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ORIGINAL ARTICLE

Post-operative pancreatitis following ERCP and EST in elderly patients with choledocholithiasis

Pancreatitis posoperatoria tras CPRE y EE en pacientes ancianos con coledocolitiasis

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Abstract

Objective: *Herein, we identified risk factors (RFs) for post-operative pancreatitis among elderly sufferers of choledocholithiasis undergoing endoscopic retrograde cholangiopancreatography (ERCP) along with endoscopic sphincterotomy (EST), and to develop a predictive model for pancreatitis occurrence.* **Methods:** *We retrospectively collected clinical data of elderly patients (≥ 65 years old) with choledocholithiasis undergoing ERCP+EST at Affiliated Liupanshui Hospital of Zunyi Medical University from January 2017 to April 2024. Participants were stratified into pancreatitis and non-pancreatitis cohorts according to their post-operative outcomes.* **Results:** *Using multivariate analysis, we determined stand-along RFs for post-operative acute pancreatitis as follows: Age under 75 years, a history of acute pancreatitis, pancreatography, difficult intubation, and multiple guidewire insertions into the pancreatic duct ($p < 0.05$). The area under the curve of the predictive model was 0.783 (95% confidence interval: 0.705-0.862), indicating good predictive capability. Calibration curves showed consistency between predicted risks and observed outcomes (Hosmer-Lemeshow test, $p > 0.05$). Clinical decision curves demonstrated the model's clinical utility.* **Conclusions:** *In elderly patients with choledocholithiasis, factors such as younger age (under 75), history of acute pancreatitis, challenging intubation, pancreatography, and multiple guidewire insertions into the pancreatic duct are significant RFs for post-ERCP pancreatitis.*

Keywords: *Endoscopic retrograde cholangiopancreatography. Endoscopic papillary sphincterotomy. Pancreatitis. Risk factor. Nomogram.*

Resumen

Objetivo: *Identificar los factores de riesgo de pancreatitis posoperatoria en ancianos con coledocolitiasis sometidos a colangiopancreatografía retrógrada endoscópica (CPRE) y esfinterotomía endoscópica (EE), y desarrollar un modelo predictivo de pancreatitis.* **Métodos:** *Recopilamos retrospectivamente datos cllos cl de pacientes de edad avanzada (anzadaños) con coledocolitiasis sometidos a CPRE + EE en el Hospital Afiliado Liupanshui de la Universidad Médica de Zunyi, desde enero de 2017 hasta abril de 2024. Los participantes se estratificaron en cohortes con pancreatitis y sin pancreatitis según sus resultados posoperatorios.* **Resultados:** *Mediante un análisis multivariable determinamos los factores de riesgo independientes para la pancreatitis aguda posoperatoria de la siguiente manera: edad < 75 años, antecedentes de pancreatitis aguda, pancreatografía, intubación difícil e inserciones múltiples de guía en el conducto pancreático ($p < 0.05$). El AUC del modelo predictivo fue de 0.783 (IC 95%: 0.705-0.862), lo que indica una buena capacidad predictiva. Las curvas de calibración mostraron coherencia entre los riesgos predichos y los resultados observados (prueba de Hosmer-Lemeshow, $p > 0.05$). Las curvas de decisión clínica demostraron la utilidad clínica del modelo.*

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Conclusiones: *En pacientes ancianos con coledocolitiasis, factores como una edad más joven (< 75 años), antecedentes de pancreatitis aguda, intubación difícil, pancreatografía y múltiples inserciones de guías en el conducto pancreático son factores de riesgo significativos para pancreatitis tras una CPRE.*

Palabras clave: *Colangiopancreatografía retrógrada endoscópica. Esfinterotomía papilar endoscópica. Pancreatitis. Factor de riesgo. Nomograma.*

Introduction

Cholelithiasis, a common digestive system disease, represents stone formation in any part of the biliary system, such as the gallbladder and bile ducts. This condition encompasses stone generation in the gallbladder, common bile duct (CBD), and intrahepatic bile duct. The disease has a complex etiology and poses treatment challenges. The incidence rate among adults in China is currently 8-13%, and this rate is increasing with the improvement of living standards[1]. Among patients with gallbladder stones, 5-15% also have CBD stones. The elderly population exhibits the highest incidence rates, with 30% of women aged 65 and 60% of those aged 80 developing cholelithiasis[2]. Endoscopic retrograde cholangiopancreatography (ERCP) along with endoscopic sphincterotomy (EST) has emerged as a key treatment for CBD stones and related biliary diseases in recent years.

Relative to classical open surgery, this approach offers the benefits of being minimally invasive, having lower risks, providing rapid recovery, and requiring shorter hospital stays, making it particularly suitable for elderly patients[3]. However, as an invasive technique, ERCP + EST involves certain risks. Thermal injury during EST can easily lead to Oddi sphincter dysfunction, and damage to the pancreatic duct sphincter can result in impaired pancreatic juice outflow, reflux, or even leakage, significantly increasing the risk of post-operative pancreatitis[4]. Studies indicate that complications following ERCP + EST occur in 10-12% of cases, including duodenal papilla bleeding, duodenal perforation, acute pancreatitis, and cholangitis, with post-operative acute pancreatitis (post-ERCP pancreatitis, post-endoscopic pancreatitis [PEP]) being the most common, occurring in 1.6-15.0% of cases[5].

The growing elderly population and the high incidence of cholelithiasis among this group highlight the importance of timely treatment to reduce treatment difficulties and survival risks. This study investigates risk factors (RFs) for pancreatitis among elderly subjects with CBD stones undergoing ERCP + EST and establishes a prediction model to forecast PEP risk, providing valuable clinical reference.

Methods

Patients and research design

We retrospectively collected data on elderly patients aged 60 years and above with CBD stones who underwent ERCP + EST treatment at Affiliated Liupanshui Hospital of Zunyi Medical University from January 2017 to December 2023. The following patients were included for analysis in this study: elderly patients aged 60 years and above diagnosed with CBD stones who underwent ERCP + EST at Liupanshui People's Hospital and passed a preoperative risk assessment confirming their eligibility for surgery. This investigation received ethical approval from the Affiliated Liupanshui Hospital of Zunyi Medical University (No. LPSSYY-2024-25). Due to the retrospective design of this investigation, the informed consent requirement was waived. Exclusion criteria encompass patients with a preoperative diagnosis of acute pancreatitis, severe cardiopulmonary insufficiency, coagulopathy, hematologic diseases, a history of gastroduodenal surgery, or incomplete clinical data. The diagnostic criteria[6] for acute pancreatitis require a meeting of two of the three following conditions: characteristic abdominal pain, circulating amylase or lipase levels over 3 times the upper normal threshold, or imaging evidence of pancreatitis on abdominal computed tomography or ultrasound.

