in evaluations of the nasal region. Although overdiagnosis was not identified as one of the most common radiological errors in the study by Kim and Mansfield,^[48] the present study suggests that this may not apply to the evaluation of certain bone fractures, highlighting the need for increased caution when assessing these specific anatomical regions.

Limitations

First, this study is inherently limited by its retrospective design. Additionally, being conducted in Türkiye at a single center may limit the generalizability of the findings because of differences in legal frameworks and forensic reporting practices across countries; nevertheless, the study clearly demonstrates the potential impact of radiological interpretation quality on the accuracy of forensic medical reports. The single-center design likely influenced the distribution of forensic case types, reflecting the regional characteristics of the study setting. Because the evaluations were based on radiological imaging requested in the emergency department, patients for whom no imaging was obtained during their emergency visit, as well as those who underwent radiological examinations at another institution after discharge, were not included in the analysis. Furthermore, the use of a single radiologist experienced in forensic radiology for image interpretation constitutes a limitation, as interobserver variability could not be assessed. Detailed information regarding the years of radiological experience of the initial readers (emergency physicians or teleradiology radiologists) was not available, which precluded comparisons aimed at elucidating potential causes of the observed findings. In addition, the absence of objective data on influential factors, such as the professional experience of emergency physicians performing the initial evaluation and the emergency department workload on the day of presentation, further limits interpretation of the underlying causes of these findings.

CONCLUSION

This study demonstrates that, unlike in routine medical practice, the most critical element in forensic cases is the establishment of an accurate diagnosis. The findings emphasize that radiological images in all forensic cases should be evaluated by in-hospital radiologists with expertise in trauma imaging and that close interdisciplinary collaboration between radiologists and forensic medicine specialists can reduce errors in forensic reporting. The presence of three or more injured regions was identified as a factor influencing forensic report outcomes in radiological evaluations. The most common errors in the radiological assessment of forensic cases were related to the evaluation of bone fractures. These errors affect not only patients' diagnosis and treatment processes but also the out-

comes of forensic reports. This issue does not arise solely from false-negative assessments; false-positive evaluations are also frequently observed, particularly in plain radiographs. Accordingly, this study recommends that emergency physicians and radiologists interpreting radiological images in forensic cases exercise increased caution, especially when evaluating the nasal region and hand bones, and further enhance their knowledge and experience in these areas.

Ethics Committee Approval: This study was approved by the Buca Seyfi Demirsoy Hospital Ethics Committee (Date: 26.03.2025, Decision No: 2025/437).

Peer-review: Externally peer-reviewed.

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ORİJİNAL ÇALIŞMA - ÖZ

Radyolojik yorumlamadaki farklılıkların adli rapor sonuçları üzerindeki etkisi: Retrospektif bir çalışma

AMAÇ: Adli vakaların değerlendirilmesinde, radyolojik görüntülemedeki yanlış yorumlamalar yalnızca hastaların tanı ve tedavi süreçlerini değil, aynı zamanda adli süreçlerini de doğrudan etkilemektedir. Bu retrospektif çalışma, radyolojik yeniden değerlendirmelerin adli raporlar üzerindeki etkisini araştırmayı amaçlamıştır.

GEREÇ VE YÖNTEM: Temmuz 2023 ile Mart 2025 tarihleri arasında, radyolojik değerlendirmeye tabi tutulan toplam 365 adli vaka retrospektif olarak incelenmiştir. Acil serviste yapılan radyolojik incelemeler (düz röntgen veya bilgisayarlı tomografi) için, radyoloji uzmanımızın yaptığı yorumlar ve vakaların adli raporları geriye dönük olarak incelenmiştir. Acil serviste istenen ve radyolog raporu bulunmayan, acil servis hekimleri tarafından değerlendirilen röntgen görüntüleri daha sonra radyoloji uzmanımız tarafından yorumlanmıştır. Bu grup 'X-ray yorumlaması' olarak tanımlanmıştır. Acil serviste istenen ve başlangıçta teleradyoloji yoluyla raporlanan BT görüntüleri daha sonra radyoloji uzmanımız tarafından yeniden yorumlanmıştır. Bu grup 'BT yorumlaması' olarak tanımlanmıştır.

BULGULAR: Radyoloğumuz tarafından yapılan yorumlamalar sonucunda, vakaların %35.3'ünde adli raporların sonuç bölümünde değişiklik meydana gelmiştir. 'BT yorumlama' grubunda (%47.8), 'X-ray yorumlama' grubuna (%34.2) kıyasla istatistiksel olarak daha yüksek oranda adli rapor sonucunda değişiklik meydana gelmiştir. Yaralanma bölgesi sayısı üç ve üzerinde olan olgularda adli rapor sonucunun değişme olasılığı anlamlı düzeyde yüksek bulunmuştur. En sık görülen hata nedeni, özellikle kraniyofasiyal ve üst ekstremité bölgelerinde gözlemlenen kemik kırıklarının yanlış yorumlanmasıdır (%84.5). Kemik kırığı değerlendirmesinde yanlış pozitif sonuçlar daha çok direkt grafilere (%73.8), yanlış negatif sonuçlar ise bilgisayarlı tomografilerde (%59.5) ortaya çıkmıştır.

SONUÇ: Bu bulgular, özellikle kemik kırıklarının değerlendirilmesinde radyolojik yanlış yorumlamaların, adli raporların sonuçlarını ve dolayısıyla adli süreçleri önemli ölçüde etkileyebileceğini göstermektedir. Çalışma, adli görüntülemeye travma konusunda deneyimli radyologların dahil edilmesinin gerekliliğini vurgulamakta ve radyoloji ile adli tıp disiplinleri arasında etkili işbirliğinin önemini ortaya koymaktadır.

Anahtar sözcükler: Adli görüntüleme; adli raporlar; adli tıp; kırık yanlış yorumlaması; tanı hataları.

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Emergency cesarean section in pregnant women with severe pulmonary hypertension: the potential role of extracorporeal life support

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ABSTRACT

BACKGROUND: The aim of this study was to present our institutional experience with periprocedural management of emergency cesarean section (CS) operations and maternal and fetal cardiac complications in pregnant women with pulmonary hypertension (PH).

METHODS: Thirteen patients who were diagnosed with PH during pregnancy and/or prior to pregnancy according to European Society of Cardiology (ESC) criteria, and who were referred to our hospital with a decision for emergency CS from an external center, were included in the study. For patients who underwent urgent surgery, the following data were recorded: demographic characteristics, time of diagnosis, treatments for pulmonary hypertension used before pregnancy, during pregnancy, and/or after CS, arterial blood gas values, pulmonary and systemic pressure values after induction and at the 12th postoperative hour, extracorporeal membrane oxygenation (ECMO) requirements, time to extubation, length of intensive care stay, and mortality rates.

RESULTS: Eight of the 13 patients were diagnosed with idiopathic pulmonary arterial hypertension (IPAH). The mean systolic systemic arterial pressure (BPs), systolic pulmonary arterial pressure (PAPs), and mean pulmonary arterial pressure were 130 ± 14.2 mmHg, 93 ± 28 mmHg, and 52 ± 17 mmHg, respectively. Six of the 13 patients required ECMO support. The one-month mortality rate was 46%.

CONCLUSION: Pregnancy in women with PH is associated with significant maternal morbidity and mortality. If the underlying etiology is IPAH, the risk of mortality is higher than in other forms of PH. Mechanical circulatory support devices, including ECMO, may serve as a temporary bridge to lung transplantation in selected cases. Therefore, early diagnosis of IPAH, timely referral of patients to specialized centers, and planning of these operations by a multidisciplinary team consisting of cardiologists, gynecologists, and cardiac anesthesiologists are necessary.

Keywords: Extracorporeal membrane oxygenation (ECMO) support; emergency cesarean section; pulmonary hypertension.

INTRODUCTION

According to the 2022 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines, pulmonary hypertension (PH) is defined as an increase in mean pulmonary arterial pressure (PAPm) ≥ 20 mmHg at rest, as assessed by

right heart catheterization (RHC). Pulmonary arterial hypertension (PAH) refers to pre-capillary PH and is characterized by a pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg and a pulmonary vascular resistance (PVR) > 2 Wood units (WU). Idiopathic pulmonary arterial hypertension (IPAH) is included in this category. Post-capillary PH is defined by a

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PAPm ≥ 20 mmHg and a PAWP > 15 mmHg.^[1,2]

Pregnancy induces significant physiological changes, including increased blood volume, stroke volume, and cardiac output, along with decreased hemoglobin levels and total PVR.^[3,4] Although these physiological changes typically revert to pregestational levels within six months postpartum, they impose substantial cardiovascular stress.^[3,5] Pregnant women with PH, particularly those with IPAH, are at high risk of cardiac failure due to increased cardiac output (CO) and pulmonary arterial pressure (PAP), which may lead to right ventricular failure. Severe complications such as refractory hypoxia, hemodynamic instability, and right ventricular failure can occur, especially in patients undergoing emergency cesarean section (CS).^[6]

The World Health Organization (WHO) classifies pregnancy in women with PH as a Class IV risk condition and strongly recommends pregnancy avoidance in such cases.^[1] Despite these substantial risks, some women with PH choose to proceed with pregnancy. Therefore, the importance of early diagnosis and PH-specific treatment is emphasized for pregnant women with PH.^[6]

Over the past decade, advancements in PAH-targeted therapies have improved the quality of life and prognosis of affected patients.^[6] However, it remains uncertain whether these improvements have translated into reduced maternal mortality. In cases of perioperative right ventricular failure or respiratory failure unresponsive to medical therapy and mechanical ventilatory support, extracorporeal life support (ECMO) should be considered. High-risk CS procedures should be performed in specialized centers with multidisciplinary teams comprising cardiologists, pulmonologists, obstetricians, and cardiac anesthesiologists.^[6-8]

This study aims to present our institutional experience in the periprocedural management of emergency CS in pregnant women with PH, with a particular focus on maternal and fetal cardiac complications.

MATERIALS AND METHODS

This retrospective study included 13 pregnant women diagnosed with PH (either prior to pregnancy or during pregnancy) according to ESC criteria who underwent emergency CS between January 2013 and 2020 at our institution. All patients were referred from external centers; seven underwent CS due to fetal distress, and six due to severe maternal hypoxia. The study adhered to the principles of the Declaration of Helsinki, and ethics committee approval (No. 2021/7/497) was obtained. Informed consent was obtained from all participants.

Demographic data, PH treatment before pregnancy and after CS, arterial blood gas measurements, pulmonary and systemic arterial pressures, ECMO requirements, duration of intubation, intensive care unit (ICU) length of stay, and mortality rates were documented.

Continuous intraoperative monitoring included five-lead electrocardiography (ECG), pulse oximetry, invasive blood pressure measurement (radial/brachial artery), and urine output. General anesthesia (GA) was administered to all patients. Following standard sterile preparation and draping, induction was achieved using propofol (1-1.5 mg/kg) and rocuronium (0.6-0.8 mg/kg). After delivery, fentanyl (1.5 mcg/kg) was administered. Additionally, 20 IU of oxytocin (Synpitan®) was infused intravenously in 500 cc of 5% dextrose. Anesthesia maintenance was achieved with 3.0-6.0% desflurane without nitrous oxide. Mechanical ventilation settings included an FiO₂ of 100%, tidal volume of 6-8 mL/kg, respiratory rate of 16/min, and positive end-expiratory pressure (PEEP) of 3-5 cmH₂O, adjusted according to blood gas analysis.

Perioperative transesophageal echocardiography (TEE) was routinely performed to assess right ventricular volume, tricuspid annular plane systolic excursion (TAPSE), and overall cardiac function. Central venous catheterization (8.5 Fr; Arrow International Inc., PA, USA) via the right internal jugular vein was performed using the Seldinger technique, followed by pulmonary artery catheterization (7F Swan-Ganz; Edwards Lifesciences, USA) for continuous PAP monitoring. Hemodynamic parameters were recorded after delivery, when patients were most stable.

Intraoperative values were recorded during periods of maximal hemodynamic stability and included systolic systemic arterial pressure (BPs), diastolic systemic arterial pressure (BPd), mean pulmonary arterial pressure (PAPm), systolic pulmonary arterial pressure (PAPs), the PAPs/BPs ratio, and ECG findings. Blood gas parameters (pH, PaO₂, PaCO₂, and SaO₂) were measured following anesthesia induction. Postoperative hemodynamic and respiratory parameters were reassessed 12 hours after surgery.

Postoperatively, all patients were transferred to the ICU under orotracheal intubation. Hemodynamic and respiratory parameters were reassessed at 12 hours postoperatively. ECMO was instituted in patients experiencing severe right ventricular failure, using peripheral veno-arterial (V-A) or veno-venous (V-V) approaches based on hemodynamic status. ECMO was applied in six patients. Two of these patients experienced persistent hemodynamic and respiratory instability despite maximal medical therapy after surgery; therefore, V-A ECMO was preferred. The remaining four patients developed respiratory instability during their intensive care unit stay and were managed with V-V ECMO. The criteria for ECMO support were as follows: patients with hemodynamic instability (mean arterial pressure [MAP] < 50 mmHg) at any stage of the operation despite inotropic support received veno-arterial ECMO. Despite conventional mechanical ventilation strategies, patients with hypercarbia (partial pressure of carbon dioxide [PaCO₂] > 60 mmHg), hypoxemia (PaO₂ < 60 mmHg or oxygen saturation $< 80\%$), and a pH ≤ 7.2 on blood gas analysis received V-V ECMO if their hemodynamic status was stable.^[9]

Statistical Analysis

Data were analyzed using SPSS version 26.0 (IBM, Chicago, IL, USA). Normality testing was applied to continuous variables, which were expressed as median (interquartile range [IQR]). Categorical variables were presented as frequencies and percentages.

RESULTS

Demographic characteristics are detailed in Table 1. The median (IQR) age was 26 (25-28) years. Of the 13 patients, eight

had IPAH, and five received PAH-specific therapy (bosentan, sildenafil) before pregnancy and after CS.

Intraoperative and postoperative hemodynamic and blood gas parameters are presented in Table 2. The duration of intubation, requirements for mechanical support, ICU and hospital length of stay, and mortality rates are summarized in Table 3. The 30-day postpartum maternal mortality rate was 46%, with deaths occurring between postpartum days 13 and 18. ECMO was required in six patients; two received perioperative V-A ECMO following intraoperative cardiac arrest, while four received postoperative V-V ECMO.

Table 1. Demographic characteristics of the patients

P	Age	Etiology	G/P	NYHA	Time to diagnosis	Pre-pregnancy treatment	C/S timing (weeks+days)
1	25	IPAH	1/1	IV	Pregestational	Bosentan	36
2	24	IPAH	2/1	IV	Gestational	-	35+1
3	40	MS	1/1	III	Pregestational	-	38+4
4	27	IPAH	1/1	IV	Gestational	-	36+4
5	25	IPAH	1/1	IV	Gestational	-	37
6	29	VSD	1/1	III	Pregestational	-	38+4
7	21	MS	1/1	III	Pregestational	-	39
8	30	ASD	2/1	III	Pregestational	-	37
9	32	IPAH	1/1	IV	Gestational	-	37+1
10	26	IPAH	1/1	IV	Pregestational	Sildenafil+iloprost	36
11	28	IPAH	1/1	IV	Pregestational	Sildenafil+bosentan	39
12	27	IPAH	1/1	IV	Pregestational	Sildenafil	34
13	25	VSD/Eisenmenger	1/1	IV	Pregestational	Sildenafil	35+6

P: Patient; G/P: Gravida/para; NYHA: New York Heart Association; IPAH: Idiopathic pulmonary arterial hypertension; C/S: Cesarean section; MS: Mitral stenosis; ASD: Atrial septal defect; VSD: Ventricular septal defect.

Table 2. Respiratory and hemodynamic parameters of the patients

	Intraoperative Period Median (IQR)	Postoperative Period Median (IQR)
pH	7.39 (7.37-7.42)	7.35 (7.25-7.39)
SaO ₂	100 (96-100)	98 (95-98)
PaCO ₂	36 (33-40)	40 (37-42.5)
PaO ₂	102 (97-106.5)	128 (123-133)
BPs (mmHg)	100 (100-110)	90 (90-97.5)
BPd (mmHg)	80 (74-85)	72 (67-76.5)
PAPs (mmHg)	58 (47.5-133)	55 (45-129)
PAPm (mmHg)	50 (29-72)	48 (32.5-70)
PAPs/BPs	0.55 (0.5-1.19)	0.61 (0.49-1.26)

SaO₂: Arterial oxygen saturation; PaCO₂: Partial pressure of arterial carbon dioxide; PaO₂: Partial pressure of arterial oxygen; BPs: Systolic systemic arterial pressure; dBP: Diastolic systemic arterial pressure; PAPs: Systolic pulmonary arterial pressure; PAPm: Mean pulmonary arterial pressure.

Table 3. Perioperative data of the patients

P	Inotropic agents	Pulmonary therapy	ECMO	ECMO initiation (day)	Extubation time (day)	ICU stay (days)	Hospital stay (days)	Cause of mortality	Mortality
1	ADR, DBX	Tad+Mac+iNO	+	7	13	13	13	Sepsis	+
2	ADR, DBX	Tad+Mac+iNO	+	End of surgery	14	14	14	MOF	+
3	-	-	-		1	3	5		-
4	ADR, DBX	Tad+Mac+iNO	+	End of surgery	1	15	15	MOF	+
5	-	Mac	-		5	10	15		-
6	-		-		0	2	6		-
7	-		-		0	2	5		-
8	-		-		0	2	7		-
9	ADR, DBX	Tad+Mas+llo+iNO	+	6	20	20	20	CVD	+
10	ADR, DBX	Mac+Sil+llo+iNO	+	4	18	18	18	Sepsis	+
11	ADR, DBX	Bos+Sil+iNO	+	3	12	12	12	Sepsis	+
12	-	Sil+Mac	-		5	15	25		-
13	-	llo+Mac	-		3	10	20		-

P: Patient; ECMO: Extracorporeal membrane oxygenation; ICU: Intensive care unit; ADR: Adrenaline; DBX: Dobutamine; Tad: Tadalafil; Mac: Macitentan; llo: Iloprost; iNO: Inhaled nitric oxide; Bos: Bosentan; Sil: Sildenafil; MOF: Multiorgan failure; CVD: Cerebrovascular disease.

Five of the six patients who died were diagnosed with IPAH. No neonatal complications were observed.

DISCUSSION

In our series of pregnant women with different forms of severe pulmonary hypertension, cesarean section was the standard mode of delivery. Various proactive post-delivery management strategies, including prolonged mechanical ventilation, parenteral iloprost, inhaled nitric oxide (10-20 ppm), inotropic agents, and extracorporeal membrane oxygenation, were implemented. PH during pregnancy carries a greater risk of clinical deterioration when the underlying etiology is idiopathic pulmonary arterial hypertension compared to other forms of PH. This increased risk is attributed to delayed diagnosis, severe hypoxia, right ventricular failure, fetal developmental anomalies, and higher maternal mortality rates.^[10] Because the patient population in our study was rare and included only patients who underwent surgery under emergency conditions, we did not have the opportunity to perform a statistical comparison between the IPAH and non-IPAH groups. Nevertheless, our clinical experience suggests that mortality and morbidity are higher in patients with IPAH, which is consistent with relevant data reported in the literature.

Additionally, delayed hospitalization, administration of general anesthesia, and the severity of PH have been identified as significant risk factors for maternal mortality in pregnant women with PH.^[11-13] Early diagnosis and treatment with PH-targeted therapies may help reduce maternal morbidity and mortality in this population.^[1]

Maternal mortality in pregnant women with PH has been reported to range from 17% to 56% in the literature.^[1,6,7,10,11,14] In our study, the maternal mortality rate was 46%, with no additional deaths occurring within the first year postpartum. A PH crisis is defined as a sudden increase in pulmonary arterial pressure, with a systolic pulmonary arterial pressure-to-systemic systolic blood pressure (sPAP/BPs) ratio exceeding 0.8.^[15] In our cohort, a PH crisis was documented in 8 of 13 patients (61%). The median (IQR) PAPm value among our patients was 50 (29-72) mmHg, consistent with the definition of severe PH. A major contributing factor to the high mortality rate was the elevated PAPs/BPs ratio (>0.8) observed in eight patients who underwent emergency CS, fulfilling the criteria for a PH crisis. Additionally, 61% of our study population had IPAH, and only five of these patients had been diagnosed prior to pregnancy and were receiving PAH-targeted therapies. These clinical characteristics may have contributed to an increased risk of clinical deterioration following emergency CS.^[10]

The most commonly reported form of PH during pregnancy is group II (post-capillary PH), which is frequently associated with mitral valve disease or other left heart pathologies. Data from the multicenter Registry of Pregnancy and Cardiac Disease (ROPAC) suggest that postpartum maternal mortality is higher in women with IPAH compared to those with group II PH.^[16] Consistent with these findings, mortality in our cohort occurred exclusively in the postpartum period.

The anesthetic management of pregnant women with PH undergoing emergency CS presents specific challenges that require proactive strategies distinct from those used in elective

CS cases.^[17,18] The risk of PH worsening during pregnancy is significant. Given the physiological and hemodynamic changes that occur during pregnancy and immediately after CS, key anesthetic goals include maintaining sinus rhythm, optimizing right ventricular preload, ensuring systemic vasoconstriction, enhancing right ventricular contractility, and reducing pulmonary vascular resistance. Impairment of atrial contraction can exacerbate right ventricular failure. Right ventricular volume status should be carefully regulated using transesophageal echocardiography and central venous pressure (CVP) monitoring. In cases of decreased preload, right ventricular contractility is impaired, whereas excessive preload can worsen tricuspid regurgitation, leading to interventricular septal deviation and further deterioration of right ventricular wall tension. Maintaining systemic vascular resistance is crucial for adequate coronary perfusion.^[19-21]

Pulmonary artery catheterization (PAC) and TEE play vital roles in ensuring hemodynamic stability. PAC is essential for assessing and managing cardiac output (CO), PAP, PVR, mixed venous oxygen saturation, cardiac preload, and right ventricular function, all of which are critical for maintaining hemodynamic stability.^[9] Intraoperative TEE allows real-time assessment of right and left ventricular function. Additionally, the evaluation of regional wall motion abnormalities can help identify the underlying causes of hemodynamic instability, assess intravascular volume status, and detect congenital anomalies such as a patent foramen ovale (PFO) or intracardiac thrombus, thereby guiding anesthetic management.^[9] The combined use of TEE and PAC measurements after anesthetic induction may enable more precise and controlled perioperative management.

Pharmacological interventions to maintain hemodynamic stability include inotropic agents (epinephrine, norepinephrine, and dobutamine), phosphodiesterase III inhibitors (milrinone), and the selective pulmonary vasodilator inhaled nitric oxide (iNO). Adequate diuresis should be maintained, and hypoxia and hypercarbia must be avoided.^[19-21,22,23] Preventing right ventricular failure and mitigating increases in PVR are key objectives in anesthetic management. The use of veno-arterial ECMO should be considered in selected patients with severe PAH, Eisenmenger's syndrome, left systemic ventricular dysfunction and/or right ventricular dysfunction.^[10,24] In our study, ECMO support was provided to patients who did not respond to medical therapy or mechanical ventilation. Six patients required inotropic support at the end of surgery, with epinephrine and dobutamine being the preferred agents. Two patients with refractory hemodynamic instability received perioperative veno-arterial ECMO support, while four hemodynamically stable patients were managed postoperatively with veno-venous ECMO in the intensive care unit.

Lung transplantation remains a critical option for patients with severe PH. However, delays in referral, prolonged waiting times, and organ donor shortages contribute to increased mortality and worsening clinical severity among patients

awaiting transplantation.^[10] Unfortunately, in our cohort, none of the patients requiring ECMO could be successfully bridged to transplantation, and those who could not be weaned from ECMO support ultimately succumbed to their illness.