Date collection

The following clinical information was acquired: sex, age, body mass index (BMI), hypertension, diabetes, prior hepatitis history (if any), smoking history, drinking history, history of acute pancreatitis, previous cholecystectomy, history of bile duct surgery, presence of ampullary diverticulum, bile duct stent, pancreatic stent, endoscopic papillary balloon dilation, bile duct diameter, difficult intubation, pancreatography, and more than two guidewire insertions into the pancreatic

duct. Biochemical indicators include total bilirubin, direct bilirubin, white blood cell count, aspartate aminotransferase, alanine aminotransferase, circulating amylase, and albumin concentration. Smoking history represented smoking ≥ 1 cigarettes daily for over 6 months; or having previously met this criterion with cessation for < 6 months. Drinking history was defined as consuming alcohol at least once a week for more than 6 months; or having previously met this criterion with cessation for < 6 months. Difficult intubation was defined as more than five intubation attempts or an intubation time of more than 10 min.

Statistics

R software version 4.3.1 was employed for all data analyses. Data with normal distribution are presented as mean ± standard deviation; while remaining data are described as a median and interquartile range (Median [Q1, Q3]) and analyzed through non-parametric Mann–Whitney U tests. Continuous data were compared using t- or rank-sum tests, while categorical data were provided as counts and percentages and assessed through the X^2 or Fisher's exact test. Two-tailed $p < 0.05$ was the significance standard. We employed univariate logistic regression for potential predictor identification, with variables showing a $p < 0.10$ considered for further analysis. Significant variables were entered into multivariate logistic regression analysis for stand-alone RFs identification for post-ERCP + EST pancreatitis (PEP), with significance indicated at $p < 0.05$. Using regression coefficients, we next generated a nomogram prediction model. Model internal verification was achieved through 1,000 bootstrap resamples, and the resulting calibration curve revealed consistency between estimated and actual outcomes. The Hosmer–Lemeshow test evaluated model fitness. The model predictive ability was assessed through the receiver operating characteristic (ROC) curve and the area under the curve. Clinical applicability was examined through the clinical decision curve.

Results

Baseline characteristics

In all, 413 patients were analysis, among which, 178 were males and 235 were females, and the mean age of all participants was 69.4 years. Among these, 39 patients developed pancreatitis post-surgery, forming the PEP group. This group represents an incidence rate of 9.4% for post-surgical pancreatitis. The remaining 374 patients did not develop pancreatitis and were categorized as the non-PEP group. The baseline data for these groups are detailed in table 1. All cases of pancreatitis in the PEP group were classified as mild to moderate, and there were no in-hospital deaths attributed to PEP.

Univariate and multivariate regression analysis

Univariate analysis identified five variables with $p < 0.1$ in this cohort: age under 75 years, a history of acute pancreatitis, difficult intubation, more than two guidewire insertions into the pancreatic duct, and pancreatography. These variables were then entered into multivariate analysis, which confirmed that all five factors were statistically significant ($p < 0.05$), thereby establishing them as stand-alone RFs for post-ERCP pancreatitis (PEP) development. A detailed summary of the results is provided in table 2.

Construction of nomogram model

Based on multivariate logistic regression, a risk prediction nomogram was developed to assess the probability of PEP among elderly patients with CBD stones undergoing ERCP and EST. This nomogram included five predictive factors illustrated in figure 1.

By summing the individual scores from these factors, a total score was calculated, which then predicted the probability of PEP. The model demonstrated excellent calibration, as the calibration curve closely approximated the ideal reference line. The Hosmer–Lemeshow test confirmed the model's fit, with $p = 0.174$, suggesting no marked difference between estimated and actual risks. The area under the ROC curve was 0.783 (95% confidence interval [CI]: 0.705-0.862), suggesting the model's strong predictive accuracy. In addition, clinical DCA indicated that using this nomogram for clinical decisions provided a substantial net benefit over a wide range of decision thresholds, specifically from 2% to 76%. The detailed results are presented in figures 2-4.

Discussion

At present, ERCP + EST is one of the primary methods for treating CBD stones. Although it offers specific advantages over traditional open surgery,

Table 1. Baseline patient characteristics

Factor	Category	Non-PEP group n = 374 (%)	PEP group n = 39 (%)	Statistical value	p
Age	≥ 75 years	106 (28.3)	5 (12.8)	4.330	0.059
	< 75 years	268 (71.7)	34 (87.2)		
Sex	Male	166 (44.4)	12 (30.8)	2.670	0.143
	Female	208 (55.6)	27 (69.2)		
BMI	≥ 24	240 (64.2)	24 (61.5)	0.106	0.880
	< 24	134 (35.8)	15 (38.5)		
Hypertension history	No	253 (67.6)	26 (66.7)	0.015	1.000
	Yes	121 (32.4)	13 (33.3)		
Acute pancreatitis history	No	345 (92.2)	30 (76.9)	8.176	0.004
	Yes	29 (7.8)	9 (23.1)		
Diabetes history	No	318 (85.0)	34 (87.2)	0.130	0.902
	Yes	56 (15.0)	5 (12.8)		
Smoking history	No	300 (80.2)	34 (87.2)	1.108	0.402
	Yes	74 (19.8)	5 (12.8)		
Drinking history	No	325 (86.9)	37 (94.9)	1.403	0.236
	Yes	49 (13.1)	2 (5.1)		
Hepatitis history	No	359 (96.0)	36 (92.3)	0.435	0.510
	Yes	15 (4.0)	3 (7.7)		
Previous cholecystectomy	No	301 (80.5)	28 (71.8)	1.645	0.283
	Yes	73 (19.5)	11 (28.2)		
Bile duct surgery history	No	303 (81.0)	35 (89.7)	1.810	0.260
	Yes	71 (19.0)	4 (10.3)		
TBil	≤ 17.1	126 (33.7)	15 (38.5)	0.358	0.674
	> 17.1	248 (66.3)	24 (61.5)		
DBil	≤ 6.8	91 (24.3)	11 (28.2)	0.285	0.735
	> 6.8	283 (75.7)	28 (71.8)		
Preoperative WBC	≤ 10.0	308 (82.4)	32 (82.1)	0.002	1.000
	> 10.0	66 (17.6)	7 (17.9)		
ALT	–	86.40 (39.25, 164.00)	70.40 (24.62, 158.12)	6367.5	0.192
AST	–	62.60 (26.90, 103.40)	45.85 (22.02, 128.57)	7141.5	0.831
Albumin	≥ 40	176 (47.1)	22 (56.4)	1.238	0.345
	< 40	198 (52.9)	17 (43.6)		
Bile duct stent	No	241 (64.4)	27 (69.2)	0.357	0.674
	Yes	133 (35.6)	12 (30.8)		
Pancreatic duct stent	No	322 (86.1)	34 (87.2)	0.035	1.000

(Continues)

Table 1. Baseline patient characteristics *(continued)*

Factor	Category	Non-PEP group n = 374 (%)	PEP group n = 39 (%)	Statistical value	p
	Yes	52 (13.9)	5 (12.8)		
Pancreatography	No	331 (88.5)	23 (59.0)	25.148	< 0.001
	Yes	43 (11.5)	16 (41.0)		
Nasobiliary tube	No	147 (39.3)	12 (30.8)	1.087	0.385
	Yes	227 (60.7)	27 (69.2)		
Difficult intubation	No	311 (83.2)	21 (53.8)	19.243	< 0.001
	Yes	63 (16.8)	18 (46.2)		
Common bile duct diameter	≤ 1 cm	164 (43.9)	20 (51.3)	0.790	0.472
	> 1 cm	210 (56.1)	19 (48.7)		
Ampullary diverticulum	No	287 (76.7)	27 (69.2)	1.092	0.396
	Yes	87 (23.3)	12 (30.8)		
Guidewire insertion into pancreatic duct	< 2 times	339 (90.6)	24 (61.5)	25.444	< 0.001
	≥ 2 times	35 (9.4)	15 (38.5)		
Endoscopic papillary balloon dilation	No	267 (71.4)	24 (61.5)	1.647	0.272
	Yes	107 (28.6)	15 (38.5)		

Note: measurement data with a skewed distribution were expressed as median (Q1, Q3); count data were expressed as counts or percentages. BMI: body mass index; PEP: post-endoscopic pancreatitis.

Table 2. Multivariate regression analysis of elderly patients with common bile duct stones complicated by pancreatitis

Factor	Regression coefficient	Standard error	z	p	OR	95% CI
Age < 75 years	1.421	0.543	2.616	0.009	4.143	1.555-13.516
History of acute pancreatitis	1.212	0.475	2.551	0.011	3.361	1.275-8.364
Pancreatography	1.199	0.469	2.555	0.011	3.317	1.313-8.351
Difficult intubation	0.876	0.419	2.090	0.036	2.400	1.040-5.417
More than twice Guidewire insertions	0.966	0.449	1.782	0.031	2.629	1.071-6.277

OR: odds ratio; CI: confidence interval.

such as being less invasive and allowing faster recovery, the technique is technically demanding and carries inherent risks. The procedure requires substantial expertise, and the associated complications should not be overlooked. Common post-operative complications of ERCP + EST include pancreatitis, infection, bleeding, and perforation. PEP is the most frequent complication, with an incidence rate ranging from 1.6% to 15.0%, and approximately 1.5% of PEP cases are moderate to severe, with a mortality rate of up to 3-5%[7]. In this study, the incidence rate of PEP after ERCP + EST was 9.4%, with all cases being mild to moderate and no in-hospital deaths reported. These results align with previous research. The elderly population has a high incidence of CBD stones, and ERCP + EST is frequently performed in this group. However, studies on PEP in elderly patients are limited. Elderly patients often have reduced physiological resistance and multiple comorbidities, which may increase the incidence of

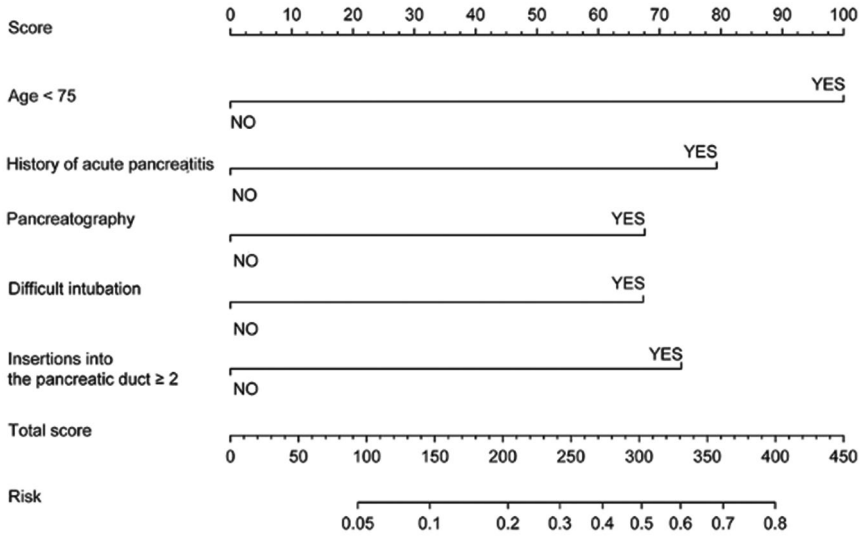

Figure 1. *Nomogram risk chart for pancreatitis in elderly patients with common bile duct stones.*

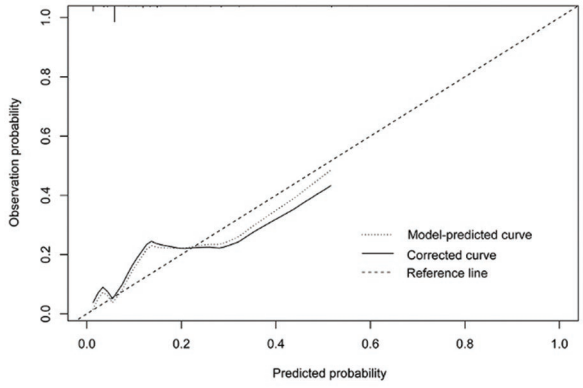

Figure 2. *Calibration curve for pancreatitis in elderly patients with common bile duct stones.*