Currently, there are no randomized controlled trials comparing general anesthesia (GA) and regional anesthesia (RA) for emergency CS in pregnant women with PH.^[17,21] However, retrospective case series published between 1997 and 2007 indicate that GA is associated with a fourfold higher mortality risk compared to RA. Epidural anesthesia, when carefully titrated, is often considered the preferred technique because it provides adequate anesthesia while minimizing hemodynamic instability.^[6,14,17,25-27] In our study, GA was administered to all patients due to the urgency of the CS procedures and the patients' inability to tolerate the delayed onset of epidural anesthesia. Additionally, GA was favored because of the unknown preoperative medical treatment status of the patients, the potential need for mechanical support during surgery, and the high pulmonary pressures observed in these critically ill patients. GA also allowed optimal anesthetic management, including maintenance of systemic vascular resistance, monitoring of right ventricular function, control of pulmonary pressure, respiratory support, and TEE-guided assessments.

The lowest gestational age at delivery among our patients was 34 weeks. Although IPAH has been associated with a higher risk of neonatal growth restriction compared to other forms of PAH during pregnancy, no neonatal complications were observed in our study.^[10]

This study has several limitations. First, the sample size was small. Second, the retrospective design limited the ability to control for confounding variables. Third, preoperative clinical data were incomplete because many patients were referred from external centers, making it difficult to assess their management before admission. Additionally, newborn follow-up data were unavailable, as neonatal care was provided at different institutions.

CONCLUSION

Pregnancy in women with PH, particularly those with IPAH, is associated with significant maternal morbidity and mortality. The anesthetic management of CS in these patients is critical and must be tailored to address the underlying pathophysiology. Early diagnosis, timely referral to specialized centers, and multidisciplinary perioperative planning involving cardiologists, obstetricians, and cardiac anesthesiologists are essential for improving outcomes. When the underlying etiology is IPAH, the risk of mortality is higher than in other forms of PH. Mechanical circulatory support devices, including ECMO, may serve as a temporary bridge to lung transplantation in selected cases.

Ethics Committee Approval: This study was approved by the Kartal Kosuyolu Yuksek İhtisas Training and Research

Hospital Ethics Committee (Date: 13.07.2021, Decision No: 2021/7/497).

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ORİJİNAL ÇALIŞMA - ÖZ

Ciddi pulmoner hipertansiyonlu gebelerde acil sezaryen seksiyi ameliyatı – Olası Extracorporeal yaşam desteği

AMAÇ: Bu çalışmadaki amacımız, pulmoner hipertansiyonlu (PH) gebelerde acil sezaryen (CS) operasyonlarının periprosedürel yönetimi ve maternal ve fetal kardiyak komplikasyonlar konusundaki klinik deneyimimizi sunmaktır.

GEREÇ VE YÖNTEM: Avrupa Kardiyoloji Derneği (ESC) kriterlerine göre gebelik ve/veya gebelik öncesi PH tanısı konulan ve dış merkezde acil CS kararı ile hastanemize sevk edilen 13 hasta çalışmaya dahil edildi. Acil olarak operasyona alınan hastaların demografik verileri, tanı zamanı, gebelik öncesi, gebelik ve/veya CS sonrası kullanılan pulmoner hipertansiyon tedavileri, arteriyel kan gazları, indüksiyon sonrası ve postoperatif 12. saat pulmoner basınç ve sistemik basınç değerleri, ekstrakorporeal membran oksijenatör (ECMO) gereksinimleri, ekstübasyon ve yoğun bakım süresi ve mortalite oranları kaydedildi.

BULGULAR: 13 hastanın sekizine idiyopatik pulmoner arteriyel hipertansiyon (İPAH) tanısı kondu. Ortalama sistolik sistemik arter basıncı (KB), PAB ve ortalama pulmoner arter basıncı sırasıyla 130 ± 14.2 mmHg, 93 ± 28 ve 52 ± 17 olarak bulundu. 13 hastadan 6'sının ECMO desteğine ihtiyacı oldu. 1 aylık mortalite oranı %46 idi.

SONUÇ: PH'lu kadınlarda gebelik, önemli derecede anne morbiditesi ve mortalitesi ile ilişkilidir. Altta yatan etiyoloji İPAH ise mortalite riski diğer PH türlerine göre daha yüksektir. ECMO dahil mekanik dolaşım destek cihazları, seçilmiş vakalarda akciğer transplantasyonuna geçici bir köprü görevi görebilir. Bu nedenle İPAH'nın erken teşhisi, hastaların merkezlere zamanında yönlendirilmesi ve bu operasyonların kardiyoloji, jinekoloji ve kardiyak anestezi uzmanından oluşan multidisipliner bir ekiple planlanması gerekmektedir.

Anahtar sözcükler: Acil sezaryen seksiyi; ECMO desteği; pulmoner hipertansiyon.

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Injury patterns and forensic report classification in motorcycle accidents: A large-scale retrospective study

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ABSTRACT

BACKGROUND: Motorcycle accidents represent a significant public health and forensic medicine issue due to their high morbidity and mortality rates. This study aimed to evaluate the demographic, clinical, and forensic characteristics of motorcycle accidents.

METHODS: A retrospective analysis was conducted on 2,445 motorcycle accident cases referred to the Department of Forensic Medicine at Eskişehir Osmangazi University Faculty of Medicine for forensic evaluation between 2020 and 2024. Demographic data, accident characteristics, helmet and alcohol use, injury patterns, Injury Severity Score (ISS) values, and forensic report classifications according to Turkish Penal Code (TCK) No. 5237 were analyzed.

RESULTS: Of these cases, 91.7% were male, with an average age of 31.8 years; the most commonly affected age group was 20–29 years. Most accidents occurred within city limits (68.1%), and the most frequent accident mechanism was collision with another vehicle (59.8%). Helmet use was reported in 36.0% of cases, while 47.0% were not wearing a helmet at the time of the accident. The most common injuries involved the lower (44.4%) and upper extremities (38.7%). Fractures most frequently affected the tibia/fibula, wrist-hand bones, and ribs. The average ISS was 9.1 ± 4.8 ; injuries were classified as mild in 59.3% of cases, moderate in 30.0%, and severe in 10.7%. According to the TCK, 66.0% of injuries were classified as “treatable with simple medical intervention.”

CONCLUSION: Motorcycle accidents are particularly common among young men, and helmet use remains low. Injuries predominantly affect the extremities, and forensic classification based on the TCK provides a distinctive contribution to forensic medicine practice. Increasing the use of protective equipment, preventing driving under the influence of alcohol, and strengthening traffic safety measures are essential.

Keywords: Motorcycle accident; injury pattern; helmet use; Injury Severity Score (ISS); Turkish Penal Code; forensic report.

INTRODUCTION

Traffic accidents continue to be one of the leading causes of death and disability worldwide and constitute a significant public health problem, particularly in low- and middle-income countries.^[1] According to the World Health Organization (WHO) 2018 report, approximately 1.35 million people die each year as a result of traffic accidents, while millions more are injured or sustain permanent disabilities.^[1]

Motorcycle users are among the highest-risk groups in road traffic accidents, with deaths in this group accounting for approximately 28% of global traffic accident-related fatalities.^[1] According to WHO data, mortality rates among motorcycle riders are particularly high in regions such as Southeast Asia and Africa.^[1] In developing countries, the widespread use of motorcycles for economic reasons has led to an increase in accidents and traumatic injuries associated with these vehicles.^[2]

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Due to their structure, motorcycle accidents expose riders and passengers to environmental trauma, resulting in a high likelihood of non-fatal but serious injuries.^[3] Studies have shown that head, lower and upper extremity, and thoracic injuries are prominent in these accidents, and that the majority of fractures occur in the leg bones, wrist and hand bones, ribs, and shoulder region.^[4,5]

The Injury Severity Score (ISS), one of the parameters frequently used to assess injury severity in motorcycle accidents, allows for evaluation of the patient's overall condition by considering the type of trauma, injury location, and the presence of multiple injuries.^[6] In this context, significant associations have been demonstrated between ISS scores and variables such as injury patterns, use of protective equipment, and the need for surgical intervention.^[6-8]

In Türkiye, a total of 1,444,260 traffic accidents occurred in 2024; 266,854 of these were fatal or injury-causing accidents. In these accidents, 6,351 people lost their lives and 385,117 people were injured.^[9] In 2024, 31.5% of vehicles involved in fatal or injury-causing accidents were motorcycles. A total of 1,228 people died and 109,832 were injured, highlighting the significant traffic safety risks faced by motorcycle users.^[9]

The literature reports that injury patterns associated with motorcycle accidents are more severe in developing countries; protective equipment usage rates are low, and most emergency department visits are related to lower extremity, head, and thoracic trauma.^[3-5] The limited number of studies conducted on motorcycle accidents in Türkiye necessitates a more detailed and comprehensive evaluation of this issue from a forensic medicine perspective. This study aims to analyze the traumatic injury profiles of individuals involved in motorcycle accidents, including protective equipment use, hospital admissions, surgery rates, ISS scores, and forensic report evaluations using multidimensional parameters.

MATERIALS AND METHODS

This study was designed as a retrospective, descriptive research. Within the scope of the study, forensic examination reports of individuals involved in motorcycle accidents who were referred to the Department of Forensic Medicine, Faculty of Medicine, Eskişehir Osmangazi University for forensic evaluation between January 1, 2020 and December 31, 2024, were retrospectively reviewed.

Only individuals who survived the motorcycle accident and underwent forensic examination were included in the study. Data were obtained from information contained in the forensic reports. Cases with missing data, illegible records, or trauma sources other than motorcycle accidents were excluded from the study.

The data were obtained from the reports using a standardized data collection form. The variables examined included age, gender, anatomical location of the injury, presence of bone fractures, soft tissue injuries (ecchymosis, abrasion,

laceration), number of affected body areas, and severity of trauma. Trauma severity was assessed based on clinical criteria such as hospitalization, need for surgical intervention, or the presence of permanent damage, if any.

Ethical approval for the study was obtained from the Non-Interventional Clinical Research Ethics Committee of Eskişehir Osmangazi University (Decision No: 20, Date: 26.06.2025). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data analysis was performed using SPSS (Statistical Package for the Social Sciences, version 27.0; IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as frequency, percentage, mean, and standard deviation. No comparative statistical tests were applied in this study.

RESULTS

In this study, a total of 2,445 cases who applied to the Department of Forensic Medicine at Eskişehir Osmangazi University Faculty of Medicine for a forensic report between 2020 and 2024 and were involved in motorcycle accidents were retrospectively evaluated. Of the cases, 91.7% (n=2,243) were male and 8.3% (n=202) were female. The mean age was 31.8 ± 10.6 years, with ages ranging from 16 to 74 years. The most common age group was 20–29 years (41.2%), followed by 30–39 years (28.7%) (Table 1).

Of the accidents, 68.1% (n=1,666) occurred in urban areas, 21.3% (n=522) on interurban roads, and 10.6% (n=257) in rural areas. The most common type of accident was vehicle collisions, accounting for 59.8% (n=1,463) of cases. This was followed by single-vehicle accidents (27.1%; n=663), collisions with stationary objects (8.9%; n=217), and collisions with pedestrians (4.2%; n=102) (Table 1).

When examining the use of protective equipment, it was determined that among the 2,029 cases with known helmet-use data, 36.0% (n=880) were wearing helmets, while 47.0% (n=1,149) were not. Helmet-use information could not be obtained for 17.0% of cases. Of the 1,724 cases with available data on alcohol use, 111 were found to be positive for alcohol. No information on alcohol use was available for the remaining 721 cases (29.4%) (Table 1).

In the assessment of traumatic findings, no injuries were identified in 27.5% of cases (n=671). When the 1,056 cases (43.2%) with only superficial soft tissue injuries (ecchymosis, abrasion, superficial laceration) and no fractures or internal organ damage were included in the evaluation, a total of 70.7% of cases had either no traumatic findings or only superficial injuries. In contrast, bone fractures and/or internal organ injuries were detected in 718 cases (29.3%). Regarding injury location, the lower extremities (44.4%) and upper extremities (38.7%) were most commonly affected, followed by the head (26.0%), face (21.6%), thorax (11.2%), and abdomen-pelvis (5.4%). In cases involving multiple regions, each affected region was counted separately (Table 1).

Table 1. Distribution of demographic, accident-related, and clinical characteristics of the cases

	Number (#)	Percentage (%)
Age, Mean±SD	31.8±10.6	
≤19	123	5.0
20-29	1,007	41.2
30-39	701	28.7
40-49	385	15.7
50-59	156	6.4
≥60	73	3.0
Sex		
Male	2,243	91.7
Female	202	8.3
Helmet Use		
Helmeted	880	36.0
Not helmeted	1,149	47
Unknown	416	17.0
Alcohol Use (Ethanol)		
Positive	111	4.5
Negative	1,613	65.9
Unknown	721	29.4
Accident Location		
Urban area	1,666	68.1
Interurban road	522	21.3
Rural area	257	10.6
Type of Accident		
Single-vehicle accident	663	27.1
Vehicle collision	1,463	59.8
Collision with a stationary object	217	8.9
Collision with a pedestrian	102	4.2
Traumatic Findings		
No injury	671	27.5
Superficial soft tissue injury	1,056	43.2
Bone fracture and/or internal organ injury	718	29.3
Injury Location*		
Lower extremities	788	44.4
Upper extremities	687	38.7
Head	461	26.0
Face	383	21.6
Thorax	199	11.2
Abdomen-pelvis	96	5.4
Hospitalization Required	934	38.2
Intensive care unit	215	23.0
General ward	719	77.0

ISS, Mean±SD	9.1±4.8	
≤8	1,449	59.3
9-15	733	30.0
≥16	263	10.7
Forensic Report Classification		
Injury treatable with simple medical intervention	1,615	66.0
Life-threatening injury	613	25.1
Permanent disability	128	5.2
Surgical intervention		
Yes	357	14.6
No	2,088	85.4
Functional Outcome		
Functional impairment	91	3.7
Loss of function	37	1.5

*In cases involving more than one injured body region, each region was counted separately.

A total of 582 cases (23.8%) had bone fractures, with the most common involving the tibia/fibula (7.5%; n=183), wrist and hand (5.3%; n=129), ribs (3.2%; n=79), clavicle (2.5%; n=61), pelvis (2.4%; n=58), humerus (1.8%; n=45), and radius/ulna (1.7%; n=42). Less frequent fractures included those of the femur (1.6%; n=39), foot bones (1.4%; n=35), skull (0.9%; n=22), and scapula (0.4%; n=11) (Table 2).

Additionally, 28 cases (1.1%) had extremity dislocation, and 11 cases (0.5%) had partial or complete amputation.

A total of 934 cases (38.2%) required hospitalization, of whom 77.0% (n=719) were treated in the ward and 23.0% (n=215) in the intensive care unit. The average length of hospital stay was 5.2±3.6 days among the 821 cases with available data (Table 1). Surgical intervention was performed in 357 cases (14.6%), including orthopedic internal fixation procedures, interventions for visceral organ injuries, and cranial operations.

The Injury Severity Score was calculated for all cases, and the average ISS was 9.1±4.8. When the ISS distribution was evaluated, 59.3% (n=1,449) of cases had mild injuries (ISS ≤8), 30.0% (n=733) had moderate injuries (ISS 9–15), and 10.7% (n=263) had severe injuries (ISS ≥16) (Table 1). The ISS score was positive only in cases with anatomical injury, whereas ISS=0 was defined for cases without traumatic findings.

Among the cases evaluated for sequelae, a total of 128 cases (5.2%) had sensory or anatomical dysfunction. In 91 cases (3.7%), a sensory organ or anatomical structure suffered permanent functional impairment, while in 37 cases (1.5%), complete loss of function developed. According to the forensic report classification, 66.0% (n=1,615) of cases were reported as “recoverable with simple medical intervention,” while 25.1% (n=613) were assessed as “life-threatening” (Table 1).

Table 2. Distribution of bone fractures by anatomical location

Fracture Location	Number (#)	Percentage (%)
Tibia and fibula	183	7.5
Wrist bones (distal radius, carpal, metacarpal, phalanx)	129	5.3
Clavicle	61	2.5
Humerus	45	1.8
Femur	39	1.6
Pelvis	58	2.4
Radius/ulna (diaphysis)	42	1.7
Foot bones (metatarsal, phalanx, calcaneus)	35	1.4
Scapula	11	0.4
Skull	22	0.9
Rib	79	3.2
Total	582	23.8

This classification was made based on the criteria defined in the relevant articles of the Turkish Criminal Code No. 5237.

DISCUSSION

This study retrospectively examined the demographic, clinical, and forensic characteristics of motorcycle accident cases referred to the Department of Forensic Medicine at Eskişehir Osmangazi University Faculty of Medicine for forensic evaluation between 2020 and 2024. Among the 2,445 cases evaluated, the majority involved young adult males, and most accidents occurred within urban areas and involved vehicle collisions. Helmet use was low, while the rate of alcohol positivity was low. Injury pattern analysis showed a predominance of lower and upper extremity injuries, with bone fractures most commonly involving the tibia/fibula and wrist/hand bones. The average ISS score indicated mild injury severity; however, approximately one-third of the cases had moderate or severe injuries. In forensic report evaluations, a substantial proportion of cases were classified as “treatable with simple medical intervention” according to the Turkish Penal Code No. 5237.

Our data revealed that 91.7% of the cases were male and 8.3% were female. The higher incidence of motorcycle accidents among males is consistent with findings reported both nationally and in the international literature.^[1-3,7,8,10,11] The fact that men exhibit riskier driving behaviors and that motorcycle use is more common among men for occupational and transportation purposes is cited as the main factor explaining this situation.^[2,7] The average age of the cases was 31.8 years, with the most common age group being 20-29 years. Similarly, studies conducted in different regions, including Ethiopia, Nigeria, and Iran, have reported that young adults are at the highest risk of motorcycle accidents.^[4,8,10] This situation is as-

sociated with young drivers' lack of experience, tendency to drive at high speeds, and inadequate compliance with traffic rules.^[7,11]

The analysis showed that 68.1% of accidents occurred in urban areas, 21.3% on interurban roads, and 10.6% in rural areas. The high proportion of urban accidents is particularly associated with heavy traffic, increased motorcycle usage, and complex road conditions.^[9,11,12] Regarding accident types, vehicle collisions were the most common (59.8%), followed by single-vehicle accidents (27.1%), collisions with stationary objects (8.9%), and collisions with pedestrians (4.2%). Similarly, a study conducted in Thailand identified vehicle collisions as the primary cause of motorcycle accidents, and data from the Turkish Statistical Institute also indicate that vehicle collisions are the leading accident mechanism in Türkiye.^[9,12] A significant proportion of single-vehicle accidents can be attributed to driver errors, speeding, road surface defects, and adverse weather conditions.^[13]

In this study, the helmet usage rate was found to be 36.0%, with 47.0% of cases not wearing a helmet at the time of the accident, while helmet-use information was unavailable for 17.0% of cases. The World Health Organization data indicate that properly worn helmets reduce the risk of death among motorcycle riders by approximately 40% and the risk of serious head injury by 70%.^[1] However, helmet usage rates in low- and middle-income countries are generally below 50%, and in some regions, they have been reported to be below 10%.^[14,15] In Türkiye, helmet usage rates vary by region, and this rate decreases significantly, particularly during short-distance urban travel.^[9] The low helmet usage rate identified in our study suggests that, despite the proven effectiveness of helmets in reducing injury severity,^[14,15] there are shortcomings in the enforcement of legal regulations and public awareness campaigns related to helmet use.

When evaluating the distribution of injury sites, the lower extremities (44.4%) and upper extremities (38.7%) were most frequently affected, followed by the head (26.0%), face (21.6%), thorax (11.2%), and abdomen-pelvis (5.4%) regions. The literature similarly indicates that lower extremity injuries are the most common type of trauma in motorcycle accidents, which is related to the structural characteristics of motorcycles and the direct exposure of the rider's lower limbs during impact.^[3,4,7,8,10,11] The prevalence of head and face injuries is directly related to helmet use and is significantly higher among riders who do not wear helmets.^[14,15] Jeffers et al.^[5] reported that lower extremity injuries, particularly those involving the foot and ankle, play a critical role in fatal accidents, while Rebollo-Soria et al.^[16] emphasized that head and face injuries are equally critical in such incidents. In our study, fractures were most commonly observed in the tibia/fibula, wrist and hand bones, and ribs, which is consistent with fracture locations reported in previous studies.^[4,5,8,10]

In our study, the mean ISS was 9.1±4.8, with 59.3% of cases

classified as mild (ISS ≤ 8), 30.0% as moderate (ISS 9-15), and 10.7% as severe (ISS ≥ 16) injuries. These findings are consistent with similar studies conducted in developing countries.^[7,8,11] The ISS is a scoring system that objectively assesses injury severity and is closely related to prognosis.^[6] Hoseinian et al.^[8] reported a severe injury rate of 12.1%, while Lin and Kraus^[7] demonstrated that ISS values are significantly associated with injury mechanism, protective equipment use, and the presence of multiple injuries. In our study, the relatively low rate of severe injury may be attributed to the fact that most cases involved only superficial injuries and that the majority of fractures were limited to the extremities.

When examining forensic report classifications, 66.0% of cases were categorized as injuries treatable with simple medical intervention, 25.1% were classified as life-threatening, and 5.2% were classified as resulting in permanent anatomical or sensory impairment or loss. This classification was based on the criteria defined in Articles 86 and 87 of the Turkish Penal Code (TCK) No. 5237. Similarly, Sataloğlu et al.^[17] reported that a substantial proportion of injuries in bicycle and motorcycle accidents were classified as minor. The forensic report classification of motorcycle accidents according to TCK criteria has rarely been addressed in the literature, highlighting the distinctive value of our study from a forensic medicine perspective. In studies conducted abroad, forensic reporting processes are generally evaluated based on injury severity scores or trauma patterns, and legal classifications vary according to national legislation.^[8,11,16] In this context, examining TCK-based forensic report classifications, which directly affect legal processes in Türkiye, in a large sample of motorcycle accident cases makes an important contribution to both forensic medicine practice and traffic safety policies.

One of the most important strengths of this study is its large sample size, which includes 2,445 motorcycle accident cases referred to the forensic medicine unit over a five-year period. Additionally, collecting data from a single center ensured that records were evaluated using the same standard procedures and increased classification consistency. Another valuable contribution of the study, from both forensic medicine and traffic safety perspectives, is the classification of injuries according to the criteria of the Turkish Penal Code No. 5237. However, the retrospective design of the study led to information loss due to record deficiencies, particularly resulting in a high “unknown” rate for variables such as helmet use, alcohol status, and accident mechanism. Furthermore, due to its single-center nature, the generalizability of the findings to the entire country is limited. Prospective, multicenter studies are recommended to more thoroughly elucidate injury patterns and the effectiveness of protective measures.

The findings indicate that motorcycle accidents continue to be a significant public health issue in terms of serious injuries and fatal outcomes. Our study sheds light on both forensic medicine practice and the development of traffic safety policies by detailing injury types, affected body regions, hel-

met and alcohol use, and forensic report classifications. In particular, forensic report classification based on the Turkish Penal Code is of critical importance, as it serves as evidence in legal proceedings. Therefore, legal regulations, awareness campaigns, and strengthened control mechanisms are needed to increase protective equipment use among motorcycle users. Additionally, effective enforcement of existing penalties for driving under the influence of alcohol and infrastructure improvements to prevent accidents will reduce injury severity as well as the burden on forensic processes.

CONCLUSION

Motorcycle accidents continue to be a significant legal and public health issue in Türkiye due to the high risk of injury and mortality. Using a large sample, our study detailed injury types, helmet and alcohol use, and legal report classifications based on the Turkish Penal Code. The findings emphasize the need to promote protective equipment use, prevent driving under the influence of alcohol, and strengthen traffic safety measures. Furthermore, multicenter and prospective studies are recommended to comprehensively evaluate injury patterns and the effectiveness of protective measures.

Ethics Committee Approval: This study was approved by the Eskişehir Osmangazi University Non-Interventional Clinical Research Ethics Committee (Date: 26.06.2025, Decision No: 20).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: A.H.Ç., K.K., Ü.Ş.; Design: K.K., A.E.; Supervision: K.K.; Resource: N.P., A.E.; Materials: K.K., Ü.Ş., A.H.Ç.; Data collection and/or processing: N.P., Ü.Ş.; Analysis and/or interpretation: K.K.; Literature review: N.P., Ü.Ş., A.H.Ç.; Writing: A.H.Ç., Ü.Ş.; Critical review: K.K., A.E.

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ORİJİNAL ÇALIŞMA - ÖZ

Motosiklet kazalarında yaralanma paternleri ve adli rapor sınıflandırması: Geniş ölçekli retrospektif bir çalışma

AMAÇ: Motosiklet kazaları, yüksek morbidite ve mortalite oranları nedeniyle önemli bir halk sağlığı ve adli tıp sorunudur. Bu çalışma, motosiklet kazalarının demografik, klinik ve adli özelliklerini değerlendirmeyi amaçlamaktadır.

GEREÇ VE YÖNTEM: 2020-2024 yılları arasında Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Adli Tıp Anabilim Dalı'na adli değerlendirme amacıyla sevk edilen 2.445 motosiklet kazası olgusu retrospektif olarak incelendi. Demografik veriler, kaza özellikleri, kask ve alkol kullanımı, yaralanma paternleri, ISS skorları ve 5237 sayılı Türk Ceza Kanunu'na (TCK) göre adli rapor sınıflandırmaları değerlendirildi.

BULGULAR: Olguların %91.7'si erkek olup, ortalama yaş 31.8 idi; en sık etkilenen yaş grubu 20-29 yaş aralığıydı. Kazaların %68.1'i şehir içinde meydana gelmiş, en sık mekanizma araçla çarpışma (%59.8) olarak bulunmuştur. Kask kullanım oranı %36.0 olup, %47.0'ı kaza sırasında kask takmamıştı. En sık yaralanmalar alt (%44.4) ve üst ekstremitelerde (%38.7) görülmüş; kırıklar en çok tibia/fibula, el-bilek kemikleri ve kaburgalarda saptanmıştır. Ortalama ISS skoru 9.1 ± 4.8 olup, olguların %59.3'ü hafif, %30.0'ı orta, %10.7'si ağır yaralanma grubunda yer almaktadır. TCK'ya göre yaralanmaların %66.0'sı "basit tıbbi müdahale ile giderilebilir" olarak sınıflandırılmıştır.

SONUÇ: Motosiklet kazaları özellikle genç erkeklerde yaygındır ve kask kullanımı düşük düzeydedir. Yaralanmalar çoğunlukla ekstremitelerde yoğunlaşmakta olup, TCK'ya göre yapılan adli sınıflandırma adli tıp uygulamalarına özgün bir katkı sağlamaktadır. Koruyucu ekipman kullanımının artırılması, alkol etkisi altında araç kullanımının önlenmesi ve trafik güvenliği önlemlerinin güçlendirilmesi gerekmektedir.

Anahtar sözcükler: Adli rapor; ISS; kask kullanımı; motosiklet kazası; Türk Ceza Kanunu; yaralanma paterni.

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Prognostic significance of radiographically detected arterial calcification in geriatric hip fracture patients: Abdominal aortic calcification as an independent predictor of mortality

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ABSTRACT

BACKGROUND: To investigate the prevalence and anatomical distribution of radiologically detected arterial calcification in the abdominal, iliac, and femoral arteries among patients aged ≥ 65 years undergoing surgical treatment for hip fracture, and to assess the impact of both the presence and localization of arterial calcification on patient survival.

METHODS: A retrospective analysis was performed on 270 patients who underwent surgical treatment for hip fractures between 2015 and 2024. The presence of arterial calcifications in the abdominal aorta, iliac arteries, and femoral arteries was assessed on plain radiographs, and their association with patient survival outcomes was investigated. In addition, demographic characteristics, fracture type, treatment modality, and intensive care unit admissions were systematically evaluated.

RESULTS: Arterial calcification was identified in 211 patients (78.1%). The mean survival time was significantly shorter in patients with arterial calcification (47.3 months, 95% CI: 40.7–53.8) compared with those without (76.9 months, 95% CI: 67.1–86.7) (Log-rank $\chi^2=17.23$, $p<0.001$). Log-rank analysis further demonstrated statistically significant differences in survival between patients with and without calcification of the abdominal aorta ($\chi^2=21.39$, $p<0.001$), iliac arteries ($\chi^2=18.21$, $p<0.001$), and femoral arteries ($\chi^2=10.91$, $p=0.001$). Cox regression analysis identified abdominal aortic calcification as an independent predictor of mortality in geriatric hip fracture patients (HR=3.43, 95% CI: 1.31–8.96, $p=0.013$), whereas iliac artery calcification (HR=1.53, $p=0.284$) and femoral artery calcification (HR=1.05, $p=0.859$) were not independently associated with survival after adjustment.

CONCLUSION: Iliac and femoral artery calcifications should not be regarded as independent predictors of mortality in geriatric patients with hip fractures. In contrast, abdominal aortic calcification has been identified as an independent prognostic determinant of mortality within this patient population.

Keywords: Abdominal aortic calcification; femoral artery calcification; hip fracture; mortality; iliac artery calcification.

INTRODUCTION

Hip fractures are traumatic injuries that cause a serious clinical and economic burden, particularly among people over the

age of 65.^[1] As the elderly population is growing worldwide, the incidence of osteoporotic hip fractures is also increasing. These fractures are associated with serious morbidity and mortality, as well as a reduced quality of life.^[2-3] According to

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projections, there will be more than six million hip fracture cases worldwide each year by 2050.^[4]

In recent years, the relationship between arterial calcification—particularly in the abdominal aorta as well as the iliac and femoral arteries—and bone health has attracted increasing attention.^[5-9] The effects of arterial calcification on bone tissue are multifaceted and complex. Primarily, arterial stiffening and luminal narrowing may lead to reduced regional blood flow, thereby limiting the delivery of osteogenic cells and essential healing factors to the bone. These pathophysiological mechanisms can contribute to delayed bone repair and increase the risk of complications, particularly regarding fracture healing.^[10] In addition, it has been shown that there is a bidirectional relationship between arterial calcification and osteoporosis, i.e., vascular calcification may coexist with low bone mineral density.^[11] Furthermore, factors such as polypharmacy, malnutrition, and immobility, which are prevalent in older ages, may increase the extent of atherosclerotic changes.^[12] Finally, the prognostic significance of arterial calcification on mortality may vary by vascular location, with calcification confined to the iliac or femoral arteries more likely representing localized disease and, therefore, having limited prognostic relevance. In contrast, abdominal aortic calcification, potentially reflecting advanced systemic atherosclerosis and its pronounced effects on central hemodynamics and end-organ perfusion, may have the greatest impact on survival.

In elderly patients undergoing surgery for hip fractures, arterial calcification not only complicates the surgical procedure by compromising bone quality but has also been associated with a higher incidence of postoperative complications—including increased bleeding, delayed wound healing, and elevated infection rates.^[13]—and independently contributes to an increased mortality risk.^[14] However, the number of studies addressing this subject in the literature is limited,^[15-17] and the effects of arterial calcification on the mortality of geriatric patients undergoing hip fracture surgery have not been clearly established.

The objective of this study was to investigate the prevalence and anatomical distribution of radiologically detected arterial calcification in the abdominal aorta, iliac arteries, and femoral arteries among patients aged ≥ 65 years undergoing surgical treatment for hip fracture, and to assess the impact of both the presence and localization of arterial calcification on patient survival. It is hypothesized that the findings of this investigation will provide a basis for the future development of alternative therapeutic algorithms for hip fracture patients identified as high-risk or with limited survival prospects.

MATERIALS AND METHODS

Following approval from the local ethics committee (Non-Pharmaceuticals and Non-Medical Devices Research Ethics Committee, Protocol No: 09.2025.25-0316), the study was conducted in accordance with the principles of the Decla-

ration of Helsinki and STROBE guidelines for observational studies. A retrospective review was conducted of patients aged 65 years and older who were admitted to the study hospital with proximal femur fractures (both femoral neck fractures and intertrochanteric fractures) between 2015 and 2024 and underwent surgical treatment. The inclusion criteria comprised patients who were:

- Aged 65 years and older,
- Admitted to the emergency department within eight hours of sustaining low-energy trauma,
- Diagnosed with proximal femur fractures (both femoral neck fractures and intertrochanteric fractures),
- Had available preoperative radiological imaging, including plain radiographs for the evaluation of arterial calcification, and complete postoperative follow-up data.

Exclusion criteria included patients with:

- Pathological fractures,
- High-energy trauma,
- Multiple fractures,
- Nonsurgical management,
- Subtrochanteric fractures,
- History of previous hip surgery and/or the need for revision surgery,
- Incomplete clinical or radiological records, incomplete follow-up data.

Following the application of these criteria, 270 patients were included in the analysis.

The surgical management of the hip fractures was determined by the specific type of fracture and its associated anatomical location (collum femoris or intertrochanteric). Intracapsular fractures were treated with partial hemiarthroplasty, while extracapsular fractures were managed with either proximal femoral intramedullary nailing or dynamic hip screw (DHS) fixation, as described in the literature.^[18] All surgical procedures were carried out under standard sterile conditions by the same surgical team. The perioperative administration of antibiotic prophylaxis, in the form of two grams of intravenous cefazolin, occurred 30 minutes prior to induction and was continued for a duration of 24 hours postoperatively. Furthermore, low-molecular-weight heparin was initiated postoperatively for thromboembolism prophylaxis.

A comprehensive evaluation was conducted, encompassing demographic variables (age and gender), fracture classification (collum femoris or intertrochanteric), and the treatment modality employed (intramedullary nailing, hemiarthroplasty, or dynamic hip screw). The anesthetic technique (general, spinal, or combined), the interval between fracture occurrence and surgery, as well as postoperative intensive care unit (ICU) admission rates, were recorded.

The primary outcome measure of the study was overall sur-

vival, which was defined as the time interval from surgery to death. During the collection of survival data, current hospital records, personal health data obtained from healthcare facilities, records from the citizen and physician access portal (e-Nabız), and the Central Population Registry System (MER-NIS) were reviewed to confirm patients' vital status. In cases where survival status was uncertain or to determine the date of death for deceased patients, first-degree relatives were contacted using telephone numbers recorded in the patients' files, and the date of death was verified.

A radiological assessment was conducted using preoperative plain radiographs, which were independently reviewed by two orthopedic surgeons (VBÖ and MG). In accordance with definitions described in the literature, vascular calcification was diagnosed when vascular structures on X-ray images of the abdomen and extremities demonstrated radiodensity similar to that of bone.^[19] The presence and anatomical distribution of calcification were evaluated within the abdominal aorta, iliac arteries, and femoral arteries. In one instance of discordant interpretation of the precise localization of the calcification, a third senior orthopedic surgeon (BG) was consulted, and the final classification was determined by consensus. Patients were categorized according to the anatomical distribution of arterial calcification, and clinical outcomes were compared across the following groups: isolated abdominal aortic calcification, iliac artery calcification (with or without concomitant abdominal aorta involvement), and femoral artery calcification (with or without concomitant abdominal aortic and iliac artery calcification). The evaluation of iliac and femoral artery calcifications was performed using anteroposterior and lateral radiographs of the hip and pelvis, while the evaluation of abdominal aortic calcifications was performed using anteroposterior and lateral radiographs of the lumbar region. All evaluated radiographs were routine radiological examinations requested in geriatric patients who were admitted to our emergency department with hip fractures. However, in two cases, anteroposterior and lateral lumbar radiographs were not available in the hospital picture archive system. Consequently, a cohort of 268 patients was evaluated for abdominal aortic calcification. The necessary radiographs for the evaluation of iliac artery and femoral artery calcifications were available for all patients (n=270).

All statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive analyses were used to summarize baseline demographic and clinical characteristics, with continuous variables reported as means and standard deviations, and categorical variables presented as frequencies and percentages. Overall survival was estimated using the Kaplan–Meier method. Survival distributions were compared between patients with and without arterial calcification—evaluated separately for the abdominal aorta, iliac arteries, and femoral arteries—using the log-rank test. The primary objective of the statistical analysis was to assess differences in survival across these calcification groups. A P-value of less than 0.05 was considered statistically significant.

RESULTS

The study population comprised 270 patients aged 65 years and over who underwent surgical treatment for hip fractures (mean age: 80.6 ± 10.3 years; male/female: 99/171). Intertrochanteric fractures were observed in 139 patients (51.5%), while collum femoris fractures were observed in 131 patients (48.5%). The treatment modalities implemented included proximal femoral nailing in 136 cases (50.4%), hemiarthro-

Table 1. Detailed demographic characteristics of the patients

	Total Number of Patients (%)
Age, years	80.56 $\pm$ 10.27
Gender	
Female	171 (63.3%)
Male	99 (36.7%)
Follow-up, months	24.87 $\pm$ 22.26
Fracture Type	
Intertrochanteric	139 (51.5%)
Collum femoris	131 (48.5%)
Fracture-to-surgery period, days	7.75 $\pm$ 6.49
Surgical Treatment	
Proximal Femoral Nailing	136 (50.4%)
Hemiarthroplasty	132 (48.9%)
Dynamic Hip Screw	2 (0.7%)
Anesthetic Technique	
General	161 (59.6%)
Spinal	82 (30.4%)
Combined	27 (10.0%)
Intensive Care Unit Stay	
Yes	192 (71.1%)
No	78 (28.9%)
Arterial Calcification (n=270)	
Yes	211 (78.1%)
No	59 (21.9%)
Abdominal Aortic Calcification (n=268)	
Yes	210 (78.4%)
No	58 (21.6%)
Iliac Artery Calcification (n=270)	
Yes	179 (66.3%)
No	91 (33.7%)
Femoral Artery Calcification (n=270)	
Yes	125 (46.3%)
No	145 (53.7%)
Patient Survival	
Yes	176 (65.2%)
No	94 (34.8%)

plasty in 132 cases (48.9%), and DHS fixation in two cases (0.7%). The most frequently preferred anesthetic technique was general anesthesia (59.6%), followed by spinal anesthesia (30.4%) and combined anesthesia (10.0%). A comprehensive list of demographic variables is provided in Table I.

During the survival analysis, 94 patients (34.8%) died, whereas 176 patients (65.2%) remained alive. The mean overall survival time was 54.2 months (95% CI: 48.4–60.0), with a 12-month survival rate of 81.4%. Arterial calcification was detected in 211 patients (78.1%), while 59 patients (21.9%) exhibited no evidence of calcification. Patients with arterial calcification demonstrated a significantly shorter mean survival time (47.3 months, 95% CI: 40.7–53.8) compared with those without calcification (76.9 months, 95% CI: 67.1–86.7) (Log-rank $\chi^2=17.23$, $p<0.001$) (Fig. 1A).

As mentioned before, unlike other cohorts ($n=270$), a cohort of 268 patients was evaluated for abdominal aortic calcification. The abdominal aortic calcification was observed in 210 out of 268 evaluable patients (78.4%). The mean survival period was 46.9 months (95% CI: 40.5–53.5) in patients with calcification versus 79.8 months (95% CI: 70.4–89.1) in those without. The application of log-rank analysis revealed a statistically significant disparity in survival outcomes between the groups ($\chi^2=21.39$, $p<0.001$) (Fig. 1B).

Iliac artery calcification was observed in 179 patients (66.3%),

while 91 (33.7%) patients exhibited no such calcification. Patients with iliac artery calcification exhibited a mean survival period of 46.1 months (95% CI: 39.0–53.1), compared with 69.4 months (95% CI: 60.3–78.5) in those without calcification. A significant difference in survival distributions was observed between the groups (Log-rank $\chi^2 = 18.21$, $p<0.001$) (Fig. 1C).

Femoral artery calcification was detected in 125 patients (46.3%), whereas 145 patients (53.7%) exhibited no evidence of calcification. The mean survival time was 45.6 months (95% CI: 37.8–53.4) in patients with femoral artery calcification, compared with 63.0 months (95% CI: 54.8–71.3) in those without calcification. A significant difference in survival distributions was observed between the groups (Log-rank $\chi^2=10.91$, $p=0.001$) (Fig. 1D).

The application of a Cox regression analysis identified abdominal aortic calcification as an independent predictor of mortality (HR=3.43, 95% CI: 1.31–8.96, $p=0.013$). Conversely, iliac artery calcification (HR=1.53, $p=0.284$) and femoral artery calcification (HR=1.05, $p=0.859$) were not found to be independently associated with survival after adjustment.

DISCUSSION

In the context of a globally aging population, hip fractures remain a major contributor to both morbidity and mortal-

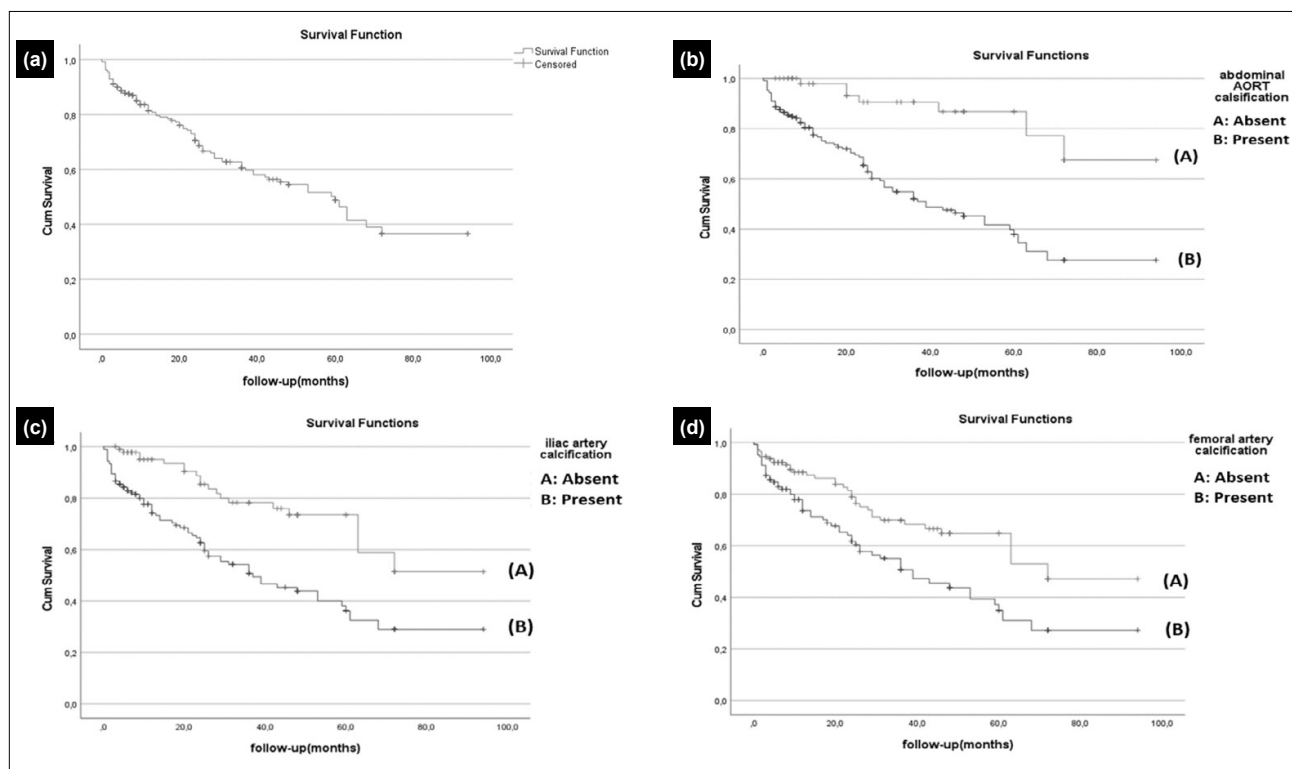


Figure 1. Cumulative Survival Curve Over the Follow-Up Period. (a) Overall survival of the study cohort following hip fracture surgery. (b) Comparison of survival between patients with and without abdominal aortic calcification. (c) Comparison of survival between patients with and without iliac artery calcification. (d) Comparison of survival between patients with and without femoral artery calcification.

ity.^[20-22] Identifying prognostic factors influencing survival and delineating high-risk patient subgroups with reduced life expectancy may facilitate the development of alternative therapeutic strategies. The principal contribution of the present study to the existing body of literature is the demonstration of the association between the presence and anatomical localization of arterial calcification and mortality among patients aged 65 years and older with hip fractures. Although the impact of arterial calcification on mortality has been well established in the literature, studies examining its predictive value in specific patient populations, such as geriatric hip fracture patients, remain limited. Furthermore, existing research has largely focused on individual arterial territories. The principal strength and novel contribution of the present study lie in demonstrating the predictive effect of three distinct arterial calcifications—both individually and in combination—on mortality among patients aged 65 years and older with geriatric hip fractures.^[15,16,23-28] The present study demonstrated that abdominal aortic calcification was an independent predictor of mortality (HR=3.43, 95% CI: 1.31–8.96, $p=0.013$). Conversely, while calcification in the iliac and femoral arteries was associated with diminished survival in unadjusted analyses (Log-rank $\chi^2=18.21$, $p<0.001$, and Log-rank $\chi^2=10.91$, $p=0.001$, respectively), these associations did not persist following multivariable adjustment (HR=1.53, $p=0.284$, and HR=1.05, $p=0.859$, respectively).

Extensive research has already demonstrated that abdominal aortic calcification is an independent and significant predictor of mortality.^[23-25] A 2021 systematic review and meta-analysis of 52 studies on the subject concluded that abdominal aortic calcification is associated with an elevated risk of fatal cardiovascular events and all-cause mortality.^[26] A study conducted in 2024 indicated that abdominal aortic calcification detected on lateral lumbar radiography was associated with all-cause mortality in older adults.^[27] A prospective cohort study published in 2025 demonstrated the association of abdominal aortic calcification with all-cause mortality and emphasized its crucial role in identifying high-risk individuals.^[28] On the other hand, the existing literature presents a conflicting set of opinions with regard to the impact of more distally located arterial calcifications on mortality. In 2021, Huynh et al. reported that iliac artery calcification is a significant predictor of mortality in patients suffering from chronic ischemia.^[29] Furthermore, Birişik et al. reported in 2021 that femoral artery calcification was associated with increased mortality after geriatric hip fractures.^[15] In contrast, the findings by Pazarci et al. in 2019 and Yolaçan and Güler in 2023 revealed that femoral artery calcification did not impact mortality in patients over 65 years of age with hip fractures.^[16] Our data contribute to this knowledge by demonstrating that the prognostic effect is not uniform across vascular territories; rather, it is the presence of abdominal aortic calcification that exerts the most significant impact on survival. This may be explained by the central hemodynamic consequences of abdominal aortic involvement, which reflects advanced systemic athero-

sclerosis and has a greater influence on end-organ perfusion than more peripheral calcifications. By contrast, calcification localized to the iliac or femoral arteries may be more indicative of localized vascular changes without the same systemic prognostic weight.

The coexistence of several arterial calcifications and their similar clinical and prognostic effects is an expected finding. Indeed, in 2024, Meer et al. reported that femoral and crural calcifications correlate with coronary artery calcification and that arterial calcification presents as a systemic process occurring simultaneously in various arterial beds.^[30] Our findings, however, are not consistent with these previously reported results. While all abdominal aortic, iliac, and femoral calcifications were found to be associated with shorter survival, regression analyses revealed that the only calcification localization with the characteristic of being an independent risk factor was the abdominal aorta. In fact, the distinction between independent and non-independent predictors holds significant clinical relevance. Although iliac and femoral calcifications were associated with reduced crude survival, they did not retain statistical significance after adjustment for confounding factors. This finding indicates that abdominal aortic calcification, which influences femoral and iliac artery calcifications, may affect mortality predictions and highlights the complexity of vascular health assessment in geriatric patients. Importantly, abdominal aortic calcification detected on routine radiographs can serve as a simple, accessible marker to identify high-risk patients without additional cost or advanced imaging. In circumstances where healthcare resources are limited, this prognostic indicator could facilitate the early identification of patients requiring closer monitoring during the perioperative period or rehabilitation pathways that are tailored to their individual needs.