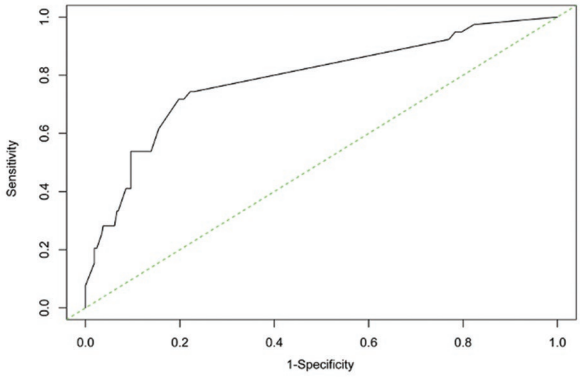

Figure 3. *Receiver operating characteristic curve for pancreatitis in elderly patients with common bile duct stones.*

post-operative complications[8]. Therefore, identifying the RFs for PEP and implementing early preventive measures are crucial. This study focused on elderly patients with CBD stones. Based on previous studies[9-11], we initially screened the variables to be collected and identified the RFs for PEP after ERCP + EST using a logistic regression model. The independent RFs identified included age under 75 years, history of acute pancreatitis, difficult intubation, pancreatography, and more than two guidewire insertions into the pancreatic duct. A clinical prediction model for PEP was constructed, and a nomogram was created to visualize the model, making it a practical tool for assessing patient risk and predicting disease occurrence.

Age is an established RF for PEP in several studies[12-15]. Younger patients are thought to be more susceptible to PEP, possibly due to the decline in pancreatic function associated with aging or pancreatic parenchymal degeneration, which leads to a reduced response to mechanical injury from ERCP. Research indicates that pancreatic exocrine function increases linearly with age up to 30 years and then begins to decline[16]. Moreover, infants under 1 year of age rarely develop PEP following ERCP[17]. Age stratification in PEP risk studies varies, with 60 years often used as the threshold, though other studies use 50, 70, or 75 years. This study focused on elderly patients aged 60 years and older and stratified them based on the World Health Organization's age classification, using

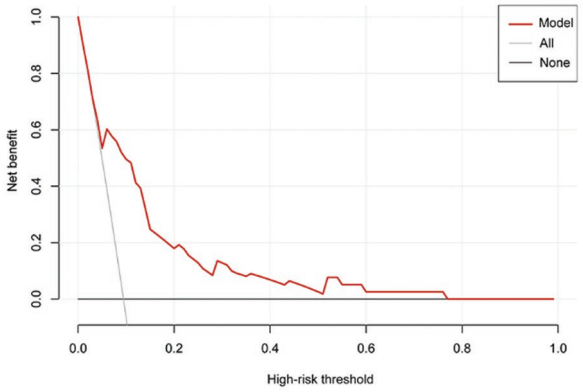

Figure 4. *Clinical decision curve for pancreatitis in elderly patients with common bile duct stones.*

75 years as the cutoff. We found that the PEP incidence was substantially elevated among the younger subgroup compared to those aged 75 years and older, with the former group having a 4.143-fold rise in risk (OR = 4.143; 95% CI, 1.555-13.516; p = 0.009). This study confirms the higher risk of PEP in relatively younger elderly patients but did not investigate those under 60 years. A study by Ergin et al.[8] found the highest PEP risk in the 21-30 years age group, though the difference was not significant. A nationwide ERCP study in Korea[14] reported a higher incidence of PEP in younger patients, with the highest rates in those under 40 years, while the incidence was lower in the elderly. In our study, the incidence of PEP was low in patients aged 75 years and older, with no cases observed in those over 80 years, likely due to age-related pancreatic changes. However, the small sample size of older patients in this study may have introduced bias. Based on these findings, it is important to inform younger patients undergoing ERCP about the risks, thoroughly evaluate their condition, and, if other RFs are present, take preventive measures to reduce the occurrence of PEP. For older patients, who often have more comorbidity and reduced physiological resistance, a thorough preoperative evaluation is necessary to determine the appropriate treatment plan[18].

The European Society of Gastrointestinal Endoscopy (ESGE) guidelines have identified prior pancreatitis history as a RF for PEP[19]. Patients with prior pancreatitis history may have underlying damage to the pancreatobiliary system, such as microinflammatory changes or metabolic damage, making them more sensitive to ERCP-related procedures. Compared with patients without a history of pancreatitis, those with such a history are at significantly higher risk for PEP due to repeated episodes of pancreatitis leading to pancreatic parenchymal damage and reduced exocrine function[20]. In this study, a history of acute pancreatitis was a significant RF, with a 3.3-fold rise in PEP risk relative to controls (odds ratio [OR] = 3.361; 95% CI, 1.275-8.364; p = 0.011). Recent studies[21] also support the association between a history of pancreatitis and the occurrence of PEP after ERCP. However, the risk of PEP may be lower among chronic pancreatitis patients. A systematic review involving 13 studies[22] revealed that chronic pancreatitis patients experienced reduced PEP incidence than controls, likely due to pancreatic atrophy and reduced enzymatic activity. This study did not include chronic pancreatitis patients, so this factor was not considered as a variable.

Procedure-related RFs identified in this study include pancreatography, more than two guidewire insertions into the pancreatic duct, and difficult intubation, consistent with previous research[23-25]. Multiple guidewire insertions or contrast medium administration into the pancreatic duct can cause chemical and mechanical damage to the ductal epithelium, leading to congestion, edema, and increased internal pressure. This can damage the acinar epithelium and ductal walls, causing membrane disruption, pancreatic tissue injury, enzyme activation, and leakage of pancreatic juice, ultimately leading to pancreatitis[26]. This study confirmed that more than two guidewire insertions into the pancreatic duct and pancreatography are RFs for PEP, with associated risks of 3.317-fold (OR = 3.317; 95% CI, 1.313-8.351; p = 0.011) and 2.400-fold (OR = 2.400; 95% CI, 1.040-5.417; p = 0.036) increases, respectively. The ESGE guidelines[19] indicate OR of 2.1-2.77 for more than one guidewire insertion and 1.58-2.72 for pancreatography. Other studies[27] have found that the risk of PEP after ERCP is positively correlated with the amount of contrast medium injected into the pancreatic duct and the number of guidewire insertions, warranting further investigation in future research.