From a rational standpoint, the identification of abdominal aortic calcification as a standalone risk factor for mortality has the potential to influence clinical decision-making. For instance, this marker could be incorporated into preoperative risk stratification algorithms alongside well-established predictors such as the American Society of Anesthesiologists (ASA) score, inflammatory markers, and frailty indices. In patients who have been identified as being particularly high-risk, clinicians may consider optimizing cardiovascular status in advance of surgery. They may also adjust surgical strategies or intensify postoperative surveillance and rehabilitation efforts. Furthermore, the acknowledgement of abdominal aortic calcification as a prognostic factor facilitates interdisciplinary collaboration, particularly between orthopedic surgeons, geriatricians, and cardiologists, in the management of these vulnerable patients.

The present study is facilitated by a relatively large, well-characterized cohort that has undergone standardized radiological assessments, in addition to comprehensive follow-up. However, it should be acknowledged that there are several limitations associated with this approach. Initially, the retro-

spective design introduces risks of selection and information bias. Secondly, although multivariable analyses were performed, this study specifically focused on the impact of visible calcification in the abdominal, iliac, and femoral arteries on mortality following geriatric hip fractures. This targeted focus was chosen because, while numerous studies have examined factors influencing hip fracture-related mortality, there remains a paucity of research addressing the prognostic role of arterial calcification in this context. Consequently, owing to the retrospective design and relatively limited sample size, several potential confounding factors associated with mortality—such as age, fracture type, comorbidity burden, Charlson Comorbidity Index, ASA score, preoperative frailty indices, nutritional status, pre-fracture nursing home residence, and comprehensive cardiovascular profiles—could not be fully accounted for. Thirdly, although the classification of calcification severity does not fully reflect the dynamic progression of vascular pathology, the absence of classification is a significant limitation. Finally, our findings derive from a single institution and may not be generalizable to other populations with differing demographics or healthcare systems.

In the future, the integration of vascular imaging with established orthopedic and geriatric risk scores has the potential to enhance the predictive accuracy for postoperative outcomes, preoperative risk stratification algorithms, and frailty indices. Interventional studies aimed at modifying vascular risk factors, improving perioperative optimization, and tailoring surgical strategies based on calcification status may further clarify the clinical utility of these findings.

CONCLUSION

A thorough understanding of the determinants of mortality in geriatric hip fracture patients is essential for accurate risk stratification, the formulation of evidence-based treatment algorithms, and the provision of appropriate counseling to patients and their caretakers. Although calcification of the iliac and femoral arteries has been associated with survival outcomes in this population, its effect appears to be contingent upon the presence of abdominal aortic calcification. Therefore, iliac and femoral artery calcification cannot be regarded as independent predictors of mortality. By contrast, abdominal aortic calcification has been identified as an independent prognostic factor for mortality in geriatric hip fracture patients aged 65 years and older. Future research should focus on prospective, multicenter studies to validate abdominal aortic calcification as a prognostic marker in hip fracture patients.

Ethics Committee Approval: This study was approved by the Marmara University Faculty of Medicine, Non-Pharmaceuticals and Non-Medical Devices Research Ethics Committee (Date: 18.04.2025, Decision No: 09.2025.25-0316).

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ORJİNAL ÇALIŞMA - ÖZ

Geriatrik yaş kalça kırıklı hastalarında radyografik olarak tespit edilen arteriyel kalsifikasyonun prognostik önemi: Mortalitenin bağımsız bir belirleyicisi olarak abdominal aort kalsifikasyonu

AMAÇ: Bu çalışmanın amacı, kalça kırığı nedeniyle cerrahi tedavi uygulanan ≥ 65 yaş hastalarda abdominal aort, iliak arterler ve femoral arterlerde radyolojik olarak saptanan arteriyel kalsifikasyonun prevalansı ve anatomik dağılımını araştırmak ve arteriyel kalsifikasyonun varlığı ile lokalizasyonunun hasta sağkalımı üzerindeki etkisini değerlendirmektir.

GEREÇ VE YÖNTEM: 2015-2024 yılları arasında kalça kırığı nedeniyle cerrahi tedavi uygulanan 270 hastanın retrospektif analizi gerçekleştirildi. Abdominal aort, iliak arterler ve femoral arterlerdeki arteriyel kalsifikasyonun varlığı düz radyografilerde incelendi ve hasta sağkalım sonuçları ile ilişkisi değerlendirildi. Ayrıca demografik özellikler, kırık tipi, tedavi yöntemi ve yoğun bakım ünitesine yatış gibi değişkenler sistematik olarak analiz edildi. **BULGULAR:** Arteriyel kalsifikasyon 211 hastada (%78.1) saptandı. Ortalama sağkalım süresi, arteriyel kalsifikasyonu olan hastalarda (47.3 ay, %95 GA: 40.7–53.8), kalsifikasyonu olmayan hastalara kıyasla (76.9 ay, %95 GA: 67.1–86.7) anlamlı derecede daha kısaydı (Log-rank $\chi^2=17.23$, $p<0.001$). Log-rank analizi ayrıca abdominal aort ($\chi^2=21.39$, $p<0.001$), iliak arterler ($\chi^2=18.21$, $p<0.001$) ve femoral arterlerdeki ($\chi^2=10.91$, $p=0.001$) kalsifikasyon varlığı ile sağkalım arasında istatistiksel olarak anlamlı farklılıklar gösterdi. Cox regresyon analizinde abdominal aort kalsifikasyonu, geriatrik kalça kırıklı hastalarda mortalite için bağımsız bir prediktör olarak belirlendi (HR=3.43, %95 GA: 1.31–8.96, $p=0.013$). Buna karşılık iliak arter kalsifikasyonu (HR=1.53, $p=0.284$) ve femoral arter kalsifikasyonu (HR=1.05, $p=0.859$) ayarlama sonrası sağkalım ile bağımsız olarak ilişkili bulunmadı. **SONUÇ:** Geriatrik kalça kırıklı hastalarda iliak ve femoral arter kalsifikasyonları mortalitenin bağımsız belirleyicileri olarak değerlendirilmemektedir. Buna karşın, abdominal aort kalsifikasyonu bu hasta grubunda mortalitenin bağımsız bir prognostik belirleyicisi olarak tanımlanmıştır.

Anahtar sözcükler: abdominal aort kalsifikasyonu; femoral arter kalsifikasyonu; iliak arter kalsifikasyonu; kalça kırığı; mortalite.

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An alternative treatment for aseptic humeral shaft nonunion: intramedullary nailing without grafting

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ABSTRACT

BACKGROUND: This study evaluates the clinical and functional outcomes of intramedullary nailing without grafting for the treatment of aseptic humeral shaft nonunion.

METHODS: Between January 2017 and January 2024, 14 patients treated at a single center for humeral shaft fractures diagnosed with nonunion and managed with intramedullary nailing without grafting were retrospectively analyzed. Demographic and clinical characteristics, union status, and preoperative and postoperative range of motion, Visual Analog Scale (VAS), QuickDASH (Quick Disabilities of the Arm, Shoulder and Hand), and Constant-Murley scores were recorded.

RESULTS: The study included 14 patients (nine women, five men) with a mean age of 49.2 ± 17.5 years (range: 26–80). Nonunion types were oligotrophic in 64.3% (n=9), atrophic in 28.6% (n=4), and hypertrophic in 7.1% (n=1) of cases. The union rate after intramedullary nailing without grafting was 78.5% (11/14). Two patients who did not achieve union underwent nail exchange with iliac autografting, resulting in a total union rate of 92.9% (13/14). The mean time to union was 4.3 ± 2.8 months (range: 2–12). The mean preoperative and postoperative QuickDASH scores were 89.4 ± 6.2 and 17.5 ± 13.3 , respectively, while the Visual Analog Scale scores were 7.7 ± 1.1 and 1.7 ± 1.1 , respectively ($p < 0.001$). Of the three patients who failed to achieve union after initial treatment, two had atrophic nonunion and one had oligotrophic nonunion. A statistically significant association was observed between nonunion type and the need for revision surgery ($p < 0.01$), with atrophic nonunions being significantly more frequent in patients requiring revision. One patient developed adhesive capsulitis, and another patient who underwent revision experienced transient radial nerve palsy with complete functional recovery. Proximal screw loosening was observed in two patients and was recorded as a minor complication.

CONCLUSION: Intramedullary nailing without grafting is an effective and safe treatment option for aseptic humeral shaft nonunion in selected patients, particularly those previously treated conservatively. However, omission of grafting in cases of atrophic nonunion or during nail exchange procedures may negatively affect healing.

Keywords: Humerus fracture; intramedullary nailing; nonunion; pseudoarthrosis; graft.

INTRODUCTION

Humerus fractures account for approximately 3–5% of all fractures.^[1] Conservative treatment is often successful; however, surgical intervention is preferred for specific indications.^[2,3]

Nonunion occurs in 8–13% of cases, leading to pain, functional loss, and the need for additional surgical intervention.^[4,5]

Plate fixation with autograft is considered the standard treatment for humeral nonunion, with reported union rates ranging from 83% to 100%. Alternative treatment options include

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intramedullary nailing (IMN), external fixators, and fibular strut grafts.^[4-7] Complications associated with plate fixation include wound issues, transient radial nerve palsy, and infection.^[4,6,8] Although less commonly used, circular external fixators have demonstrated union rates of 93–100%; however, they are associated with patient non-compliance, pin-site infections, and prolonged treatment duration.^[9,10]

Grafting, particularly iliac autografting, is commonly used in atrophic and oligotrophic nonunions.^[4,11] Nevertheless, donor-site pain and prolonged operative time are notable disadvantages. Bone morphogenetic protein (BMP) offers the advantage of shorter operative times but is associated with high costs.^[12,13]

Intramedullary nailing, with or without grafting, minimizes dissection and reduces the risks of infection and neurovascular injury.^[14] However, shoulder pain, joint stiffness, and lower union rates have been reported as potential limitations.^[14-16] This study investigates the efficacy of intramedullary nailing without grafting for aseptic humeral shaft nonunion in the absence of significant bone loss.

MATERIALS AND METHODS

After obtaining local ethics committee approval, 22 patients who underwent surgery for humeral nonunion at a single center between 2017 and 2024 were retrospectively analyzed. Of these patients, 15 were treated with IMN without graft, five with IMN plus autograft, and four with plate fixation plus autograft. Fourteen patients older than 18 years, with a follow-up period longer than 12 months, who were treated for traumatic humeral shaft fracture nonunion with intramedullary nailing without graft were included in the study. One patient was excluded due to the lack of follow-up. Patients with infected nonunion, pediatric patients, patients with nerve damage from previous surgery, fractures within 5 cm of the joint line, and pathologic fractures were excluded. Nonunion was defined as fractures showing no signs of union on X-ray imaging at least six months after trauma, accompanied by clinical pain or pathologic motion at the fracture site. The type of nonunion was evaluated according to the Weber and Cech classification.^[17]

Demographic and clinical data, including age, sex, fracture side, dominant arm, prior treatment, time to nonunion surgery, and follow-up duration, were collected from medical records. Radiographic data included fracture type (AO/OTA classification [Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association]), fracture location, and nonunion type.

All surgeries were performed by a single surgeon (F.A.) with 30 years of experience in trauma and nonunion surgery, using the InSafeLOCK® Humerus Nail (TST Rakor Tibbi Aletler, Istanbul, Türkiye). This cannulated, round nail allows distal locking with an internal Endopin without the need for an additional incision. It features a 3-cm distal segment angled 5°

anteriorly and a 4-mm Ti6Al7Nb Endopin that anchors to the posterior cortex, allowing up to 6 mm of compression via a proximal set screw.

Surgical Technique

Surgeries were performed under general anesthesia in the beach-chair position using an antegrade approach. For closed reduction, the fracture ends were reamed until a hemorrhagic surface was observed. If closed reduction was not feasible, the fracture site was exposed using a deltopectoral (proximal), anterolateral (middle), or posterior (distal) approach. Scar tissue was debrided, the fracture was reduced, and reaming was initiated. After insertion of a nail of appropriate diameter and length, the nail was locked distally using an Endopin. Following adequate compression, the proximal nail was fixed with two or three screws. Identification and protection of the radial or ulnar nerve were performed when these structures were at risk.

Postoperative Rehabilitation and Follow-up

Early active and passive motion was initiated postoperatively. A sling was recommended for two weeks, except during exercises. Physical therapy was initiated at six weeks in patients with limited shoulder or elbow range of motion. Follow-up evaluations were performed monthly for the first six months, every three months during the first year, every six months during the second year, and annually thereafter.

Union rate, shoulder and elbow range of motion, and functional scores were evaluated at follow-up visits. Anteroposterior (AP) and lateral radiographs of the humerus were obtained at each visit. Radiographic union was defined as union of the fracture in at least three cortices, with callus or trabecular formation, obliteration of the fracture line, and/or cortical continuity. Clinically, union was defined as the absence of motion and pain at the fracture site.^[17] Shoulder and elbow motion were measured using a goniometer. The Visual Analog Score (VAS), the shortened version of the Disabilities of the Arm, Shoulder, and Hand (QuickDASH) questionnaire, and the Constant-Murley Score were administered to evaluate the patients' subjective functional status preoperatively and at the last follow-up visit.^[18-20] Based on Constant-Murley shoulder scores, outcomes were categorized as excellent (80-100), good (60-80), moderate (40-60), poor (20-40), and very poor (0-20).^[21]

All functional and radiologic assessments were performed by an independent observer (M.D.). Complications, including nerve palsy, nonunion, malunion, infection, and hardware loosening, were recorded.

Statistical Analysis

For evaluation of the findings obtained in the study, statistical analyses were performed using NCSS (Number Cruncher Statistical System) 2020 Statistical Software (NCSS LLC, Kaysville, Utah, USA). Descriptive statistical methods were used to evaluate the study data: quantitative variables were

expressed as mean, standard deviation, median, minimum, and maximum values, while qualitative variables were presented as frequencies and percentages. The Shapiro-Wilks test and box plot graphs were used to assess the normality of data distribution.

For within-group comparisons of non-normally distributed variables in two related samples, the Wilcoxon signed-rank test was used. For comparison of qualitative data, Fisher's exact test and the Fisher-Freeman-Halton test were applied. Results were evaluated at a 95% confidence interval, with statistical significance set at $p < 0.05$.

Written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethics approval was granted by the local institutional ethics committee (Date: 25.09.2025, No: 2025/0177).

RESULTS

This study included 14 patients (nine women, five men) with a mean age of 49.2 ± 17.5 years (range: 26–80) and a mean follow-up of 37.5 ± 23.8 months (range: 12–85). The mean time from the initial fracture to nonunion surgery was 13.5 ± 9.8 months (range: 6–40). Eleven patients had received prior conservative treatment, and three had undergone intramedullary nailing. Nonunion types were oligotrophic in 64.3% ($n=9$), atrophic in 28.6% ($n=4$), and hypertrophic in 7.1% ($n=1$) of cases.

Intramedullary nailing without grafting achieved union in 78.5% (11/14) of cases after the initial surgery. Of the 11 patients with prior conservative treatment, 90.9% (10/11) achieved union, while one patient declined revision due to age and comorbidities (Fig. 1). Of the three patients requiring nail exchange without grafting, two (66.7%) did not achieve union (Fig. 2) and subsequently underwent revision with iliac

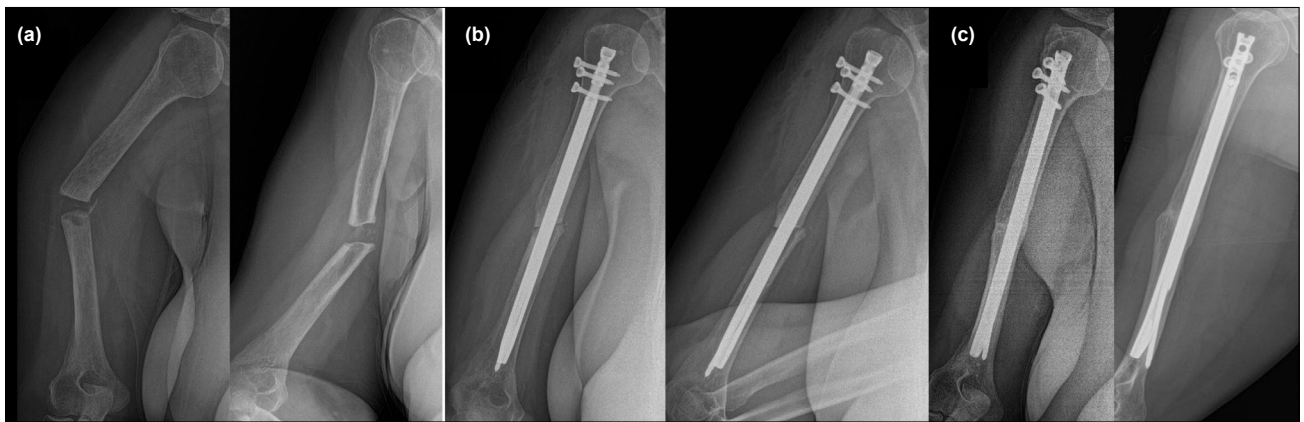


Figure 1. Closed reduction and compressive nailing were performed in a patient who underwent intramedullary nailing without grafting for nonunion 24 months after the initial fracture. Complete union was achieved. (a) Preoperative radiographs. (b) Early postoperative radiographs. (c) Radiographs at the second postoperative year.

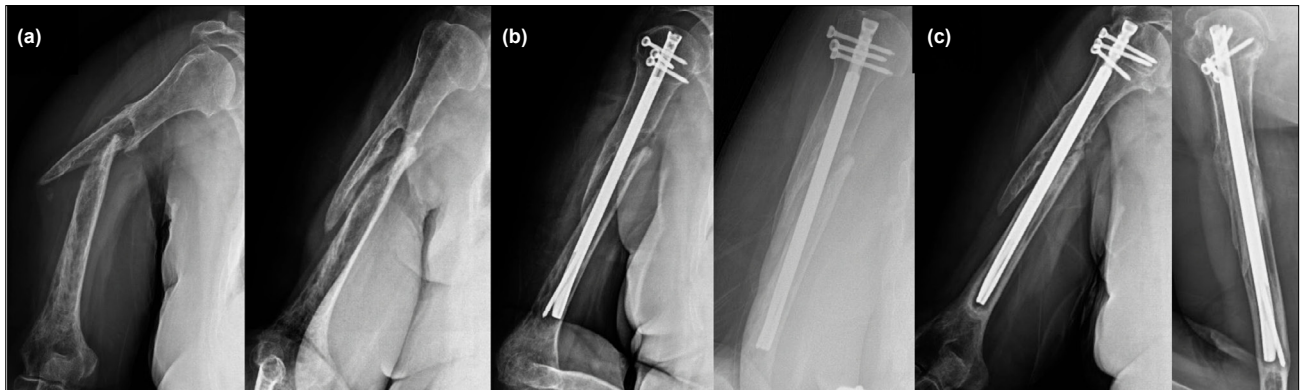


Figure 2. Open reduction and compressive nailing were performed in a patient who underwent intramedullary nailing without grafting for nonunion 12 months after the initial fracture. Postoperative union was not achieved, and the patient declined reoperation. (a) Preoperative radiographs. (b) Early postoperative radiographs. (c) Radiographs at the second postoperative year showing lysis around the nail and screw, supporting the diagnosis of nonunion.

Table I. Patient demographics, treatment, and outcomes

Age/ Sex	Side	First-Line Treatment	Prior Surgery (n)	Nonunion Type	Graft	Total Surgeries (n)	Follow-up (mo)	Union Time (mo)	Complications/ Further Treatment	Final VAS	Final QuickDASH	Final Shoulder ROM (Flex/Ext/Abd, °)	Final Elbow ROM (Flex/Ext, °)	Constant- Murley Score
28/M	R	IMN	1	Atrophic	Iliac	3	73	4	Revision with grafting and exchange nailing	2	5.0	180/50/180	135/0	95
26/M	R	Conservative	0	Oligotrophic	-	1	71	3	None	0	0.0	180/40/180	140/0	99
61/F	R	Conservative	0	Hypertrophic	-	1	64	2	One proximal screw loosening	3	27.5	170/15/140	135/0	80
46/F	R	IMN	1	Atrophic	Iliac	3	64	5	Transient radial nerve palsy (fully recovered); revision with grafting and exchange nailing	2	2.3	170/40/170	135/0	95
28/F	L	Conservative	0	Oligotrophic	-	1	60	2	None	2	17.5	170/45/170	130/0	95
58/F	R	Conservative	0	Oligotrophic	-	1	38	5	None	0	9.1	175/45/95	130/0	95
39/F	L	Conservative	0	Oligotrophic	-	1	32	2	None	4	42.5	100/15/80	135/0	77
35/M	R	Conservative	0	Oligotrophic	-	1	31	8	Two proximal screws loosened	2	17.5	170/30/100	135/0	98
80/F	R	Conservative	0	Oligotrophic	-	1	24	-	Nonunion; declined further surgery	3	31.8	100/30/90	135/0	64
42/F	R	IMN	1	Atrophic	-	2	17	2	None	2	17.5	170/30/170	135/0	85
66/F	L	Conservative	0	Oligotrophic	-	1	14	12	None	2	20.0	170/45/100	120/0	82
74/F	R	Conservative	0	Oligotrophic	-	1	13	4	None	2	27.5	100/30/80	135/-10	73
60/M	R	Conservative	0	Atrophic	-	1	12	3	None	1	0.0	170/45/170	135/0	95
46/M	R	Conservative	0	Oligotrophic	-	1	12	4	Adhesive capsulitis	0	29.5	100/30/80	135/-10	60

M: Male; F: Female; R: Right; L: Left; IMN: Intramedullary nailing; VAS: Visual Analog Scale; QuickDASH: Quick Disabilities of the Arm, Shoulder, and Hand; ROM: Range of motion; Flex: Flexion; Ext: Extension; Abd: Abduction; mo: Months.

autograft, achieving union. The total union rate was 92.9% (13/14). The mean union time was 4.3 ± 2.8 months (range: 2–12).

The mean preoperative and postoperative QuickDASH scores were 89.4 ± 6.2 and 17.5 ± 13.3 , respectively, while the VAS scores were 7.7 ± 1.1 and 1.7 ± 1.1 , respectively. These differences were statistically significant ($p < 0.001$). The mean Constant-Murley score at the last follow-up visit was 85.2 ± 12.9 (range: 60–99).

Shoulder flexion measured with a goniometer was $152.5 \pm 34.6^\circ$ (range: 100–180), shoulder abduction was $134.6 \pm 43.0^\circ$ (range: 80–180), and shoulder extension was $35.3 \pm 11.3^\circ$ (range: 15–50). Elbow flexion was $133.9 \pm 4.8^\circ$ (range: 120–140), and elbow extension was $-1.4 \pm 3.6^\circ$ (range: 0 to -10).

Complications

Nonunion persisted in three patients after the initial surgery; two achieved union after nail exchange with grafting. One patient developed adhesive capsulitis, and two experienced proximal screw loosening. One revision patient had transient radial nerve palsy with full recovery (Table 1).

The nonunion type of the two patients who underwent revision was atrophic, while the nonunion type of the other patient with persistent nonunion who declined revision surgery was oligotrophic. There was a statistically significant difference in nonunion types according to revision status ($p = 0.009$; $p < 0.01$). The success of IMN without grafting was statistically lower in atrophic-type nonunions.

DISCUSSION

In the present study, the results of intramedullary nailing without grafting in the treatment of aseptic humeral nonunion without significant bone loss were evaluated. The union rate after the first nonunion surgery was 78.5% (11/14). In other studies in which humeral nonunions were treated with IMN without grafting, the union rates after the first nonunion surgery ranged from 29% to 62%.^[6,22] In this study, the total union rate after revision with grafting was 92.9%, while union rates in studies in which IMN with grafting was performed for nonunion ranged from 56% to 100% (mean: 88%).^[6,8,14,15] These results appear to be consistent with the literature.

In 10 (90.9%) of 11 patients with previous conservative treatment resulting in nonunion, union was achieved with IMN without grafting. In a study by Verbuggen et al.,^[23] union was achieved with IMN without grafting in seven (41.1%) of 17 patients who had previously been treated conservatively and subsequently developed nonunion. There are very few studies on IMN without grafting for the treatment of nonunion, and in general, reported union rates have been low. Dujardin et al.^[22] reported an overall union rate of 62% after IMN without grafting in a group previously treated conservatively or with nails. Accordingly, the union rates in patients with prior conservative treatment in this study appear satisfactory

compared to the literature.^[6,22,23]

In a study by Fininkila et al.,^[24] the union rate of exchange nailing without grafting in nonunions was 38% (5/13), and in a study by McKee et al.,^[25] the union rate of exchange nailing without grafting in nonunions was 40% (4/10). Lin et al.^[26] reported a union rate of 95.65% (22/23) after the first attempt at exchange nailing with grafting in patients previously treated with nails who developed nonunion, and Li et al.^[15] reported a 100% union rate after exchange nailing with grafting in a 12-patient case series with a similar patient group. Including the present study, union rates of exchange nailing without grafting are considerably lower than those achieved with grafting. Grafting combined with exchange nailing may increase the likelihood of success in nonunion surgery.^[6,8,15,26]

The mean union time was 4.3 ± 2.8 months (range: 2–12). In the literature, union time after interventions for nonunion is generally reported as 3–5 months, and the findings of the present study are consistent with previous studies.^[27]

Among patients undergoing surgery for nonunion, nine were classified as oligotrophic, one as hypertrophic, and four as atrophic. Of the three patients who experienced persistent nonunion after the initial surgery, two had atrophic nonunion and one had oligotrophic nonunion. The union rate for atrophic nonunions after the first surgery was 50% (2/4). Subsequent union in these cases was achieved with exchange nailing and grafting. In the current study, the success rate of intramedullary nailing without grafting was statistically lower for atrophic nonunions ($p = 0.009$).

There are many biological and mechanical factors that need to be addressed in the treatment of nonunion. In hypertrophic nonunions, mechanical factors are primarily implicated, whereas in atrophic nonunions, disruption of local biology is considered the main cause. Factors leading to deterioration of local biology include excessive soft tissue dissection from previous surgeries, impaired blood supply, decreased local growth factors, and infection.^[14,23,27] Giannoudis et al.^[28] stated that both local biological factors should be corrected and mechanically stable fixation should be provided in nonunion surgery, emphasizing that grafts may be required to improve local biology after adequate fixation. In the present study, the low union rates observed in patients with atrophic nonunion treated with fixation without grafting, along with successful union after revision with grafting, suggest that grafting may be more appropriate in atrophic nonunions.

In nonunion surgery, iliac crest autograft is among the most frequently employed methods, serving as an adjunct to mechanical stabilization. Its notable advantages include ease of application, low associated morbidity for the patient, and a demonstrated capacity to increase union rates. However, its use is not without drawbacks. Disadvantages include the need for extensive dissection when applied to nonunion areas, the potential for nerve damage, and considerable donor site morbidity.^[13,14] Rajan et al. reported that 26% of patients

still had pain at the donor site and 13% had numbness radiating to the thigh at one year postoperatively in patients who received an iliac autograft. Accordingly, they reported that iliac autograft harvesting should be limited in the absence of an absolute indication.^[29]

Preoperative and postoperative mean QuickDASH scores were 89.4 ± 6.2 and 17.5 ± 13.3 , respectively, while Visual Analog Scale scores were 7.7 ± 1.1 and 1.7 ± 1.1 , respectively ($p < 0.001$). At the last follow-up visit, the Constant-Murley score was 85.2 ± 12.9 (range: 60-99). According to the Constant-Murley score, 10 patients were classified as very good and four patients as good. At the last follow-up visit, shoulder flexion was $152.5 \pm 34.6^\circ$ (range: 100-180), shoulder abduction was $134.6 \pm 43.0^\circ$ (range: 80-180), shoulder extension was $35.3 \pm 11.3^\circ$ (range: 15-50), elbow flexion was $133.9 \pm 4.8^\circ$ (range: 120-140), and elbow extension was $-1.4 \pm 3.6^\circ$ (range: 0 to -10). The results were quite satisfactory except for two patients. Outcomes were mediocre in one patient who failed to achieve union and declined reoperation, and in another patient who was treated for adhesive capsulitis after surgery. Shoulder and upper extremity function can be well preserved after IMN in the treatment of nonunion when an appropriate surgical technique is used.^[14,15,23]

In two patients in this study, proximal screw loosening was observed after union and was considered a minor complication. Nonunion occurred in three patients, and union was achieved in two after revision surgery. One patient who underwent revision developed transient radial nerve palsy with complete functional recovery. One patient developed postoperative adhesive capsulitis. In a systematic review, Peters et al.^[6] reported total complication rates of 12% for nonunion surgeries with plate and graft, 15% for IMN with graft, and 8% for IMN without graft. While local infection and nerve disorders are more common after osteosynthesis with plating, shoulder-related problems (rotator cuff tear, shoulder impingement, adhesive capsulitis) and union problems are more common after nailing. In a prospective study by Singh et al.^[8] comparing patients with nonunion treated with plate and nailing, no statistically significant difference was found between the groups in terms of nonunion; one patient in the nail group had nonunion requiring revision, and two patients in the plate group developed transient radial palsy that completely resolved. In a study by Martinez et al.^[30] comparing nonunion patients treated with plate and nailing, no statistically significant difference in complications was reported; three patients in the nail group healed with acceptable angulation, and three patients in the plate group developed transient radial palsy that completely resolved. Many studies have reported that nailing is safer in terms of radial nerve palsy, whereas plate osteosynthesis is safer in terms of union-related complications.^[6,8,30]

This retrospective study is limited by its small sample size and lack of a control group. Prospective, controlled studies with larger cohorts are needed to validate these findings.

Intramedullary nailing without grafting is an effective and safe treatment for aseptic humeral shaft nonunion in selected patients, particularly those with prior conservative treatment. However, omitting grafting in cases of atrophic nonunion or nail exchange may negatively affect healing.

Ethics Committee Approval: This study was approved by the Göztepe Prof. Dr. Süleyman Yalçın City Hospital Ethics Committee (Date: 25.09.2025, Decision No: 2025/0177).

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ORİJİNAL ÇALIŞMA - ÖZ

Aseptik humerus shaft kaynamama tedavisinde alternatif bir yöntem: Greftsiz İntramedüller çivileme

AMAÇ: Bu çalışma, aseptik humerus cisim psödoartroz tedavisinde greftsiz intramedüller çivilemenin klinik ve fonksiyonel sonuçlarını değerlendirmektedir.

GEREÇ VE YÖNTEM: Ocak 2017-Ocak 2024 tarihleri arasında, tek merkezde humerus cisim kırığı nedeniyle psödoartroz tanısı almış ve greftsiz intramedüller çivileme ile tedavi edilmiş 14 hasta retrospektif olarak incelendi. Demografik ve klinik özellikler, kaynama durumu, ameliyat öncesi ve sonrası eklem hareket açıklığı, Görsel Analog Skala (VAS), QuickDASH ve Constant-Murley skorları kaydedildi.

BULGULAR: Çalışmaya yaş ortalaması 49.2±17.5 yıl (26-80) olan 14 hasta (9 kadın, 5 erkek) dahil edildi. Psödoartroz tipleri olguların %64.3'ünde (n=9) oligotrofik, %28.6'sında (n=4) atrofik, %7.1'inde (n=1) hipertrofik olarak saptandı. Greftsiz intramedüller çivileme sonrası kaynama oranı %78.5 (11/14) idi. Kaynama sağlamayan 2 olguya iliak otograft ile çivi değişimi uygulandı ve toplam kaynama oranı %92.9'a (13/14) ulaştı. Ortalama kaynama süresi 4.3±2.8 ay (2-12 ay) idi. Ameliyat öncesi ve sonrası QuickDASH skorları sırasıyla 89.4±6.2 ve 17.5±13.3; VAS skorları ise 7.7±1.1 ve 1.7±1.1 bulundu (p<0.001). İlk tedavi sonrası kaynamayan 2 olgunun psödoartroz tipi atrofik, birinin ise oligotrofikti. Revizyon gerektiren olgularda atrofik psödoartroz oranı anlamlı derecede yüksek bulundu (p<0.01). Bir hastada adeziv kapsülit gelişti, revizyon uygulanan başka bir hastada ise geçici radial sinir felci gözlemlendi ve tam fonksiyonel iyileşme sağlandı. İki hastada proksimal vida gevşemesi minör komplikasyon olarak kaydedildi.

SONUÇ: Greftsiz intramedüller çivileme, özellikle daha önce konservatif tedavi uygulanmış seçilmiş hastalarda aseptik humerus cisim psödoartroz için etkili ve güvenli bir tedavi seçeneğidir. Ancak atrofik psödoartroz veya çivi değişimi gereken olgularda greft kullanılmaması iyileşme sürecini olumsuz etkileyebilir.

Anahtar sözcükler: Greft; humerus kırığı; intramedüller çivileme; kaynamama; psödoartroz.

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Prophylactic chorioretinectomy in deadly weapon-related open globe injuries

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ABSTRACT

BACKGROUND: To evaluate the anatomical and functional outcomes of pars plana vitrectomy (PPV) combined with prophylactic chorioretinectomy (CR) in patients with deadly weapon-related open globe injuries (DWOGLs).

METHODS: Medical records of patients who underwent PPV and prophylactic CR for open globe injuries (OGIs) caused by deadly weapons between November 2016 and October 2024 were retrospectively reviewed. Demographic characteristics, injury type, cause of injury, zone of injury, intraocular foreign body (IOFB) exit/impact site, best-corrected visual acuity (BCVA), proliferative vitreoretinopathy (PVR) rates, anatomical success, and globe survival were evaluated.

RESULTS: Of a total of 283 OGIs, 41 eyes from 35 patients who underwent PPV with prophylactic CR for deadly weapon-related trauma were included in the analysis. The mean age was 30.9 ± 9.4 years, and 88.6% of the patients were male. Perforating injuries were observed in 38 eyes (92.7%), and penetrating injuries associated with an IOFB in 3 eyes (7.3%). The causes of injury included improvised explosive devices in 20 eyes (48.8%), hand grenades in 11 eyes (26.8%), landmines in 8 eyes (19.5%), and rocket-propelled grenades in 2 eyes (4.9%). The IOFB exit/impact site was located in the posterior pole in 38 eyes (92.7%), of which 22 (53.6%) were outside the vascular arcades, 12 (29.3%) within the vascular arcades, and 4 (9.7%) adjacent to the optic disc. The mean initial BCVA was 2.62 ± 0.98 logMAR, with 90.2% of eyes presenting between light perception and counting fingers. PPV was performed at a mean of 5.9 ± 2.7 days after primary repair. Of these eyes, 43.9% had retinal detachment. The mean number of PPV procedures was 2.6 ± 1.1 . C3F8 gas endotamponade was used in 51.2% of cases. At a mean follow-up of 32.8 ± 16.6 months, the final BCVA improved significantly to 1.18 ± 1.20 logMAR ($p < 0.001$), with 68.3% achieving $\geq 20/200$ vision. At final follow-up, the rates of PVR, anatomical success, and globe survival were 14.6% (6/41), 85.4% (35/41), and 87.8% (36/41), respectively.

CONCLUSION: Pars plana vitrectomy combined with prophylactic CR appears to be an effective treatment option for DWOGLs, offering prevention of PVR development and achieving high anatomical success, favorable globe survival, and meaningful visual improvement despite severe ocular trauma.

Keywords: Chorioretinectomy; deadly weapon; intraocular foreign body; ocular trauma, open globe injury; penetrating eye injury; perforating eye injury; proliferative vitreoretinopathy.

INTRODUCTION

Open globe injuries (OGIs) are among the leading causes of ocular morbidity and blindness worldwide.^[1] Globally, the incidence of OGI is 3.5 per 100,000 individuals per year, corresponding to approximately 203,000 cases annually.^[2] The long-term prognosis is largely influenced by the severity of

the initial mechanical damage as well as the biological processes of wound healing and scar development. Proliferative vitreoretinopathy (PVR), which develops secondary to scarring in 40-60% of OGIs, remains a major limiting factor for both visual and anatomical rehabilitation.^[3-5]

Within the spectrum of OGIs, deadly weapon-related OGIs

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(DWOGLs) represent a particularly severe subset due to the high-velocity nature of ballistic trauma and the extensive structural damage. Firearm injuries involving the face and head are associated with substantial morbidity and mortality.^[6] Although research on firearm-associated ocular injury (FAOI) is limited, available data highlight its significant impact on vision.^[7,8] In one of the few studies addressing FAOI, hopra et al.^[9] reported that 44% of survivors treated at two New York City hospitals suffered long-term visual disability, underscoring the devastating ocular consequences of firearm trauma. Despite these findings, population-level and mechanism-specific data on FAOI remain scarce, and the true burden of deadly weapon-related ocular trauma is likely underestimated.

Given the high risk of PVR and anatomical failure in severe OGLs, various surgical strategies have been explored to mitigate post-traumatic scarring. In 1987, Zivojnovic first proposed a surgical method aimed at excising incarcerated retinal tissue and associated scar tissue at the site of perforation.^[10] Later, in 2004, Kuhn et al.^[12] introduced prophylactic chorioretinectomy (CR) for the management of intraocular foreign bodies (IOFBs) that penetrate the globe or for globe ruptures with scleral involvement extending posterior to the extraocular muscle insertions. In this technique, within the first 100 hours following injury, all incarcerated retina at the wound site is removed using a vitrector, and the surrounding retina and choroid at the exit wound are ablated with diathermy along a narrow circumferential zone approximately 1 mm in width of exposed sclera.^[11] Early data from an international, prospective, multicenter investigation led by the United States Eye Injury Registry in collaboration with the American Society of Ocular Trauma indicated that CR reduced PVR rates from approximately 60% to below 10%. Subsequent series have consistently reported favorable visual outcomes and similarly low PVR rates in eyes treated with this approach.^[13-18]

Despite accumulating evidence supporting the role of prophylactic CR in reducing PVR following severe ocular trauma, data specifically focusing on DWOGLs remain limited. In this study, we aimed to evaluate the anatomical and functional outcomes of prophylactic CR combined with pars plana vitrectomy (PPV) in patients with DWOGL treated at a major tertiary ocular trauma referral center in Türkiye.

MATERIALS AND METHODS

This retrospective study was approved by the local institutional review and ethics board (IRB #2025-617). The study adhered to the principles of the Declaration of Helsinki. Medical records of patients who underwent PPV and prophylactic CR for OGLs caused by deadly weapons between November 2016 and October 2024 were retrospectively reviewed. Patients with missing medical records, those who presented with end-stage ocular conditions that precluded further treatment (e.g., phthisis bulbi), and those with a follow-up period of < 12 months were excluded from the analysis.

All but one of the patients were managed initially at outside centers and were subsequently referred after primary globe repair, including closure of the scleral defect and restoration of globe integrity. Following primary globe repair, all patients underwent orbital computed tomography and B-scan ultrasonography at our clinic. The injuries were categorized according to the Birmingham Eye Trauma Terminology (BETT) classification of ocular trauma.^[19] The present study includes only eyes with severe posterior segment involvement considered to be at high risk for PVR and therefore managed with PPV combined with prophylactic CR. Accordingly, all included injuries consisted either of perforating injuries with posterior exit wounds involving Zone 2 or Zone 3, or penetrating injuries associated with a deep-impact IOFB, defined as extension into the choroid with or without scleral involvement. In addition, the ocular trauma score (OTS) was retrospectively determined as described by Kuhn et al.^[20] All eyes demonstrated light perception or better visual acuity prior to surgical repair.

Surgical Technique

All surgical procedures were performed by an experienced vitreoretinal surgeon (AHD) under general anesthesia using three-port, 23-gauge or 25-gauge PPV with a non-contact wide-field viewing system (EIBOS, Moller-Wedel GmbH, Germany). When indicated, pars plana lensectomy or phacoemulsification was carried out at the surgeon's discretion. The vitrectomy was performed utilizing triamcinolone acetate to improve visualization of any residual vitreous at the posterior pole, particularly around the impact site. The macular internal limiting membrane was peeled only in cases where the retinal lesion was located close to the fovea. When required, perfluorocarbon liquid (PFCL) was used as intraoperative retinal tamponade to stabilize the posterior retina. After complete vitreous removal, the retina was examined for incarceration or direct injury, including deep impact by an IOFB. The chorioretinectomy was subsequently carried out using a vitreous cutter to excise incarcerated retinal tissue, extending through the choroid to expose bare sclera at sites of deep impact or IOFB perforation. Endodiathermy at maximum power was applied to demarcate the CR area, and transient elevation of infusion pressure to 60 mmHg was used to minimize intraocular bleeding. After removal of damaged tissue, endolaser retinopexy was applied circumferentially to the margins of the chorioretinectomy within healthy retina wherever possible, sparing the posterior pole. All cases underwent a fluid-air exchange followed by long-acting gas (perfluoropropane, C3F8) or silicone oil (1000 or 5000 centistokes) endotamponade.

Outcome Measures

Demographic and clinical data extracted from patient records included age, sex, laterality, injury type (mechanism), cause of injury, location of entrance (zone), and IOFB exit/impact site, time to vitreoretinal surgery, best-corrected visual acuity (BCVA) before and after surgery, number of vitreoretinal surgeries, rate of PVR, anatomical outcome, and globe survival.

The primary outcome measures were BCVA, rate of PVR, anatomical success, and globe survival at the final follow-up examination. Additional documented findings included corneal scarring/corneal decompensation and direct macular injury secondary to the IOFB.

Best-corrected visual acuity values were expressed in logarithm of the minimum angle of resolution (logMAR) notation as described by Ferris et al.^[21] Hand movements (HM) and counting fingers (CF) vision were assigned logMAR values of 3.0 and 2.0, respectively, according to the method proposed by Holladay.^[22] In this study, light perception (LP) was given a logMAR value of 4.0,^[14] whereas no light perception (NLP) was not assigned a logMAR value.

Proliferative vitreoretinopathy was defined as the presence of any epiretinal or subretinal membrane proliferation. Anatomical success was defined as complete retinal attachment in the absence of silicone oil tamponade. Globe survival was defined as complete retinal attachment, intraocular pressure above 6 mmHg, and BCVA of LP or better.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows (Version 21.0; IBM Corp., Armonk, NY, USA). A p-value of <0.05 was considered statistically significant. Descriptive statistics were used to summarize demographic and clinical characteristics. Continuous variables were presented as mean $\pm$ standard deviation (SD) or median (range), as appropriate. Categorical variables were expressed as numbers (n) and percentages (%). Changes in BCVA between baseline and final follow-up were analyzed using the Wilcoxon signed-rank test.

RESULTS

Of 283 OGIs presenting during the study period, 41 eyes from 35 patients who underwent PPV with prophylactic CR for deadly weapon-related trauma were included in the analysis. Patient demographics, injury characteristics, and associated clinical findings are presented in Table 1. The mean age was 30.9 ± 9.4 years (median 28 years, range 19–61 years). Among the 35 patients, 31 were male (88.6%) and 4 were female (11.4%). Twenty-two (53.6%) right eyes and 19 (46.4%) left eyes were injured, whereas 6 (17.1%) patients experienced bilateral eye injuries.

The majority of eyes (38 eyes, 92.7%) had perforating eye injuries, while 3 (7.3%) eyes had an IOFB associated with deep impact. The causes of injury included improvised explosive devices (IED) in 20 eyes (48.8%), hand grenades in 11 eyes (26.8%), landmines in 8 eyes (19.5%), and rocket-propelled grenades (RPG) in 2 eyes (4.9%). With respect to the location of entrance (zone), zone 3 involvement was most frequent (58.5%), followed by zone 2 (24.4%) and zone 1 (17.1%). All IOFB exit/impact sites, except for 3, were located posterior to the equator. Among these, 22 (53.6%) were located outside the vascular arcades, 12 (29.3%) within the vascular

arcades, and 4 (9.7%) adjacent to the optic disc. The mean initial BCVA was 2.62 ± 0.98 logMAR (range: 0.70–4.00 logMAR). Initial BCVA ranged from LP to CF in 90.2% of the eyes.

Surgical procedures, anatomical, and visual outcomes are summarized in Table 2. Patients underwent PPV with prophylactic CR surgery with a mean interval time of 5.9 ± 2.7 days (range: 0–17 days) following the primary globe repair. In half of the eyes (22 eyes, 53.6%), C3F8 was preferred as the endotamponade. The mean number of PPV surgeries in each eye was 2.6 ± 1.1 (range: 1–5), with a total of 105 surgeries. The mean follow-up following surgery was 32.8 ± 16.6 months (range: 13–71 months).

The mean final BCVA was 1.18 ± 1.20 logMAR (range: 0.10–4.00 logMAR), representing a statistically significant improvement compared with baseline values ($p < 0.001$). Final BCVA ranged from 20/200 to NLP, with 28 (68.3%) patients attaining a BCVA of 20/200 or better. Corneal scarring or decompensation was observed in 4 (9.7%) patients, while direct macular injury caused by IOFB impact accounted for severe vision loss in 10 (24.4%) patients. PVR rates following initial PPV were 29.3% (12 of 41 eyes), decreasing to 14.6% (6 of 41 eyes) by the end of follow-up. The anatomical success rate was 85.4% (35 of 41 eyes), and the globe survival rate was 87.8% (36 of 41 eyes). Silicone oil was left in five eyes due to persistent hypotony.

Among eyes presenting with severe visual impairment at baseline, 20 eyes (48.8%) had HM or LP vision. In this subgroup, the mean baseline BCVA was 3.50 ± 0.51 logMAR and improved significantly to 1.80 ± 1.32 logMAR at final follow-up ($p < 0.001$). Eight eyes (40.0%) achieved a final BCVA of $\geq 20/200$. Anatomical success was achieved in 14 eyes (70.0%), and globe survival was maintained in 15 eyes (75.0%).

Eighteen eyes (43.9%) presented with retinal detachment (RD) at the time of PPV. In this subgroup, the mean final BCVA was 1.79 ± 1.40 logMAR. PVR developed in 12 eyes (66.7%) after the initial PPV and persisted in 6 eyes (33.3%) at final follow-up. Anatomical success was achieved in 12 eyes (66.7%), and globe survival was maintained in 14 eyes (77.8%).

DISCUSSION

Deadly weapon-related open globe injuries represent one of the most devastating forms of ocular trauma, frequently associated with high-velocity impact, profound posterior segment damage, and a markedly elevated risk of PVR, which remains a major driver of anatomical failure and poor functional recovery. In this context, the present study evaluated PPV combined with CR in a homogeneous cohort of patients with DWOGI and demonstrated that this proactive surgical strategy is associated with meaningful visual improvement ($\geq 20/200$ vision in 68.3% of eyes), high anatomical success (85.4%), favorable globe survival (87.8%), and a low final PVR rate (14.6%) despite severe ocular damage.