Difficult intubation is defined as an intubation time of 10 min or more, or more than five intubation attempts. Causes of difficult intubation include anatomical abnormalities of the duodenal papilla, ampulla, and surrounding structures, as well as operator technique variability. Difficult intubation can cause sphincter spasm, papillary congestion, and edema, leading to increased biliary pressure and impaired outflow of

pancreatic juice and bile, resulting in pancreatitis. It is considered an independent RF for PEP[28]. In this study, difficult intubation was identified as a RF, with a 1.7-fold increase in PEP risk when the intubation time exceeded 10 min or more than five intubation attempts were made. The ESGE guidelines[19] reported OR of 1.76-14.9 for difficult intubation, and a recent clinical study[10] revealed that the PEP incidence among patients with difficult intubation was elevated by 5.8 folds relative to controls, with a proportional increase in PEP risk with the number of intubations attempts and duration[29]. At present, no studies have shown a correlation between difficult intubation and age. To mitigate the risks associated with these procedural factors, clinicians should enhance their technical skills, minimize technical errors, reduce the injection of contrast medium during ERCP to prevent chemical damage to the pancreatic duct, and employ guidewire and pre-cut techniques to aid intubation. This approach can increase the success rate of intubation, reduce mechanical injury to the pancreatic duct, and prevent pancreatitis.

This investigation was limited by several factors: First, because of its retrospective design, it may be subject to data bias compared to prospective studies; second, the small sample size and moderate level of evidence may result in selection and information bias; third, this study was a single-center investigation, with internal validation only and no external validation. Larger, multicenter prospective clinical investigations are warranted to assess the external applicability of the proposed model.

Conclusion

PEP is a common complication among elderly patients with CBD stones undergoing ERCP and EST. This study identified age under 75 years, history of acute pancreatitis, pancreatography, difficult intubation, and more than two guidewire insertions into the pancreatic duct as significant RFs for PEP. A nomogram was generated for PEP risk prediction following ERCP and EST, enabling early identification of patients at risk. The validation results suggest that the model is feasible and provides clinical value and guidance. Therefore, thorough pre-operative evaluation, identification of RFs, strict adherence to indications and contraindications, and enhanced procedural training are essential to minimize complications in patients undergoing ERCP and EST.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply. This study was conducted with approval from the Ethics Committee of This investigation received ethical approval from the Affiliated Liupanshui Hospital of Zunyi Medical University (No. LPSSYY-2024-25).

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

A strategy for the one-stage treatment of open Pilon fractures based on an accelerated rehabilitation surgical concept

Una estrategia para el tratamiento en una sola etapa de las fracturas de pilón abiertas basada en un concepto quirúrgico de rehabilitación acelerada

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Abstract

Objective: *The objective of the study was to study the strategy of one-stage emergency treatment of open Pilon fracture with the concept of accelerated rehabilitation surgery.* **Methods:** *The data of 18 patients with open Pilon fracture treated by first-stage emergency debridement, fracture internal fixation, bone grafting, negative pressure closed drainage covering the wound, leg incision reduction, and second-stage skin grafting or flap transfer in the Department of Orthopedics of our hospital from January 2014 to December 2018 were retrospectively analyzed. Joint surface reduction was evaluated by radiological evaluation criteria such as Burwell-Charnley, fracture healing quality was evaluated by Merchant score, and ankle joint function was evaluated by Tornetta and other criteria at the last follow-up.* **Results:** *All 18 patients were followed up, and the anatomical reduction rate was 94% (17/18) according to radiological evaluation criteria such as Burwell-Charnley. According to Merchant scoring criteria, the fracture healing rate was 83.3% (15/18). At the last follow-up, the ankle function was evaluated according to Tornetta and other criteria, and the excellent rate was 88.9% (16/18).* **Conclusions:** *Using the concept of accelerated rehabilitation surgery to treat open Pilon fractures in the first emergency can effectively avoid soft-tissue complications and is an effective treatment strategy.*

Keywords: *Open Pilon fracture. Emergency incisional reduction and internal fixation. Vacuum sealing drainage. Accelerated rehabilitation surgery.*

Resumen

Objetivo: *Estudiar la estrategia de tratamiento de emergencia en una sola etapa de la fractura abierta de pilón con el concepto de cirugía de rehabilitación acelerada.* **Métodos:** *Se analizaron retrospectivamente los datos de 18 pacientes con fractura abierta de pilón tratados en primera etapa con desbridamiento de emergencia, fijación interna de fractura, injerto óseo, drenaje cerrado a presión negativa cubriendo la herida, reducción de la incisión de la pierna y transferencia de injerto de piel en una segunda etapa o colgajo, en el servicio de ortopedia de nuestro hospital, de enero de 2014 a diciembre de 2018. La reducción de la superficie articular se evaluó por criterios de evaluación radiológica como Burwell-Charnley, la calidad de la cicatriz de la fractura se evaluó por la puntuación de Merchant y la función articular del tobillo se evaluó según Tornetta y otros criterios en el último seguimiento.* **Resultados:** *Se realizó seguimiento a los 18 pacientes, con una tasa de reducción anatómica del 94% (17/18) según los criterios de evaluación radiológica Burwell-Charnley. Según los criterios de Merchant, la tasa de curación de la fractura fue del 83.3% (15/18). En el último seguimiento, la función del tobillo fue evaluada de acuerdo con Tornetta y otros criterios, y fue excelente en el 88.9% (16/18).* **Conclusiones:** *El uso del concepto de cirugía de rehabilitación acelerada*

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para tratar fracturas abiertas de pilón en la primera emergencia puede evitar eficazmente las complicaciones de los tejidos blandos y es una estrategia de tratamiento eficaz.