The demographic and injury characteristics of our cohort

Table 1. Patient demographics, injury characteristics, and associated clinical findings

Patient	Age	Sex	Eye	Injury type	Cause of injury	Location of entrance site (Zone)	Location of IOFB exit /impact site	APD	RD	OTS
1	19	M	OD	Perforating	Hand grenade	Zone 1	within the vascular arcades	Yes	No	46
2*	23	M	OD	Perforating	Land mine	Zone 3	outside the vascular arcades	No	Yes	45
			OS	Perforating		Zone 3	adjacent to the optic disc	Yes	No	46
3*	28	M	OD	Perforating	IED	Zone 1	outside the vascular arcades	No	No	76
			OS	Perforating		Zone 3	within the vascular arcades	No	Yes	45
4	61	M	OD	Penetrating	Hand grenade	Zone 1	anterior to the equator	No	No	70
5	32	M	OS	Perforating	IED	Zone 3	within the vascular arcades	Yes	Yes	35
6	33	F	OD	Perforating	IED	Zone 2	anterior to the equator	No	No	76
7	26	M	OS	Perforating	IED	Zone 3	within the vascular arcades	No	No	56
8	25	M	OD	Perforating	Hand grenade	Zone 3	within the vascular arcades	Yes	Yes	35
9	28	M	OS	Perforating	IED	Zone 3	outside the vascular arcades	No	No	56
10*	29	M	OD	Perforating	IED	Zone 2	outside the vascular arcades	No	Yes	45
			OD	Perforating		Zone 3	within the vascular arcades	No	Yes	45
11	25	M	OS	Perforating	IED	Zone 3	outside the vascular arcades	No	Yes	45
12	21	M	OD	Perforating	Land mine	Zone 1	outside the vascular arcades	No	Yes	45
13	33	M	OD	Penetrating	Hand grenade	Zone 1	outside the vascular arcades	No	No	70
14*	27	M	OD	Perforating	Hand grenade	Zone 2	outside the vascular arcades	No	No	56
			OS	Perforating		Zone 3	within the vascular arcades	No	Yes	45
15	35	F	OS	Perforating	IED	Zone 2	outside the vascular arcades	No	No	56
16	36	M	OD	Penetrating	Hand grenade	Zone 2	outside the vascular arcades	No	No	70
17	38	M	OS	Perforating	IED	Zone 3	within the vascular arcades	No	No	56
18	24	M	OD	Perforating	Land mine	Zone 3	outside the vascular arcades	No	No	56
19	28	M	OS	Perforating	Hand grenade	Zone 2	adjacent to the optic disc	Yes	No	46
20	23	M	OD	Perforating	IED	Zone 3	outside the vascular arcades	No	Yes	45
21*	28	M	OD	Perforating	IED	Zone 3	outside the vascular arcades	No	Yes	45
			OS	Perforating		Zone 2	outside the vascular arcades	No	No	56
22	47	M	OD	Perforating	Land mine	Zone 3	outside the vascular arcades	No	No	56
23	33	M	OS	Perforating	Land mine	Zone 3	outside the vascular arcades	No	No	76
24	24	M	OS	Perforating	Hand grenade	Zone 2	outside the vascular arcades	Yes	Yes	35
25	27	M	OS	Perforating	IED	Zone 1	outside the vascular arcades	No	No	56
26	52	F	OD	Perforating	Land mine	Zone 2	adjacent to the optic disc	Yes	Yes	35
27	25	M	OS	Perforating	IED	Zone 3	within the vascular arcades	No	Yes	45
28	37	M	OD	Perforating	Hand grenade	Zone 3	outside the vascular arcades	Yes	No	66
29	61	F	OD	Perforating	IED	Zone 3	outside the vascular arcades	No	No	56
30*	29	M	OD	Perforating	IED	Zone 3	within the vascular arcades	No	Yes	45
			OS	Perforating		Zone 3	within the vascular arcades	No	Yes	45
31	25	M	OS	Perforating	RPG	Zone 1	anterior to the equator	No	No	56
32	23	M	OD	Perforating	Land mine	Zone 3	adjacent to the optic disc	Yes	Yes	35
33	29	M	OS	Perforating	RPG	Zone 3	outside the vascular arcades	Yes	No	46
34	33	M	OS	Perforating	IED	Zone 3	within the vascular arcades	No	Yes	45
35	36	M	OD	Perforating	Hand grenade	Zone 2	outside the vascular arcades	No	No	56

APD: Afferent pupillary defect; BCVA: Best corrected visual acuity; CF: Counting fingers; F: Female; HM: Hand motion; IED: Improvised explosive device; LP: Light perception; M: Male, OD: Right eye; OS: Left eye; OTS: Ocular trauma score; RD: Retinal detachment; RPG: Rocket-propelled grenades. * Patient who underwent surgery on both eyes.

Table 2. Surgical procedures, anatomical and visual outcomes

Patient	Time to first PPV, days	Endo tamponade	PPVs, n	Follow-up, mo	Initial BCVA (decimal)	Corneal scar/ corneal decompensation	Macular injury	PVR after first PPV	PVR at the end of follow-up	Final BCVA (decimal)	Anatomical success	Globe survival
1	10	C3F8 gas	2	55	CF	No	No	No	No	0.6	Yes	Yes
2*	5	silicone oil	3	26	HM	No	No	Yes	No	0.1	Yes	Yes
3*	5	silicone oil	2	26	LP	No	No	No	No	CF	Yes	Yes
	7	C3F8 gas	1	14	0.1	No	No	No	No	0.3	Yes	Yes
4	4	silicone oil	4	14	HM	No	Yes	No	Yes	NLP	No	Yes
	4	C3F8 gas	1	46	CF	Yes	No	No	No	0.5	Yes	Yes
5	12	silicone oil	3	14	LP	No	Yes	Yes	Yes	LP	No	No
6	5	C3F8 gas	1	23	0.2	No	No	No	No	0.8	Yes	Yes
7	5	C3F8 gas	2	17	HM	No	Yes	No	No	0.2	Yes	Yes
8	17	silicone oil	3	21	LP	No	Yes	Yes	Yes	LP	No	No
9	4	C3F8 gas	2	35	HM	No	No	No	No	0.5	Yes	Yes
10*	5	silicone oil	3	16	CF	No	No	No	No	0.4	Yes	Yes
11	5	silicone oil	5	16	CF	No	Yes	Yes	No	CF	Yes	Yes
	8	C3F8 gas	2	23	CF	No	No	Yes	No	0.4	Yes	Yes
12	5	C3F8 gas	2	49	LP	Yes	No	Yes	No	0.3	Yes	Yes
13	6	C3F8 gas	2	61	CF	No	No	No	No	0.7	Yes	Yes
14*	7	C3F8 gas	2	35	CF	No	No	No	No	0.4	Yes	Yes
15	5	silicone oil	4	35	LP	No	Yes	Yes	No	HM	Yes	Yes
16	10	C3F8 gas	1	71	CF	No	No	No	No	0.6	Yes	Yes
17	0	C3F8 gas	1	54	CF	No	No	No	No	0.7	Yes	Yes
18	6	C3F8 gas	2	32	CF	No	No	No	No	0.5	Yes	Yes
19	5	C3F8 gas	2	25	CF	No	No	No	No	0.3	Yes	Yes
20	9	C3F8 gas	2	36	CF	No	No	No	No	0.1	Yes	Yes
21*	7	C3F8 gas	3	19	HM	No	No	No	No	0.2	Yes	Yes
22	6	silicone oil	4	63	LP	No	No	No	Yes	NLP	No	No
	3	C3F8 gas	2	63	CF	No	No	No	No	0.2	Yes	Yes
23	6	C3F8 gas	2	32	CF	No	No	No	No	0.2	Yes	Yes
24	6	C3F8 gas	2	38	0.1	No	No	No	No	0.2	Yes	Yes
25	8	silicone oil	4	13	HM	No	No	Yes	No	0.1	Yes	Yes
26	5	C3F8 gas	2	26	HM	Yes	No	No	No	0.3	Yes	Yes
27	5	C3F8 gas	2	14	CF	No	No	Yes	No	0.1	Yes	Yes
28	6	silicone oil	5	26	LP	No	Yes	Yes	Yes	NLP	No	No
29	4	C3F8 gas	2	49	0.1	No	No	No	No	0.4	Yes	Yes
30*	6	silicone oil	3	12	CF	No	No	No	No	0.1	Yes	Yes
31	4	silicone oil	4	57	LP	No	Yes	Yes	Yes	NLP	No	No
	4	silicone oil	5	57	LP	No	Yes	Yes	No	LP	Yes	Yes
32	4	silicone oil	2	28	HM	Yes	No	No	No	CF	Yes	Yes
33	4	silicone oil	3	27	HM	No	No	No	No	0.1	Yes	Yes
34	5	silicone oil	2	25	HM	No	No	No	No	CF	Yes	Yes
35	6	silicone oil	4	22	LP	No	Yes	No	No	CF	Yes	Yes
36	4	silicone oil	2	32	CF	No	No	No	No	0.5	Yes	Yes

BCVA: Best corrected visual acuity; C3F8: Perfluoropropane; CF: counting finger; F: Female; HM: Hand motion; LP: Light perception; Mo: Months; NLP: No light perception; PPV: Pars plana vitrectomy; PVR: Proliferative vitreoretinopathy. * Patient who underwent surgery on both eyes.

highlight the extreme severity of the included cases. The vast majority of eyes sustained perforating injuries, and most IOFB exit/impact sites were located posterior to the equator, with 43.9% of eyes showing initial RD. Importantly, injuries were predominantly caused by high-energy explosive devices, including IED (48.8%), hand grenades (26.8%), landmines (19.5%), and RPG (4.9%), which are known to produce combined blast and ballistic effects with extensive posterior segment damage. In a historical DWOI series from our department, reported by Sobacı et al.,^[23] zone 3 involvement and explosive mechanisms such as landmines and hand grenades were associated with the worst visual outcomes, with PVR accounting for 30.4% of postoperative failures. Similarly, large clinical series of perforating OGLs with posterior exit wounds and deep-impact IOFBs have demonstrated high-risk injury patterns.^[13-16] Weichel et al.^[13] reported that 87.5% of eyes had preoperative RD, and 56.2% had direct macular injury, while Ozdek et al.^[14] noted posterior pole involvement in 77% of perforating injuries in their chorioretinectomy series. Against this background, the patient population included in the present study represents a worst-case scenario within the spectrum of OGLs, underscoring the clinical relevance of achieving the outcomes reported herein.

The timing of vitreoretinal intervention represents another critical determinant of posttraumatic outcomes. In our series, PPV with prophylactic CR was performed at a mean of 5.9 ± 2.7 days following primary globe repair, and 43.9% of eyes already demonstrated RD at the time of PPV. This finding reflects both the severity of the initial trauma and the rapid onset of posterior segment pathology characteristic of deadly weapon injuries. Experimental and clinical studies indicate that cellular mediators of PVR, including retinal pigment epithelial cells and fibroblasts, begin proliferating within hours after trauma, particularly in the presence of intravitreal hemorrhage.^[24] Accordingly, early removal of the vitreous scaffold and elimination of incarcerated retinal tissue at the wound or impact site represent biologically plausible strategies to interrupt the cascade leading to irreversible scarring.^[25,26] Supporting this concept, Ferreira et al.^[15] reported superior functional outcomes with early vitrectomy with prophylactic CR in perforating injuries, with 58% of early-treated eyes achieving $\geq 40/200$ compared with 17% in delayed cases. The rationale for even earlier intervention is further emphasized by Kuhn and Schrader, who demonstrated that PPV combined with prophylactic CR performed within 100 hours in high-risk injuries was associated with a 16% PVR rate and no cases of PVR originating from the CR site.^[17] Although the average timing in our cohort extended beyond this ≤ 100 -hour window, our results suggest that a prophylactic CR strategy may still confer substantial benefit when surgery is performed during the first post-injury week in a tertiary referral setting.

Despite profoundly poor baseline visual acuity (most eyes presenting with LP or CF vision), significant functional improvement was observed over long-term follow-up, with fi-

nal BCVA improving to 1.18 ± 1.20 logMAR and 68.3% of eyes achieving $\geq 20/200$ vision. This degree of functional recovery is notable, given the clinically relevant proportion of direct macular injury and posterior pole involvement in the cohort. In comparison, Monteiro and Meireles reported $\geq 20/200$ vision in 64.5% of eyes following prophylactic CR,^[16] whereas Ozdek et al.^[13] reported $\geq 20/200$ in 30.8% of eyes despite 100% globe survival.^[14] Similarly, a comparative analysis of chorioretinectomy versus non-chorioretinectomy in combat-related ocular injuries demonstrated that final BCVA $\geq 20/200$ was achieved in 54% of the chorioretinectomy group, compared with only 11% in the non-chorioretinectomy group. Taken together, these outcomes indicate that prophylactic CR may confer a substantial protective effect on visual function in severely traumatized eyes. The relatively high proportion of eyes retaining ambulatory vision, despite extensive posterior segment involvement and frequent macular damage, underscores the potential role of this approach in mitigating the long-term functional consequences of devastating ocular injuries.

The most critical finding of the present study relates to PVR prevention. Historical cohorts of severe OGLs, in particular those involving perforating mechanisms or deep-impact IOFBs, have consistently reported PVR rates exceeding 40–60%.^[3-5] In contrast, the final PVR rate in our series was 14.6%, despite the inclusion of exclusively high-risk eyes with extensive posterior segment involvement. Although PVR developed in 29.3% of eyes after the initial PPV, subsequent surgical interventions resulted in a substantial reduction to 14.6% at final follow-up, suggesting that prophylactic CR confers a sustained protective effect rather than merely delaying scar formation. These findings are consistent with prior CR-based strategies. Kuhn and Schrader reported a 16% PVR rate following PPV and prophylactic CR in high-risk injuries,^[17] whereas Monteiro and Meireles observed a final PVR rate of 6.5%, noting that PVR incidence decreased after additional surgeries, particularly when even partial CR was initially performed.^[16] Similarly, Ferreira et al.^[15] and Ozdek et al.^[14] reported final PVR rates of 11% and 15.3%, respectively, in their chorioretinectomy series.

Anatomical success and globe survival represent particularly meaningful outcomes in this context. In our cohort, anatomical success was achieved in 85.4% of eyes and globe survival in 87.8%, with a minority requiring long-term silicone oil tamponade due to persistent hypotony. These results compare favorably with other published series. Monteiro and Meireles reported anatomical success of 80.6% and globe survival of 96.8%,^[16] while Ozdek et al.^[14] reported globe survival of 100% with retinal attachment in 84.6% of eyes. In a ruptured globe following blunt trauma mechanism, Mura et al.^[18] reported globe survival of 100%, anatomical success of 73%, and a PVR rate of 13% following large CR for blunt ruptured globes, with $\geq 20/200$ vision in 67% of eyes, showing similar outcomes despite differing injury etiologies. These cross-

study comparisons support the concept that chorioretinectomy-based strategies can promote globe preservation and stable retinal attachment in eyes at high risk of tractional scarring.

The strengths of the present study include a well-defined, homogeneous DWOI cohort, long follow-up, and consistent surgical technique performed by an experienced vitreoretinal surgeon. By focusing on a high-risk subgroup rather than a broad ocular trauma spectrum, the study provides clinically actionable insights into the management of eyes most likely to develop PVR and catastrophic anatomical failure. Limitations include the retrospective design and absence of a contemporaneous non-CR control group, which limits definitive causal inference. However, ethical and practical considerations render randomized comparisons challenging in this setting, particularly given the historically poor outcomes associated with similar injury patterns.

CONCLUSION

In conclusion, PPV combined with prophylactic CR appears to be an effective and biologically sound strategy for managing DWOIs at high risk for PVR. By proactively addressing retinal incarceration and minimizing the cellular drivers of post-traumatic scarring, this approach can achieve low final PVR rates (14.6%), high anatomical success (85.4%), and favorable globe survival (87.8%) despite extensive posterior segment trauma. Future prospective and multicenter studies are warranted to further refine patient selection and optimize surgical timing. However, current evidence supports the consideration of prophylactic chorioretinectomy as an integral component of the surgical management of the most severe forms of ocular trauma.

Ethics Committee Approval: This study was approved by the Health Sciences University Gülhane Scientific Research Ethics Committee (Date: 23.12.2025, Decision No: 2025-617).

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ORJİNAL ÇALIŞMA - ÖZ

Ölümcül silahlara bağlı açık göz yaralanmalarında profilaktik koryoretinektomi

AMAÇ: Ölümcül silahlara bağlı açık göz yaralanmalarında (AGY) pars plana vitrektomi (PPV) ve profilaktik koryoretinektomi (KR) cerrahisinin anatomik ve fonksiyonel sonuçlarının değerlendirilmesi

GEREÇ VE YÖNTEM: Kasım 2016-Ekim 2024 arasında ölümcül silahlara bağlı AGY nedeniyle PPV ve profilaktik KR uygulanan olgulara ait tıbbi kayıtlar retrospektif olarak incelendi. Demografik özellikler, yaralanmanın tipi, yaralanma nedeni, yaralanma zonu, göz içi yabancı cisim (GİYÇ) etki/ çıkış yeri, en iyi düzeltilmiş görme keskinliği (EİDGK), proliferatif vitreoretinopati (PVR) oranları, anatomik başarı ve glob sağkalımı değerlendirildi.

BULGULAR: Toplam 283 AGY olgusundan, ölümcül silahlara bağlı AGY nedeniyle PPV ve profilaktik KR uygulanan 35 hastaya ait 41 göz analize dahil edildi. Olguların yaş ortalaması 30.9±9.4 yıl olup, %88.6'sı erkekti. Gözlerin 38'inde (%92.7) perforan, 3'ünde (%7.3) GİYÇ ile birlikte penetran yaralanma mevcuttu. Yaralanma nedenleri 20 gözde (%48.8) el yapımı patlayıcı, 11 gözde (%26.8) el bombası, 8 gözde (%19.5) mayın ve 2 gözde (%4.9) roketatar idi. Yabancı cisim çıkış/etki bölgesi olguların 38'inde (%92.7) arka kutup yerleşimli olup; bunların 22'sinde (%53.6) vasküler ark dışında, 12'sinde (%29.3) vasküler ark içinde ve 4'ünde (%9.7) optik disk komşuluğundaydı. Başlangıç EİDGK ortalaması 2.62±0.98 logMAR olup, gözlerin %90.2'si ışık hissi pozitifliği ile parmak sayma aralığındaydı. PPV primer tamirden ortalama 5.9 ±2.7 gün sonra uygulandı ve cerrahi sırasında olguların %43.9'unda retina dekolmanı mevcuttu. Ortalama PPV sayısı 2.6±1.1 idi. Olguların %51.2'sinde endotamponad olarak C3F8 gaz kullanıldı. Ortalama 32.8±16.6 aylık takip sonunda sonuç EİDGK 1.18±1.20 logMAR'a anlamlı şekilde düzeldi (p<0.001). Olguların %68.3'ünde son EİDGK 20/200 ve üzerinde idi. Postoperatif son kontrolde PVR oranı %14.6 (6/41), anatomik başarı oranı %85.4 (35/41) ve glob sağkalım oranı %87.8 (36/41) idi.

SONUÇ: Ölümcül silahlara bağlı açık göz yaralanmalarında PPV ile kombine profilaktik KR, ileri derecede posterior segment hasarına rağmen PVR gelişimini önleyebilen ve yüksek anatomik başarı, glob sağkalımı ve anlamlı görsel iyileşme sağlayan etkili bir tedavi seçeneği olarak görülmektedir.

Anahtar sözcükler: Açık göz yaralanması; göziçi yabancı cisim; koryoretinektomi; oküler travma; ölümcül silah; penetran göz yaralanması; ölümcül silah; perforan göz yaralanması; proliferatif vitreoretinopati.

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Temporary hemodynamic response with resuscitative endovascular balloon occlusion of the aorta (REBOA) during cardiopulmonary resuscitation in a case of traumatic cardiac arrest

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ABSTRACT

Uncontrolled hemorrhagic shock due to trauma is a life-threatening condition requiring rapid intervention. Every minute in the management of these patients is valuable. In recent years, resuscitative endovascular aortic balloon occlusion (REBOA) has emerged as a valuable tool in emergency and trauma practice, providing additional time for the patient, particularly in cases where surgical hemostasis is delayed. A 62-year-old male patient with no known comorbidities was transported to our tertiary trauma center after receiving five minutes of cardiopulmonary resuscitation (CPR) and intubation at an external facility following a high-energy traffic accident. Upon presentation, the patient's blood pressure was 50/20 mmHg and pulse rate was 128 beats/min. He had extensive pelvic trauma, lower extremity trauma, major soft tissue loss, and vascular and bone injuries. He underwent hemostatic resuscitation along with whole-body computed tomography (CT) imaging; however, cardiac arrest recurred after imaging. During CPR, simultaneous imaging studies revealed no trauma or bleeding in the brain or thorax. REBOA was planned for the patient. Temporary return of spontaneous circulation (ROSC) was achieved 38 minutes after REBOA. During this period, the patient received a total of six units of packed red blood cells, three units of fresh frozen plasma, two units of cryoprecipitate, and calcium replacement. The REBOA procedure was performed by emergency physicians and cardiovascular surgeons who had received hands-on training using a REBOA simulation model developed by our team. However, despite achieving a temporary hemodynamic response, the patient could not be stabilized for surgical intervention and was pronounced deceased. In this case, we share the first REBOA experience of emergency department physicians trained with a locally produced simulation model. We believe that simulation-based training will contribute to physician experience and direct field application in rare or rapidly evolving emergencies.

Keywords: Resuscitative endovascular balloon occlusion of the aorta (REBOA); simulation training; cardiopulmonary resuscitation (CPR); trauma; hemorrhagic shock; iliac artery injury.

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INTRODUCTION

Uncontrolled hemorrhagic shock due to trauma is a clinical condition with high mortality that requires rapid intervention. Especially in pelvic and intra-abdominal bleeding, temporary stabilization of circulation during the preoperative period is of critical importance. In recent years, with improvements in emergency services, critical care units, surgical teams, and equipment, resuscitative endovascular balloon occlusion of the aorta (REBOA) has gained increasing attention in emergency and trauma medicine.^[1,2] REBOA, which requires advanced training and specialized equipment, may offer a window of opportunity for patients in traumatic cardiac arrest by allowing time for surgical intervention.

In this case report, we discuss a patient who presented with extensive soft tissue loss and major vascular and skeletal injuries, developed hemodynamic instability followed by cardiac arrest, and received REBOA during ongoing cardiopulmonary resuscitation (CPR). The procedure was performed by emergency physicians trained using a domestically developed REBOA simulator. The case also evaluates the contribution of this locally produced simulation model to the clinical training process for such high-risk scenarios.

CASE REPORT

A 62-year-old male patient with no known comorbidities was transferred to our tertiary care center following a high-energy motor vehicle collision. He was initially taken to the nearest healthcare facility, approximately one hour from our hospital. Cardiopulmonary resuscitation was initiated there for about five minutes before spontaneous circulation was restored, followed by endotracheal intubation. The patient received tranexamic acid, tetanus prophylaxis, triple antibiotics, three units of packed red blood cells, and one unit of fresh frozen plasma. A norepinephrine infusion was initiated, and the patient was transferred to our hospital due to the need for multidisciplinary surgical management.

Upon arrival, the patient had spontaneous circulation, was intubated, and remained hypotensive (blood pressure 50/30 mmHg). Open fractures of the pelvis and right lower extrem-



Figure 1. The patient was taken to the resuscitation area, where CPR was initiated.

ity were noted, including multiple fractures of the right tibia, fibula, and femur, as well as a comminuted fracture of the right iliac wing. There were extensive soft tissue loss and laceration extending from the lower abdomen to the perineum, including the external genitalia. No peripheral pulse was palpable in the left lower extremity.

To stabilize the patient, a massive transfusion protocol was initiated while the norepinephrine infusion continued. Blood samples were collected for surgical preparation, and whole-body computed tomography (CT) was performed. Laboratory findings revealed hemoglobin 4.1 g/dL, hematocrit 11%, pH 6.94, base excess -22, lactate 4.82 mmol/L, creatinine 2.36 mg/dL, and urea 35.41 mg/dL (Table 1).

CT imaging showed no traumatic findings in the brain or cervical spine. Fractures were noted in the proximal left humerus and the second and fifth left ribs. A subcapsular hematoma in the liver and a grade I splenic laceration were

Table 1. Main laboratory findings

Parameter	Value
Hemoglobin	4.1 g/dL
Hematocrit	11%
pH	6.94
Base excess	-22
Lactate	4.82 mmol/L
Creatinine	2.36 mg/dL
Urea	35.41 mg/dL



Figure 2. Extensive pelvic and lower extremity fractures, including pubic diastasis.

also observed. Additionally, there were extensive pelvic and lower extremity fractures, including pubic diastasis. No blood flow was visualized distal to the left external iliac artery. In contrast, flow was present in the right internal iliac, external iliac, and common femoral arteries. The Injury Severity Score (ISS) was calculated as 59. Toward the end of the CT scan, the patient developed cardiac arrest.

The patient was deemed a suitable candidate for REBOA and was taken to the resuscitation area, where CPR was initiated. The cardiovascular surgery and orthopedic teams were informed (Fig. 1, 2).

To facilitate faster catheterization, external mechanical chest compressions were applied to minimize motion artifacts during CPR. Approximately five hours after the trauma occurred, a 9F, 11-cm femoral sheath was inserted into the right common femoral artery with the assistance of the cardiovascular surgery team. Although a linear ultrasound probe was used to locate the femoral artery, trauma-induced anatomical



Figure 3. Extensive pelvic and lower extremity fractures, including pubic diastasis.

changes hindered vascular identification (Fig. 3). The bladder was gently displaced cephalad using sterile towels, and a vessel-like structure with a tubular lumen was identified. Ultrasound was used again to confirm arterial identity. A Mustang 10×60 mm balloon dilation catheter was introduced via the sheath. Due to anatomical distortion, the umbilicus could not be used as a reference point, and the balloon was advanced to a depth of 28 cm and inflated in Zone 3. Position was confirmed with direct radiography and ultrasonography. Due to the presence of a suspicious subcapsular hepatic hematoma on CT, the balloon was deflated and repositioned into Zone 1. The balloon was inflated sequentially with 6 mL and 8 mL of saline, achieving pressures of 9.6 and 11 atm, respectively (Fig. 4).

Thirty-eight minutes after REBOA deployment, return of spontaneous circulation (ROSC) was achieved. The patient developed ventricular fibrillation three times and was successfully defibrillated into normal sinus rhythm (Fig. 5). After the return of spontaneous cardiac activity, jugular venous dis-



Figure 4. Balloon was repositioned into Zone 1.

tension, carotid pulsation, and myocardial contractility were confirmed by bedside ultrasound (Fig. 6). However, before the patient could be transferred to the operating room, another cardiac arrest occurred. A total of 131 minutes of CPR was performed from arrival until death. Approximately 310 minutes had passed since the trauma and 100 minutes since REBOA deployment. Death was confirmed by the absence of cardiac motion on bedside ultrasound (Table 2).

During resuscitation, the patient received a total of six units of packed red blood cells, three units of fresh frozen plasma, two units of cryoprecipitate, 450 mg of calcium gluconate, and 4000 mL of intravenous fluids.

DISCUSSION

According to the Adult Trauma Life Support Guideline, emergency resuscitative thoracotomy is an invasive surgical intervention performed to achieve direct control of intrathoracic



Figure 5. Normal sinus rhythm was detected on the monitor.



Figure 6. Jugular venous distension and carotid pulsation were confirmed by bedside ultrasound.

Table 2. Chronological clinical timeline

Time	Description
0 min (Trauma)	High-energy traffic accident
~60 min	External hospital: 5 min CPR → ROSC, intubation, fluids and blood products, norepinephrine initiated
~120 min	Transfer to tertiary trauma center
Admission to our center	BP 50/30 mmHg, tachycardia, extensive pelvic and lower extremity trauma
+ CT (Trauma center)	Brain/thorax normal; liver subcapsular hematoma, grade I splenic laceration, iliac artery flow loss
End of CT	Cardiac arrest; CPR initiated
~30 min (after CT)	REBOA performed (Zone 3, then Zone I)
+38 min (post-REBOA)	Transient ROSC; defibrillated to sinus rhythm
+100 min (post-REBOA)	Re-arrest; total of 131 min CPR
~310 min (5 h 10 m after trauma)	Exitus/Death confirmed

Min: Minute; CPR: Cardiopulmonary resuscitation; ROSC: Return of spontaneous circulation; CT: Computed tomography; BP: Blood pressure.

injuries, decompress pericardial tamponade, and occlude the aorta to prevent exsanguination, thereby aiming to stabilize the patient's condition.^[3,4] Similarly, the Joint Trauma System Clinical Practice Guidelines declare left anterolateral thoracotomy as the gold standard technique for aortic occlusion in cases of cardiac arrest secondary to trauma.^[5] However, in traumatic arrests resulting from isolated abdominal aortic injuries or pelvic fractures, its application remains limited due to the induction of a broader ischemic region and the requirement for a more invasive surgical approach.^[5] REBOA, conversely, has emerged as an alternative aortic occlusion strategy in carefully selected patients.

REBOA is an invasive approach used to achieve temporary hemodynamic stabilization in patients with non-compressible hemorrhage, particularly in pelvic and abdominal trauma, before definitive surgical control is possible.^[6] Compared to emergency resuscitative thoracotomy, REBOA offers a less invasive alternative for selected trauma patients requiring aortic occlusion.

The success of REBOA implementation depends on patient selection, timing, operator experience, logistical preparedness, associated injuries, and the need for concurrent cardiopulmonary resuscitation.^[7] Education and training are crucial for the effective and safe execution of this procedure. According to the Joint Trauma System Clinical Practice Guidelines, providers must have comprehensive knowledge of device usage, indications, and potential complications before attempting REBOA. Successful training should include both didactic and hands-on components, preferably using high-fidelity simulators, perfused cadavers, or live tissue models.^[8]

In the study by Brenner et al.,^[9] the Basic Endovascular Skills for Trauma (BEST) course is described as a model in which participants are trained in endovascular techniques, including REBOA, using perfused cadavers. The training includes ultra-

sound-guided common femoral artery access, percutaneous and open cannulation, and arterial repair.

In our case, all providers had completed REBOA training through a national course supported by the Emergency Medicine Specialists Association, in collaboration with cardiovascular surgeons. The training utilized a simulation model—ZMD—designed and developed by our team, which includes ultrasound-compatible and anatomically realistic modules for common femoral artery access, sheath placement, guidewire manipulation, and balloon deployment.

This REBOA simulation model was actively used in REBOA training courses in 2024 and has since entered the process of commercial licensing. It represents not only an educational innovation but also a translational contribution bridging simulation and real-world application. Despite the providers' proficiency with ultrasound, trauma-related anatomical distortions and extensive soft tissue loss limited the effectiveness of sonographic guidance, rendering vascular access a rate-limiting step in this case.

REBOA success is heavily influenced by patient selection criteria. While these criteria have evolved, common parameters are emphasized across trauma centers. Brenner et al.^[10] suggest that REBOA can be applied in patients with subdiaphragmatic life-threatening hemorrhage and in those who are unresponsive or transiently responsive to resuscitation, including traumatic arrest.

Similarly, Glaser et al.^[11] recommend REBOA in cases of blunt or penetrating abdominal, pelvic, or junctional trauma with systolic blood pressure <90 mmHg and no or transient response to initial resuscitation. They also caution against its use in patients with severe thoracic injuries or penetrating neck, chest, or extremity trauma.

Hadley et al.^[12] emphasize that REBOA may be effective in

patients with systolic blood pressure (SBP) <80 mmHg due to pelvic or extremity hemorrhage and traumatic arrest but is not recommended for intrathoracic bleeding.

In our case, upon arrival at the emergency department, the patient's SBP was <80 mmHg, prompting the initiation of a massive transfusion protocol and CT imaging. The absence of brain or thoracic hemorrhage on CT during concurrent CPR strongly supported the indication for REBOA. Earlier REBOA implementation may have improved circulatory outcomes.

The method of REBOA application and the preferred balloons for aortic occlusion have evolved over time. The first use of intra-abdominal aortic balloon occlusion (IABO) catheter for traumatic bleeding was reported in 1954 by Lieutenant Colonel (LTC) Carl Hughes, who described the use of an intra-aortic balloon occlusion catheter inserted through a IO-F arterial sheath.^[13]

The need for repair of the common femoral artery (CFA) after the use of high-French sheaths and the increasing traumatic nature of battlefield injuries led to institutional efforts to develop new sheaths and REBOA catheters.^[14]

Increasing awareness of the REBOA procedure has led healthcare professionals to implement it to support trauma patients. However, the lack of infrastructure in healthcare systems, prolonged transfer times for patients who could benefit from REBOA to well-equipped hospitals, and the increased risk of visceral organ damage due to prolonged balloon occlusion have prompted research into and trials of variations such as partial REBOA and intermittent REBOA.^[15]

In our case, REBOA was performed using a REBOA kit prepared from existing equipment available at our hospital. The balloon used did not completely obstruct distal blood flow, making the procedure a spontaneous partial REBOA.

CONCLUSION

In severe trauma cases, especially those involving iliac artery injury and profound hemorrhagic shock, REBOA can be technically feasible and potentially beneficial during ongoing CPR. It may provide critical time for surgical intervention by temporarily stabilizing circulation. However, the success of REBOA is contingent on appropriate patient selection, timely application, team experience, and management of concurrent injuries. In this case, one of the key enabling factors for REBOA application during CPR was the simulation-based training and technical readiness achieved through the locally developed REBOA model. Further studies are warranted to evaluate the role of simulation-based training in improving clinical outcomes of REBOA in traumatic arrest.

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Ö.G.; Design: S.Ö., U.Ç., Ö.A., Ö.G.; Supervision: S.Ö., S.G., F.Ç., Ö.G.; Resource: S.Ö., Ö.A., K.G., Ö.G.; Materials: S.Ö., Ö.A., K.G.; Data collection and/or processing: Ö.A., K.G., U.Ç., F.Ç.; Analysis and/or interpretation: S.Ö., S.G., F.Ç., K.G., Ö.G.; Literature review: S.Ö., S.G., U.Ç., F.Ç., K.G.; Writing: S.Ö., U.Ç.; Critical review: S.Ö., S.G., Ö.A., U.Ç., K.G., F.Ç., Ö.G.

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OLGU SUNUMU - ÖZ

Travmatik kardiyak arrest olgusunda kardiyopulmoner resüsitasyon sırasında REBOA ile geçici hemodinamik yanıt

Travmaya bağlı kontrolsüz hemorajik şok, hızlı müdahale gerektiren yaşamı tehdit eden bir durumdur. Bu hastaların yönetimindeki her bir dakika altın değerindedir. Son yıllarda resüsitatif endovasküler aort balon oklüzyonu (REBOA), özellikle cerrahi hemostazın geciktiği durumlarda hastaya ek zaman kazandırarak acil ve travma pratiğinde değerli bir araç olarak öne çıkmaktadır. Bilinen ek hastalığı olmayan 62 yaşında erkek hasta, yüksek enerjili bir trafik kazası sonrası götürüldüğü dış merkezde 5 dakika kardiyopulmoner resüsitasyon (KPR) uygulandıktan ve entübe edildikten sonra üçüncü basamak travma merkezimize sevk edilmiştir. Hastanın başvuru anındaki kan basıncı 50/20 mmHg, nabız 128 atım/dakika idi. Hastada geniş pelvik travma, alt ekstremitte travması, majör yumuşak doku kaybı, vasküler ve kemik yaralanmaları mevcuttu. Hemostatik resüsitasyonla birlikte tüm vücut tomografi görüntülemesi yapılan hastada görüntüleme sonrasında tekrar kardiyak arrest gelişti. KPR sırasında eş zamanlı görüntüleme tetkikleri de incelenen hastada beyin ve toraks bölgesinde travma ve kanama tespit edilmedi ve hastaya REBOA uygulanması planlandı. REBOA uygulandıktan 38 dakika sonra geçici spontan dolaşım dönüşü (ROSC) sağlandı. Hastaya bu süreçte toplam 6 ünite eritrosit süspansiyonu, 3 ünite taze donmuş plazma, 2 ünite kriyopresipitat ve kalsiyum replasmanı yapıldı. REBOA işlemi, ekibimiz tarafından geliştirilen REBOA simülasyon modeli ile uygulamalı eğitim almış acil tıp hekimleri ve kalp damar cerrahi hekimleri tarafından gerçekleştirildi. Ancak geçici hemodinamik yanıt sağlanmasına rağmen hasta cerrahi müdahale için stabilize edilememiş ve eksitus kabul edilmiştir. Bu vakada yerel olarak üretilmiş bir simülasyon modeli ile eğitilmiş Acil servis hekimlerinin ilk REBOA deneyimi paylaşıldı. Nadir görülen veya hızlı müdahale edilmesi gereken acil durumlarda simülasyon temelli eğitimlerin hekim deneyimi kazanmasında ve doğrudan saha uygulamasına katkı sağlayacağını düşünmekteyiz.

Anahtar sözcükler: REBOA, simülasyon eğitimi, KPR, travma, hemorajik şok, iliak arter yaralanması

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Intraoperative diagnosis and endoscopic management of iatrogenic common bile duct injury during laparoscopic cholecystectomy: A case report

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ABSTRACT

Although laparoscopic cholecystectomy (LC) is considered the gold standard treatment for symptomatic gallstone disease, iatrogenic bile duct injury remains a rare but serious complication. We present a case of a Strasberg type D bile duct injury that was diagnosed intraoperatively and successfully managed with endoscopic retrograde cholangiopancreatography (ERCP) during the same session, and we discuss it in light of the current literature. A 46-year-old female patient underwent LC for a hydropic and edematous gallbladder. During difficult dissection, a bile leak was observed from the posterior wall of the common hepatic duct, consistent with a Strasberg type D injury. The endoscopy team was consulted intraoperatively, and ERCP was performed. Cholangiography confirmed the leak, and a plastic stent was placed from the common hepatic duct to the ampulla. The operation was completed with drainage of the subhepatic area. Postoperatively, the patient remained clinically stable. At the sixth postoperative week, follow-up ERCP revealed complete healing with no evidence of leakage, and the stent was removed. The patient had an uneventful recovery, with normal biochemical parameters on follow-up. Early recognition of iatrogenic bile duct injury is the most critical factor influencing prognosis. The literature reports intraoperative detection rates between 25% and 32%, whereas delayed diagnosis is associated with higher morbidity, additional surgical interventions, and prolonged hospital stay. Endoscopic management, particularly in Strasberg type C and type D injuries where ductal continuity is preserved, has shown high success rates (89–96%) and represents a reliable alternative to surgery. This case highlights that multidisciplinary collaboration and intraoperative endoscopic intervention provide a minimally invasive and effective option for the management of bile duct injuries during LC.

Keywords: Laparoscopic cholecystectomy; Strasberg type D; bile duct injury; endoscopic retrograde cholangiopancreatography (ERCP); intraoperative management.

INTRODUCTION

Laparoscopic cholecystectomy (LC) is widely regarded as the gold standard treatment for symptomatic gallstone disease and remains one of the most frequently performed surgical procedures worldwide.^[1] Despite its minimally invasive nature, one of the most serious complications associated with LC is iatrogenic bile duct injury (BDI).^[2] The incidence of iatrogenic common bile duct injury has been reported to range between 0.3% and 0.7%.^[3,4]

Timely recognition of intraoperative complications and their management with minimally invasive techniques during the same session can significantly improve patient outcomes.^[5] Factors that increase the risk of BDI include anatomical variations, severe inflammation, fibrosis, and adhesions from previous surgeries. The most common underlying cause, however, is misidentification of the biliary anatomy. Furthermore, the surgeon's level of experience and the chosen dissection technique directly influence the likelihood of injury.^[6]

The Strasberg classification is the most widely used system

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for defining these injuries and guiding appropriate treatment strategies.^[7] Type D injuries, in particular, are characterized by partial defects in the bile duct wall while preserving ductal continuity, making them suitable for endoscopic management. In such cases, endoscopic sphincterotomy and stent placement can achieve successful outcomes.^[6,8]

Recent evidence emphasizes that early intraoperative recognition combined with minimally invasive management markedly improves long-term prognosis. Within this framework, endoscopic retrograde cholangiopancreatography (ERCP) with stent placement has emerged as a safe and effective alternative to surgery, especially in Strasberg type C and type D injuries.^[9,10]

Herein, we report a case of a Strasberg type D iatrogenic common bile duct injury identified intraoperatively during LC and successfully managed with ERCP in the same session, and we review the case in the context of the current literature.

CASE REPORT

A 46-year-old female patient presented with right upper quadrant pain and dyspeptic complaints. Ultrasonography and magnetic resonance cholangiopancreatography (MRCP) performed at an outside institution revealed a hydropic gallbladder with wall thickening. Preoperative biochemical tests were within normal limits.

For this case report, written informed consent was obtained from the patient during the treatment process for participation in the study, as well as for the publication of any potentially identifiable clinical data and images included in the manuscript.

The patient underwent laparoscopic cholecystectomy under general anesthesia using the standard four-port technique. Intraoperatively, the gallbladder was noted to be markedly edematous and hydropic. As the gallbladder could not be manipulated adequately with laparoscopic instruments, decompression with a Veress needle was performed, aspirating 40 mL of infected biliary fluid. Dissection was then initiated by elevating the gallbladder from Hartmann's pouch.

During dissection, bile leakage was observed from the posterior wall of the common hepatic duct, consistent with a Strasberg type D injury (Fig. 1). The endoscopy team was immediately consulted, and intraoperative ERCP was performed. Cholangiography confirmed the bile leak (Fig. 2). A plastic stent was placed from the common hepatic duct to the ampulla, and subsequent control cholangiography demonstrated no further extravasation (Fig. 3). Laparoscopic cholecystectomy was then completed, and a drain was placed in the subhepatic space.

The postoperative course was uneventful, and the patient remained clinically stable. At six weeks, follow-up biochemical tests were normal, and ERCP confirmed complete healing of the injury with no evidence of bile leakage; the stent was re-

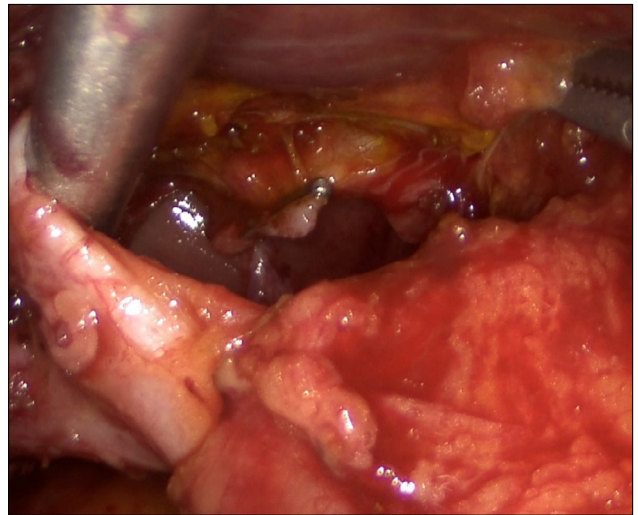


Figure 1. Intraoperative laparoscopic view demonstrating a Strasberg type D iatrogenic bile duct injury. During difficult dissection in laparoscopic cholecystectomy for a hydropic and edematous gallbladder, a partial defect with bile leakage was observed on the posterior wall of the common hepatic duct.

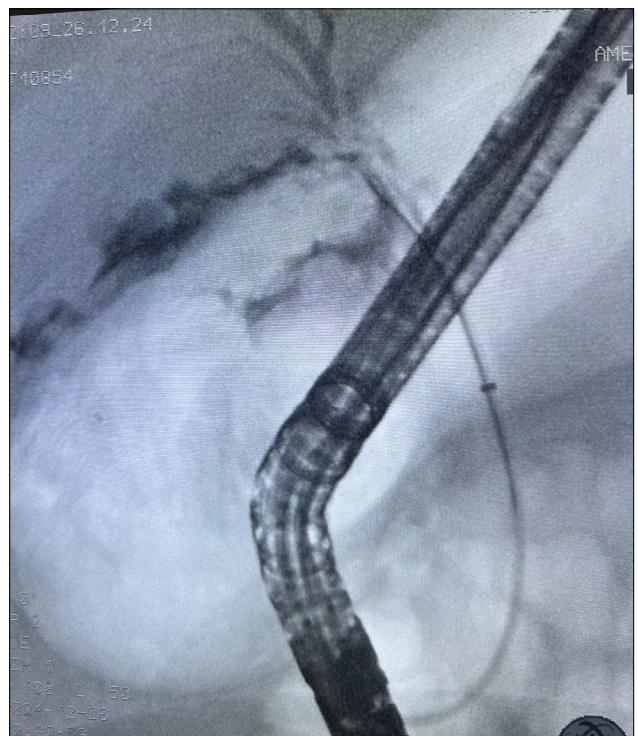


Figure 2. Intraoperative endoscopic retrograde cholangiopancreatography (ERCP) image demonstrating cholangiographic findings. Contrast extravasation is visible from the posterior wall of the common hepatic duct, confirming a Strasberg type D bile duct injury during laparoscopic cholecystectomy.

moved accordingly (Fig. 4). The patient was discharged without complications. At the fourth and eighth postoperative months, biochemical parameters and physical examinations remained normal, with no evidence of late complications.



Figure 3. Intraoperative endoscopic retrograde cholangiopancreatography (ERCP) image during stent placement. A plastic biliary stent was introduced through the common bile duct into the duodenum following identification of a Strasberg type D injury, providing internal biliary drainage.

DISCUSSION

Although the incidence of iatrogenic bile duct injury during laparoscopic cholecystectomy is low, such injuries have a significant impact on patient morbidity and mortality. The most common causes are difficult dissection due to severe inflammation, edema, or anatomical variations.^[2,9] In our case, dissection was challenging because of a markedly hydropic and edematous gallbladder, resulting in a Strasberg type D injury on the posterior wall of the common hepatic duct.

Recognition of bile duct injuries during the intraoperative period is the most critical factor influencing prognosis. The rate of intraoperative detection is reported to be approximately 25-32% in the literature.^[2] Delayed diagnosis is associated with higher complication rates, the need for additional surgical interventions, and prolonged hospital stays.^[11,12] In our patient, the injury was promptly identified intraoperatively, which was possible due to a low threshold of suspicion, and was managed successfully in the same session.

Endoscopic therapy represents a safe and effective option, particularly for Strasberg type C and type D injuries where bile duct continuity is preserved.^[9,10,13] Recent studies have reported success rates of 89-96% with endoscopic sphincterotomy and stent placement.^[14,15] Similarly, in our case, ERCP with plastic stent placement was performed intraoperatively, and follow-up ERCP at six weeks demonstrated complete healing with uneventful stent removal. This outcome is consistent with the high success rates reported in the literature.

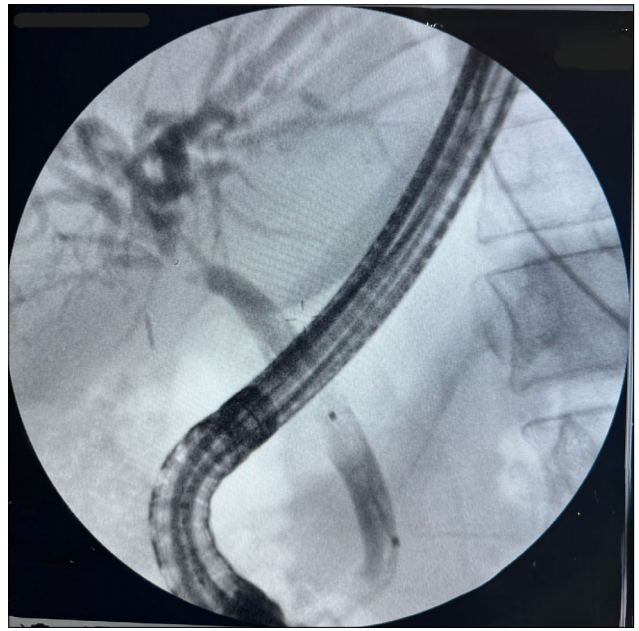


Figure 4. Follow-up endoscopic retrograde cholangiopancreatography (ERCP) image performed at 6 weeks after stent removal. Control cholangiography demonstrates normal opacification of the biliary tree without evidence of contrast extravasation, confirming complete healing of the Strasberg type D bile duct injury.

The surgeon's experience, dissection technique, and a multidisciplinary approach are essential elements in the management of bile duct injuries.^[16,17] Alternative strategies, such as the fundus-first or subtotal cholecystectomy techniques, may improve safety in difficult cases, but they do not completely eliminate the risk of injury, especially in the presence of severe inflammation.^[18] Therefore, meticulous intraoperative observation by the surgeon and close coordination with the endoscopy team are critical for early recognition and successful treatment.

In conclusion, this case demonstrates that a Strasberg type D bile duct injury occurring during LC can be diagnosed intraoperatively and managed successfully with endoscopic stenting in the same session. Consistent with the current literature, early recognition, minimally invasive approaches, and multidisciplinary teamwork are indispensable for achieving optimal patient outcomes.