Palabras clave: *Fractura abierta de pilón. Reducción incisional de emergencia y fijación interna. Drenaje sellado al vacío. Cirugía de rehabilitación acelerada.*

Introduction

Pilon fractures, involving the lower shinbone (tibia) near the ankle joint, are the most complex fractures in foot and ankle injuries. Caused by high-impact events, they account for a small portion (1%) of all lower leg fractures but a significant number (7-10%) of tibia fractures[1]. The tibia's minimal soft-tissue covering makes these fractures prone to severe soft-tissue damage and instability (10-30% are open fractures, often accompanied by fibula fractures)[2]. Despite significant developments in the treatment of these fractures in recent years, a staged approach with initial external fixation followed by internal fixation after soft-tissue healing remains common, especially for severe fractures (AO/OTA type C). However, this approach can lead to lengthy hospital stays, external fixation loosening, increased infection risk, and delayed surgery hindering proper bone alignment[3]. Open Pilon fractures present a treatment dilemma. While there is no consensus on urgent fracture fixation, early wound debridement and fracture stability maintenance are crucial[4]. This study explores the effectiveness of a one-stage surgical approach for open Pilon fractures, building on the concept of accelerated rehabilitation surgery. This technique combines emergency debridement, internal fixation, bone grafting, and Vacuum-assisted closure therapy (VSD) with drainage in a single surgery, potentially minimizing complications associated with staged procedures. We retrospectively analyzed 18 open Pilon fracture patients treated at our hospital's Department of Traumatology and Orthopedics between January 2014 and December 2018. The aim was to evaluate the clinical efficacy of this one-stage surgical strategy.

Methods

Inclusion and exclusion criteria

Inclusion criteria

- Unilateral open Pilon fracture with time of injury ≤ 6 h;
- Combined with ipsilateral lower fibula fracture;
- Patients underwent emergency one-stage debridement, incision and internal fixation, reduction of the calf incision, and negative-pressure closure and drainage; and
- Complete clinical data with more than 1 year of follow-up.

Exclusion criteria

- Multiple injuries, combined with other fractures of the foot and ankle;
- Closed Pilon fracture, Gustilo III C;
- Pathologic fracture; and
- Poor physical condition, inability to tolerate emergency surgery, or incomplete follow-up data.

General information

Eighteen patients admitted to our Department of Traumatology and Orthopedics between January 2014 and December 2018 with open Pilon fractures were retrospectively analyzed according to the inclusion criteria. These patients included 14 males and 4 females, with ages ranging from 24 to 58 years old (average 40.2 years). All fractures were fresh and combined with ipsilateral lower fibula fractures. The causes of injury were: car accident (6 cases), fall from height (8 cases), and heavy object smash (4 cases). Gustilo fracture classification revealed: 3 type I, 4 type II, 6 type IIIA, and 5 type IIIB fractures. OA/ATO fracture classification identified 8 type 43-B and 10 type 43-C fractures. Ruedi-Allgower typing showed 6 type II and 12 type III fractures (Table 1). Preoperative workup routinely included frontal and lateral X-rays, CT scan, and three-dimensional reconstruction of the affected ankle joint.

Surgical techniques

Upon admission, patients received cefoperazone sulbactam sodium sedation followed by a quick physical examination. General anesthesia was administered in the operating room. Patients were positioned

Table 1. Patient demographics and mechanism of injury

Age (year)	Age range
Mean (and standard deviation)	40.2 ± 2.3
Median (range)	40.2 (24~58)
Sex	
Male	14 (78)
Female	4 (22)
Mechanisms of injury	6 (33)
Car accident injury	
Fall from a height	8 (45)
Bruise	4 (22)
AO fracture classifification	
B1	2 (11)
B2	3 (17)
B3	3 (17)
C1	2 (11)
C2	4 (22)
C3	4 (22)
Ruedi-Allgower classifification	
II	6 (33)
III	12 (67)
Gustilo classifification	
I	3 (17)
II	4 (22)
IIIA	6 (33)
IIIB	5 (28)

The values are given as the number of patients, with the percentage in parentheses.

supine on the healthy side. The wound was thoroughly debrided after initial evaluation of soft tissue damage and contamination. This debridement involved using soap, water, hydrogen peroxide, saline, and iodine volts to clean the trauma, remove contaminants, and deactivate devitalized soft tissues. Large bone fragments with blood flow were preserved for potential repair.

After initial debridement, the surgical field was disinfected with a surgical sheet. The original trauma site was extended, and further debridement was performed to eliminate contaminants and bone fragments from the bone surface. The fracture ends were again irrigated with hydrogen peroxide, iodine, and a large amount of saline. Gloves and instruments were changed, and the surgical procedure continued according to the preoperative plan.

The first incision was made posterolaterally on the fibula, followed by anatomical reduction and strong internal fixation. A straight incision was made on the anterolateral aspect of the tibial crest to access and examine the distal tibial articular surface. The crushed four-column cortex of the distal tibia was addressed (Fig. 1).

Iliac bone graft was harvested from the ipsilateral side to reconstruct any articular surface defects based on the degree of collapse. Cancellous bone from the distal tibia was used to restore the articular surface flatness. An L-shaped locking steel plate (Zimmer) was applied to the distal tibia to achieve fracture fixation and maintain articular surface alignment. The medial column was stabilized with two Kirschner pins inserted after anatomical reduction of the inner ankle.

The posterior tibial tendon soft tissue was repositioned to cover the traumatic defect. Following internal fixation, the tibial incision was thoroughly irrigated again with hydrogen peroxide and saline solution before suturing. To achieve tension-free closure of the anterior tibial incision, various techniques were employed based on calf tension. These techniques included: anterolateral calf reduction, posterior shallow reduction, posterior deep reduction, or medial and lateral full reduction. Barbed wire was used for tension-free closure of the skin edges. Finally, a VSD was placed over the original open incision and the reduction incision for drainage. The VSD was changed weekly until the trauma healed (Fig. 2).

Second stage wound management: following the one-stage surgery, the VSD was removed based on the granulation tissue formation within the trauma. The lateral reduction incision was tightened with barbed wire, and the skin edges were approximated without tension. The tension of the anterior tibial incision was maintained. The granulation tissue of the original open wound was assessed. If wound closure was possible, the skin defect area was measured. A medium-thickness flap was harvested from the ipsilateral thigh to cover the defect. The harvested skin was meshed with an oleo-sand dressing and shaped into a medium-thickness flap for transplantation onto the defect area. The resurfaced area was covered with a VSD, which was removed 1 week later to assess flap viability (Figs. 3 and 4).