CONCLUSION

Iatrogenic bile duct injury remains one of the most challenging complications of laparoscopic cholecystectomy, with a significant impact on patient outcomes despite its low incidence. Early intraoperative recognition of these injuries is the most critical factor in reducing morbidity and preventing further interventions. Our case highlights that a Strasberg type D bile duct injury, when promptly identified, can be successfully managed with endoscopic stenting during the same operative

session. This minimally invasive approach provided complete healing without complications and avoided the need for additional surgery. In line with current evidence, early diagnosis, timely endoscopic intervention, and multidisciplinary collaboration are essential for optimizing outcomes in patients with iatrogenic bile duct injury.

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OLGU SUNUMU - ÖZ

Laparoskopik kolesistektomi sırasında gelişen iatrojenik koledok yaralanmasının intraoperatif tanısı ve endoskopik tedavisi: Bir olgu sunumu

Laparoskopik kolesistektomi (LK), semptomatik safra taşı hastalığının tedavisinde altın standart olarak kabul edilse de, iatrojenik safra yolu yaralanmaları nadir fakat ciddi komplikasyonlar arasında yer almaktadır. Bu çalışmada, Strasberg Tip D koledok yaralanmasının intraoperatif tanısı ve aynı seansta endoskopik retrograd kolanjiyopankreatografi (ERCP) ile başarılı tedavisi sunulmakta ve literatür eşliğinde tartışılmaktadır. Kırk altı yaşındaki kadın hasta, hidropik ve ödemli safra kesesi nedeniyle LK'ye alındı. Zorlu disseksiyon sırasında ana hepatik kanalın posterior duvarında safra kaçağı izlendi ve Strasberg Tip D yaralanma tanımlandı. İntraoperatif dönemde endoskopi ekibi çağrılarak ERCP uygulandı. Kolanjiografide kaçak doğrulandı ve hepatik kanaldan ampullaya plastik stent yerleştirildi. Operasyon tamamlanarak subhepatik alana dren kondu. Postoperatif dönemde hasta stabil seyir gösterdi. Altıncı haftada yapılan kontrol ERCP'de kaçığın tamamen iyileştiği görüldü ve stent çıkarıldı. Takiplerde komplikasyon gelişmedi ve biyokimyasal parametreler normal seyretti. İatrojenik safra yolu yaralanmalarının erken tanınması hasta prognozunu doğrudan etkileyen en kritik faktördür. Literatürde intraoperatif tanı oranlarının %25–32 arasında olduğu bildirilmekte, gecikmiş tanı ise daha yüksek morbidite, ek cerrahi girişimler ve uzamış hastanede kalış süreleriyle ilişkilendirilmektedir. Özellikle Strasberg Tip C ve Tip D yaralanmalarda endoskopik tedavi, kontinuitenin korunduğu durumlarda yüksek başarı oranları (%89–96) ile güvenilir bir seçenektir. Bu olgu, multidisipliner yaklaşımın ve intraoperatif endoskopik müdahalenin, safra yolu yaralanmalarının yönetiminde cerrahiye alternatif, minimal invaziv ve etkili bir yöntem olduğunu göstermektedir.

Anahtar sözcükler: ERCP; intraoperatif yönetim; laparoskopik kolesistektomi; safra yolu yaralanması; Strasberg Tip D.

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Cauda equina syndrome caused by intradural migration of a bullet: A rare case presentation

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ABSTRACT

Intradural migration of a bullet within the spinal canal represents an exceptionally uncommon clinical scenario and carries the potential for progressive or delayed neurological decline. Although such fragments may initially remain silent, their subsequent movement within the spinal canal can create significant diagnostic and therapeutic challenges. In this report, we present an unusual and instructive case of cauda equina syndrome that developed secondary to the delayed caudal migration of an intradural bullet fragment. We further provide a detailed discussion of the diagnostic evaluation, surgical management, and clinical decision-making considerations associated with this condition. A 32-year-old male patient sustained a gunshot injury in 2022. Initial imaging demonstrated that the bullet had penetrated the spinal canal and become lodged intradurally at the L1-L2 level, although the patient exhibited no neurological deficits at that time. He was, therefore, managed conservatively with routine follow-up. Approximately 2.5 years later, the patient presented with the sudden onset of bilateral lower extremity weakness, progressive gait impairment, and new-onset urinary incontinence. Computed tomography revealed that the intradural bullet fragment had migrated caudally to the S2 vertebral level, resulting in significant compression of the cauda equina nerve roots. Urgent surgical intervention was undertaken, consisting of a partial bilateral laminectomy at the S1-S2 level and microsurgical extraction of the bullet. Postoperative neurological recovery was substantial, with marked improvement in motor function and complete resolution of urinary symptoms. Although intradural bullet fragments may initially appear clinically insignificant in patients who present without neurological deficits, delayed migration poses a serious risk for the development of cauda equina syndrome and other potentially irreversible complications. This case highlights the importance of maintaining a high index of suspicion and considering early prophylactic surgical extraction when intradural localization is identified, even in neurologically intact individuals. Early intervention may prevent severe late complications such as neurological deterioration, infectious sequelae arising from contaminated missile tracts, and possible lead toxicity related to chronic intradural exposure.

Keywords: Cauda equina syndrome; intradural bullet migration; spinal gunshot injury.

INTRODUCTION

Cauda equina syndrome (CES) is a rare but serious neurosurgical emergency that typically results from compression of the lumbosacral nerve roots. Although lumbar disc herniation is the most common cause, spinal gunshot injuries, though uncommon, can also lead to CES through direct trauma or delayed complications. Retained intradural bullets within the spinal canal carry the risk of delayed migration, infection, or lead toxicity, even in initially asymptomatic patients. Intradu-

ral migration of a bullet to the sacral region is exceptionally rare and may result in progressive neurological deterioration. Here, we present a rare case of delayed intradural bullet migration from the L1-L2 to the S2 level, leading to CES, and discuss its clinical implications and management considerations.^[1-3]

CASE PRESENTATION

A 32-year-old male was admitted to the emergency department in May 2022 after sustaining a gunshot wound. On ad-

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Figure 1. A cortical defect approximately 9–10 mm in diameter, corresponding to the bullet entry trajectory, is observed in the right half of the L3 vertebral body, accompanied by a mildly osteoporotic appearance. Axial lumbar CT sections reveal a clear disruption of cortical continuity.

mission, he was hemodynamically stable and neurologically intact. Contrast-enhanced abdominal computed tomography (CT) revealed a Grade I liver laceration and perforations of the duodenum and colon. Emergency laparotomy was performed by the general surgery team. The same CT scan demonstrated a cortical defect approximately 9–10 mm in diameter in the right half of the L3 vertebral body, corresponding to the bullet entry trajectory and accompanied by mild porotic changes (Fig. 1). In sagittal CT sections, the bullet was visualized within the spinal canal at the L1–L2 level, consistent with intradural localization. The entry wound was noted in the right lower abdominal quadrant, and no exit wound was identified. The patient was discharged after stabilization, with neurosurgical follow-up recommended.

During outpatient follow-up, the patient remained asymptomatic, and serial CT scans confirmed that the bullet had not migrated.

In November 2024, approximately 2.5 years after the injury, he presented with progressive bilateral leg weakness, gait imbalance, urinary incontinence, and saddle anesthesia. Neurological examination revealed full motor strength in the upper extremities, while in the lower extremities, muscle strength was 3+/5 on the right and 4+/5 on the left. Laboratory and systemic evaluations revealed no findings suggestive of lead intoxication or infection. New lumbosacral CT scans demonstrated caudal migration of the bullet to the S2 level, compressing the cauda equina nerve roots (Fig. 2).

The patient underwent urgent surgery. Under general anesthesia and in the prone position, a midline incision was made at the L5–S3 level, followed by bilateral partial laminectomy at S1–S2. The dura was opened under microscopic visualization, revealing the bullet within the intradural space. The foreign body was carefully dissected and removed without injury to adjacent nerve roots. The sacral rootlets were clearly visualized, and the dural defect was repaired primarily (Fig. 3). The wound was closed in anatomical layers.

Postoperatively, the patient's lower extremity strength improved significantly, and urinary incontinence resolved. No cerebrospinal fluid (CSF) leakage or wound infection occurred. He was discharged in good condition and referred for rehabilitation, with plans for long-term follow-up.

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

DISCUSSION

Gunshot wounds to the spine are high-energy traumas that frequently result in permanent neurological deficits involving the spinal cord and nerve roots. Such damage may occur due to direct compression by the bullet itself, bone fragments, or disc material. Most cases reported in the literature involve complete paraplegia. In rare instances, however, the bullet may compromise the annulus fibrosus, increase intradiscal pressure, and indirectly lead to spinal cord compression. Importantly, spinal cord injury may occur even without direct penetration of the spinal canal, as the concussive effect of the bullet's impact on the vertebra can be sufficient to cause damage.^[4] In our case, the absence of any initial motor, sensory, or autonomic deficits suggests that the bullet initially settled in a relatively harmless position. However, the subsequent development of symptoms due to delayed migration demonstrates that early neurological silence may be misleading in terms of long-term clinical prognosis.

Most vertebral injuries caused by gunshots are considered stable. Nonetheless, bullets lodged in the lumbar region can damage pedicles or facet joints, potentially leading to acute or delayed instability. When the integrity of the pedicles and facets is preserved, spinal instability is unlikely to develop. In our patient, no signs of spinal instability were observed in the early phase, and spinal CT scans showed no evidence of vertebral fracture or collapse. Therefore, conservative management was initially chosen. However, the emergence of neurological symptoms in the delayed phase underscores the



Figure 1. (a) Sagittal CT image obtained at initial presentation following a gunshot injury demonstrates a hyperdense foreign body consistent with a bullet core located within the spinal canal at the L1–L2 vertebral level. (b) Axial CT scan at the same level (L1–L2) reveals the intrathecal location of the bullet core within the right posterolateral portion of the spinal canal. (c) Preoperative sagittal lumbosacral CT image shows a hyperdense foreign body, approximately 9–10 mm in size, consistent with a bullet core located within the spinal canal at the S1–S2 vertebral level. These findings indicate caudal migration of the intrathecal bullet core from the L1–L2 level. (d) Preoperative axial lumbosacral CT image of the same patient reveals a hyperdense intrathecal foreign body measuring 15×12 mm, localized in the right posterolateral portion of the spinal canal at the S1–S2 level, confirming caudal migration of the bullet core. (e) Postoperative sagittal lumbosacral CT image shows the surgical defect from the partial laminectomy performed at the S1–S2 level. The previously occupied intrathecal space now appears vacant, and no residual bullet-related foreign body density is observed. (f) Postoperative axial CT image of the same patient demonstrates a bony defect corresponding to the laminectomy at the S1–S2 level. No intrathecal foreign body is detected, indicating complete surgical decompression.

need to consider not only structural but also functional and dynamic factors in clinical evaluation.^[5]

Intradural bullet migration was first described in 1916, and the main contributing factors are gravity, CSF flow, and respiratory movements.^[6] Physiological forces such as coughing, peristalsis, and body positioning have also been implicated in the literature.^[7] In our case, the bullet initially located at the L1–L2 level had migrated to the S2 level 2.5 years later. Despite multiple imaging studies during follow-up, no migration was noted until the final evaluation. This suggests that migration may have occurred suddenly over a short period. The passive nature of this movement, likely triggered by positional factors, aligns with findings in previous reports.^[8] The damage caused by a bullet is not limited to mechanical impact; thermal energy, mass effect, and toxic potential due to its metallic composition can also result in significant pathophysiological consequences. In cases without an exit wound, the bullet's location should be thoroughly investigated even if the patient is asymptomatic. In our patient, no exit wound was observed, and although the bullet was intrathecal, it did not initially cause clinical symptoms. This highlights the importance of timely removal of foreign bodies within the spinal canal due to the potential risks of migration, infection, and neurological deterioration.^[9]

CSF fistula formation due to a bullet in the spinal canal significantly increases the risk of meningitis and constitutes an absolute indication for surgical removal.^[10] Additionally, if the bullet perforates the colon before entering the spinal canal, the risk of infection becomes even higher. In our case, initial evaluation revealed colonic perforation, and emergency laparotomy was performed. The patient did not develop early postoperative infection or meningitis, supporting the



Figure 1. (a) Intraoperative microscopic view demonstrating the careful dissection and excision of the bullet core located between the sacral nerve roots (*) following dural opening at the S1–S2 level. The proximity of the lead fragment to adjacent neural structures is directly visualized. (*) Sacral nerve root. (b) Macroscopic appearance of the excised bullet core following removal. The foreign body was measured against a standard surgical ruler and found to be approximately 15×12 mm in size.

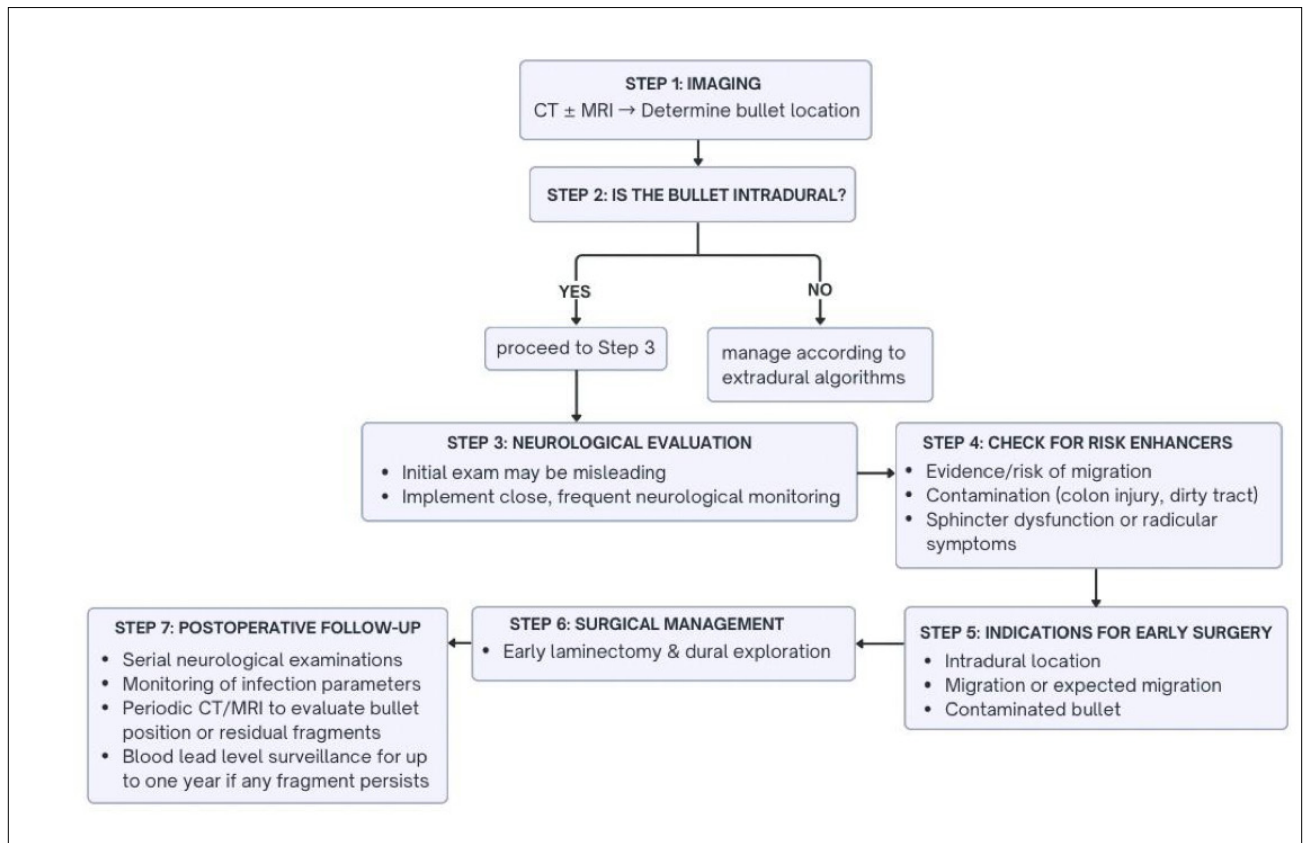


Figure 4. Proposed clinical algorithm for the evaluation and management of retained bullet fragments within the spinal canal.

effectiveness of the chosen surgical approach and antimicrobial therapy.^[11] However, as demonstrated in our case, when neurological symptoms arise due to migration, surgical intervention becomes unavoidable. Therefore, the decision for surgery should be individualized, taking into account the patient's clinical status, bullet location, spinal stability, and associated injuries.^[1,12]

Intradural free-floating bullets can complicate surgical intervention. To prevent cranial migration during manipulation, reverse Trendelenburg positioning and gentle dissection techniques may be employed.^[13] In our patient, microsurgical dissection was performed, the bullet was successfully removed, the sacral nerve rootlets were visualized, and the dural defect was closed primarily. No postoperative CSF leakage or infection was observed.

Bullets are typically composed of lead, and their toxic effects may manifest in the long term. Blood lead levels peak approximately 3 months after injury and can cause systemic symptoms such as microcytic anemia, encephalopathy, and peripheral neuropathy.^[14] Therefore, regular monitoring of lead levels is recommended for at least one year in patients with retained bullets. Although our patient did not show signs of lead toxicity, the risk should always be considered. Similar cases have been reported in the literature. For instance, Tanguy et al. also advocated surgical removal

of a caudally migrated bullet associated with meningitis three months post-injury.^[15] Even bullets located in the posterior fossa have been reported to migrate into the spinal canal, causing tetraplegia and necessitating urgent surgery. Cagavi et al. described a case of spontaneous caudal migration from L3 to S2 with partial neurological improvement following surgery. Likewise, in our case, a bullet initially considered stable eventually migrated, resulting in severe neurological symptoms and notable clinical improvement after surgery.^[9,16]

The management of retained intradural bullets remains controversial, with no universally accepted guidelines regarding the timing of surgical removal. Waters and Adkins emphasized that early removal of bullet fragments within the spinal canal can reduce the risk of delayed neurological deterioration, lead toxicity, and infection.^[17] Similarly, Ghori et al. reported a case of delayed cauda equina syndrome due to bullet migration and advocated early surgical intervention to prevent irreversible damage.^[18] Harsha and Thomas also described complete neurological recovery after delayed surgery, underscoring the potential for favorable outcomes even in late presentations. Based on accumulated evidence, early removal of intradural bullets (particularly those located in the lumbosacral region) should be considered when feasible, provided that the patient's neurological and systemic status

allows for safe intervention.^[19]

Gunshot wounds to the lumbosacral spine require meticulous evaluation, particularly when the projectile is located intradurally. Although our patient initially exhibited an intact neurological examination, early imaging clearly demonstrated an intradural bullet. Prior literature strongly indicates that an initially preserved neurological status in such cases may be misleading, as intradural projectiles are prone to late migration and may produce delayed cauda equina syndrome, progressive radiculopathy, or sphincter dysfunction.^[20,21] Although the patient was not taken to surgery at first admission, strict and frequent neurological monitoring was maintained in the early period. However, relying solely on neurological stability without addressing the mechanical and inflammatory risks associated with an intradural bullet presents a potential for avoidable deterioration. Moreover, the patient had undergone colon surgery during the same initial period, suggesting a contaminated bullet tract. Contamination of an intradural foreign body significantly increases the risk of meningitis, arachnoiditis, and other delayed infectious complications. This combination (contamination risk plus intradural migration potential) represents a strong indication for early operative management. Recent illustrative cases have highlighted the technical feasibility and benefit of early extraction for preventing late neurological decline, while additional reports emphasize the challenges in ‘catching’ highly mobile bullets within the dural sac.^[22,23] Bassani et al. further emphasize that even neurologically intact patients with an intradural bullet may warrant early surgical consideration due to the risks of migration, inflammation, or late neurological deterioration, underscoring that the absence of deficits does not eliminate the need for timely intervention.^[24] Our case illustrates that even with appropriately close neurological surveillance, delayed deterioration can occur when the underlying risk factors (migration and contamination) are present. Therefore, this case reinforces the importance of prioritizing early surgical exploration in patients with intradural bullet localization, even in the absence of immediate neurological deficits. It is conceivable that earlier removal at the time of the initial presentation might have prevented the development of cauda equina syndrome in our patient.

Based on current literature and our clinical experience, the structured algorithm presented in Figure 4 provides a systematic and practical framework for the evaluation and management of retained bullet fragments within the spinal canal. This stepwise approach is intended to facilitate early identification of high-risk patients, guide appropriate imaging and neurological monitoring, and assist in timely surgical decision-making when indicated. In lumbosacral gunshot injuries with suspected intradural localization, applying these management principles is essential to prevent serious complications such as migration, infection, and delayed neurological deterioration (Fig. 4).

CONCLUSION

Although intradural bullet fragments may initially remain asymptomatic, delayed migration can lead to significant neurological deterioration. In our case, the patient’s intact early neurological status prompted initial observation; however, the later development of cauda equina symptoms ultimately necessitated surgical removal. This underscores that a normal early neurological examination does not guarantee long-term stability. Based on current evidence, early surgical extraction should be strongly considered in patients with suspected intradural bullet fragments. We believe that the clinical decision algorithm proposed in this study may assist clinicians in identifying high-risk patients at an earlier stage and in preventing delayed neurological compromise.

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OLGU SUNUMU - ÖZ

İntradural kurşun migrasyonuna bağlı gelişen cauda equina sendromu: Nadir bir olgu sunumu

AMAÇ: Spinal kanal içerisinde bir mermi çekirdeğinin intradural yer değiştirmesi son derece nadir görülen bir klinik durumdur ve zamanla ortaya çıkabilen ilerleyici nörolojik bozulma açısından önemli riskler taşır. Bu tür olgularda başlangıçta herhangi bir belirti olmayabilir; ancak yabancı cismin spinal kanal içinde daha sonraki dönemde migre olması tanısal ve tedaviye yönelik ciddi güçlükler oluşturabilir. Bu çalışmada, intradural mermi çekirdeğinin gecikmiş kaudal migrasyonu sonucunda gelişen nadir bir kauda ekuina sendromu olgusunu sunuyor ve tanısal değerlendirme, cerrahi tedavi ile klinik karar verme sürecine ilişkin ayrıntılı bir tartışma yapıyoruz. Otuz iki yaşındaki erkek hasta 2022 yılında ateşli silah yaralanması geçirdi. İlk görüntüleme mermi çekirdeğinin spinal kanala penetre olarak L1-L2 seviyesinde intradural olarak yer aldığı saptandı; ancak hastada o dönemde herhangi bir nörolojik defisit bulunmadığından konservatif yaklaşım ve düzenli takip planlandı. Yaklaşık 2,5 yıl sonra hasta, ani başlangıçlı her iki alt ekstremitede güçsüzlük, yürüme bozukluğu ve yeni gelişen üriner inkontinans ile başvurdu. Yapılan bilgisayarlı tomografi tetkikinde intradural mermi çekirdeğinin kaudal yönde S2 seviyesine doğru migre olduğu ve kauda ekuina köklerinde belirgin kompresyona yol açtığı görüldü. Bu bulgular üzerine acil cerrahi müdahale yapıldı ve S1-S2 seviyesinde bilateral parsiyel laminektomi ile mermi çekirdeği mikroskopik teknikle çıkarıldı. Ameliyat sonrası dönemde motor fonksiyonlarda belirgin düzelme izlendi ve üriner semptomlar tamamen geriledi. Her ne kadar intradural mermi çekirdekleri başlangıçta asemptomatik seyredebilse de, geç dönemdeki migrasyon ciddi ve geri dönüşümsüz nörolojik bozulmaya yol açabilir. Bu olgu, başlangıçta nörolojik defisiti olmayan hastalarda dahi intradural lokalizasyon saptandığında, geç komplikasyonları önlemek amacıyla erken cerrahi çıkarımın güçlü biçimde değerlendirilmesi gerektiğini göstermektedir. Erken müdahale, kauda ekuina sendromu gibi ileri derecede nörolojik bozulmaların yanı sıra, kontamine mermi traktına bağlı enfeksiyöz komplikasyonlar ve uzun dönem intradural kurşun maruziyetine bağlı toksisite risklerini azaltmada önemli rol oynayabilir.

Anahtar sözcükler: Cauda equina sendromu; intradural kurşun migrasyonu; spinal ateşli silah yaralanması.

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