Postoperative treatment

Postoperative management included cefoperazone sulbactam sodium for infection prevention, lower limb elevation to reduce swelling, low-molecular-weight heparin to prevent blood clots, and initial short leg cast immobilization. VSD was used in two phases: Phase I employed a pressure of 0.03 MPa to facilitate drainage of deep-seated contaminants, while Phase II utilized a lower pressure of 0.015 MPa to promote uniform skin graft adherence and prevent pressure-induced tissue

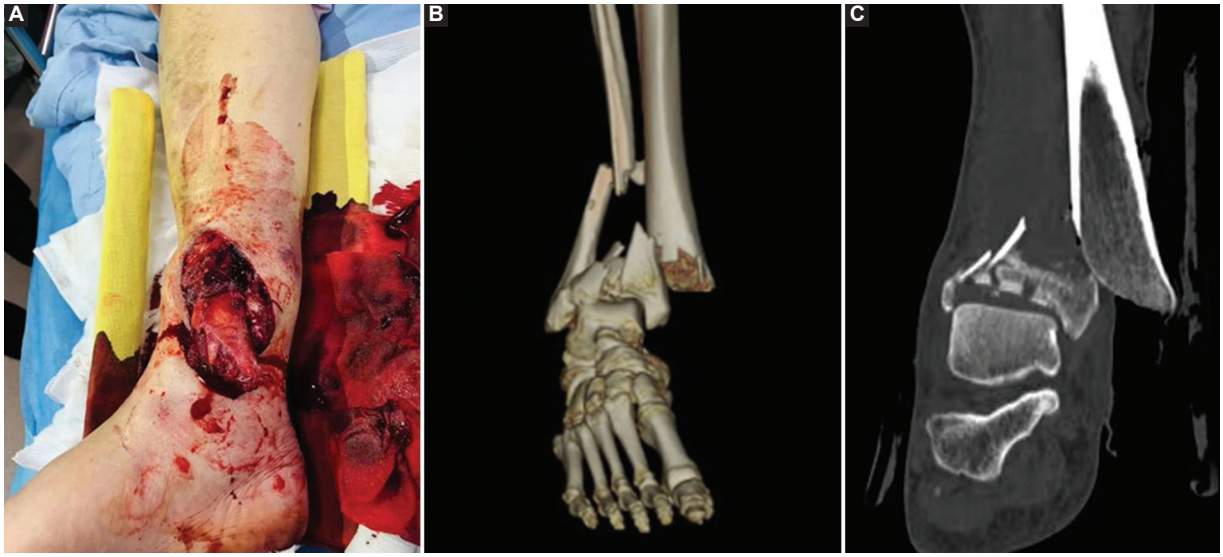

Figure 1. A: *examination of the right ankle reveals a soft tissue defect on the medial aspect of the distal tibia. The exposed distal tibia is contaminated.* **B** *and* **C:** *a post-injury computed tomography scan confirms a comminuted fracture of the distal tibia with bone defects on the articular surface.*

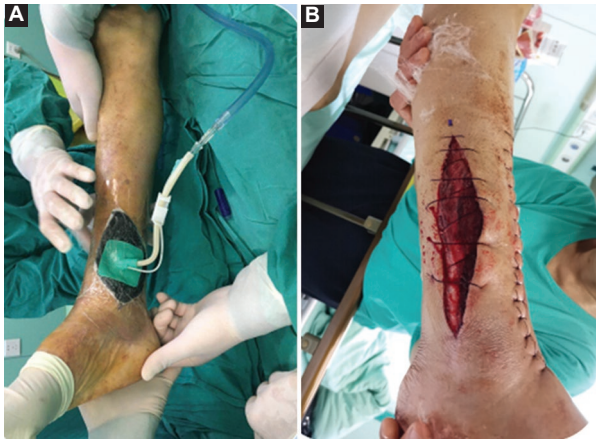

Figure 2. A: *following intraoperative debridement, a VSD was applied to cover the medial defect, effectively converting the open wound (Phase I) into a closed wound.* **B:** *the lateral fibula reduction incision was closed with barbed wire positioned close to the skin edge without tension to prevent skin retraction. The VSD provided continuous drainage, and the barbed wire tension was gradually adjusted as swelling subsided. VSD: Vacuum-assisted closure device.*

death. Physiotherapy began on the second postoperative day with quadriceps muscle strengthening exercises in bed. Four weeks after surgery, the cast was removed, and the affected limb was immobilized with crutches for non-weight-bearing ambulation in bed.

Evaluation of the efficacy of treatment

Treatment efficacy was evaluated by observing flap survival at the defect site 2 weeks after surgery, followed by assessment of flap shape, color, and sensation recovery during the final follow-up visit. Imaging examinations were performed at the outpatient clinic at weeks 1, 4, 8, and 12 to assess fracture healing, length of hospitalization, wound healing time, and potential complications like bone nonunion.

Evaluation of articular surface resurfacing

The Burwell and Charnley[5] radiologic criteria were used to assess the quality of distal tibial articular surface resurfacing after surgery. This evaluation includes: (1) Anatomical repositioning, which refers to the ideal alignment with minimal displacement. There should be no inward or lateral displacement of the medial and lateral ankle, no angular displacement, and minimal longitudinal displacement (< 1 mm) of the medial and lateral ankle. In addition, the posterior ankle block should have a proximal displacement of < 2 mm, and there should be no talar displacement; (2) Reset is possible, which indicates acceptable alignment with some displacement. There is still no medial or lateral displacement of the medial and lateral ankle, and no angular displacement. However, the longitudinal displacement of the medial and lateral ankle can range from 2 to 5 mm, and the proximal displacement of the posterior ankle block can also be between 2 and 5 mm. There should still be no talar displacement; (3) Poor repositioning, which signifies significant displacement of the bones, potentially

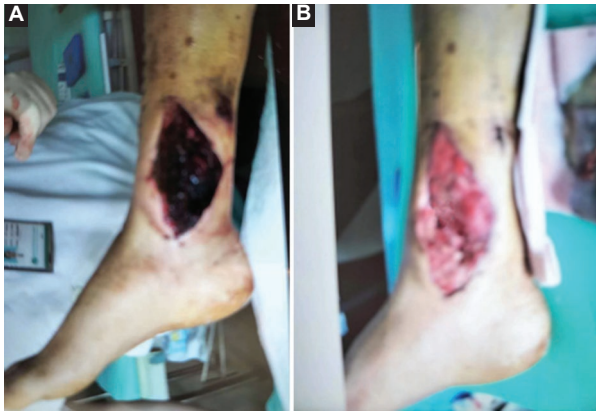

Figure 3. A: *after 1 week of VSD therapy covering the wound, the dressing was removed for wound evaluation. The wound bed appeared healthy with good granulation tissue and minimal edema. The VSD therapy was then reapplied.* **B:** *in another scenario, the VSD was used for 2 weeks. Upon removal, the wound appeared fresh and exhibited healthy, well-vascularized granulation tissue. The surgical procedure (implantation) was then performed. VSD: Vacuum-assisted closure device.*

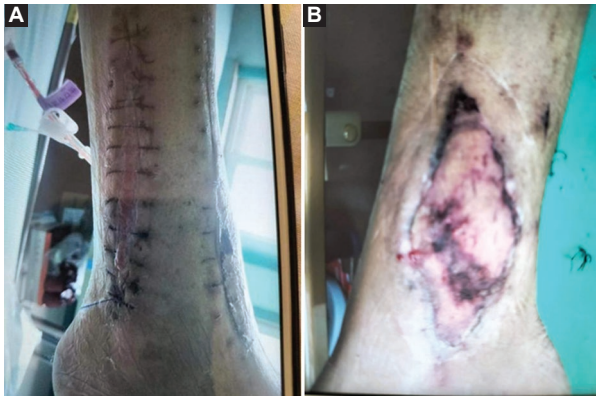

Figure 4. A: *after 1 week, the lateral VSD on the fibula was removed. The incision swelling had subsided, the edges were close together, and the barbed wire sutures were removed.* **B:** *the medial VSD was removed, revealing a viable skin flap with good color. VSD: Vacuum-assisted closure device.*

requiring further surgical intervention. This category includes any medial or lateral displacement of the medial or lateral ankle, a posterior displacement of the lateral ankle > 5 mm, or any talar displacement.

Evaluation of fracture healing

The Merchant[6] scale was employed to assess patient outcomes following surgery. This scale considers various factors, including function, pain level, gait, X-ray review, ankle stability, and mobility. The Merchant scale assigns a rating based on these criteria:

- Excellent: patients experience no pain in the affected area after surgery, and their joints move freely without impacting daily life;
- Good: patients may experience occasional pain that is manageable and has minimal impact on daily activities. Joint mobility is mostly restored;
- Fair: patients experience noticeable pain, sometimes requiring oral pain medication. Their joint movement is restricted, leading to some limitations in daily activities;
- Poor: patients experience significant pain and require pain injections for severe pain. Their joint movement is severely limited, affecting their ability to perform daily tasks independently.

Evaluation of ankle function

The Tornetta[7] criteria were used to assess ankle function after surgery. These criteria categorize function based on pain level, range of motion, and any angular deformity:

- Excellent: no pain, with excellent ankle movement (dorsiflexion > 5°, plantarflexion > 40°) and minimal angular deformity (< 3°).
- Good: occasional pain, manageable with readily available non-steroidal anti-inflammatory medications (NSAIDs). Ankle movement is acceptable (dorsiflexion 0-5°, plantarflexion 30-40°) with some valgus (outward angulation) deformity (3-5°) and limited inversion (< 3°).
- Fair: pain that interferes with daily activities and requires pain medication for relief. Ankle movement is further restricted (dorsiflexion – 5-0°, plantarflexion 25-30°) with a greater valgus deformity (5-8°) and some inversion limitation (3-5°).
- Poor: Intractable pain with severely limited ankle movement (dorsiflexion < –5°, plantarflexion < 25°). Significant valgus deformity (> 8°) and substantial inversion limitation (> 5°) are present.

General results

All 18 patients in our group were followed for a duration ranging from 14 to 27 months, with an average follow-up of 18.8 months. Complete bone healing was achieved in all fractures, with an average healing time of 4.2 months (range: 3-5 months). The average hospitalization time was 24.2 days (standard deviation [SD] ± 5.3), and the average wound healing time was 14.5 days (SD ± 1.6).

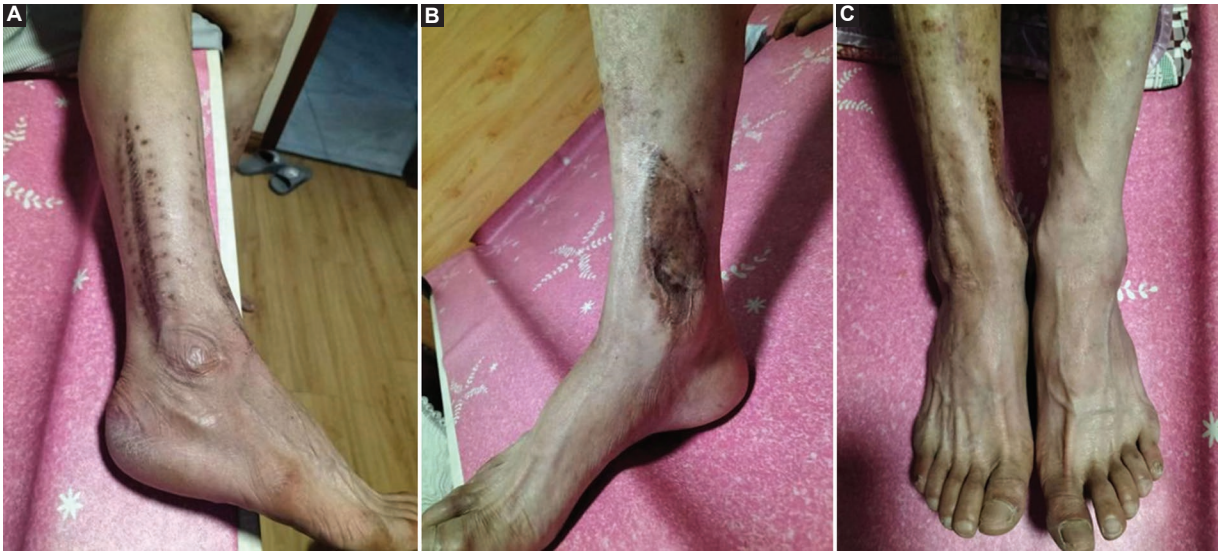

Figure 5. A-C: *at the last follow-up visit, the incision was well healed, the color and sensation of the skin flap at the traumatic defect implant were normal, and the mobility of the ankle joint was good.*

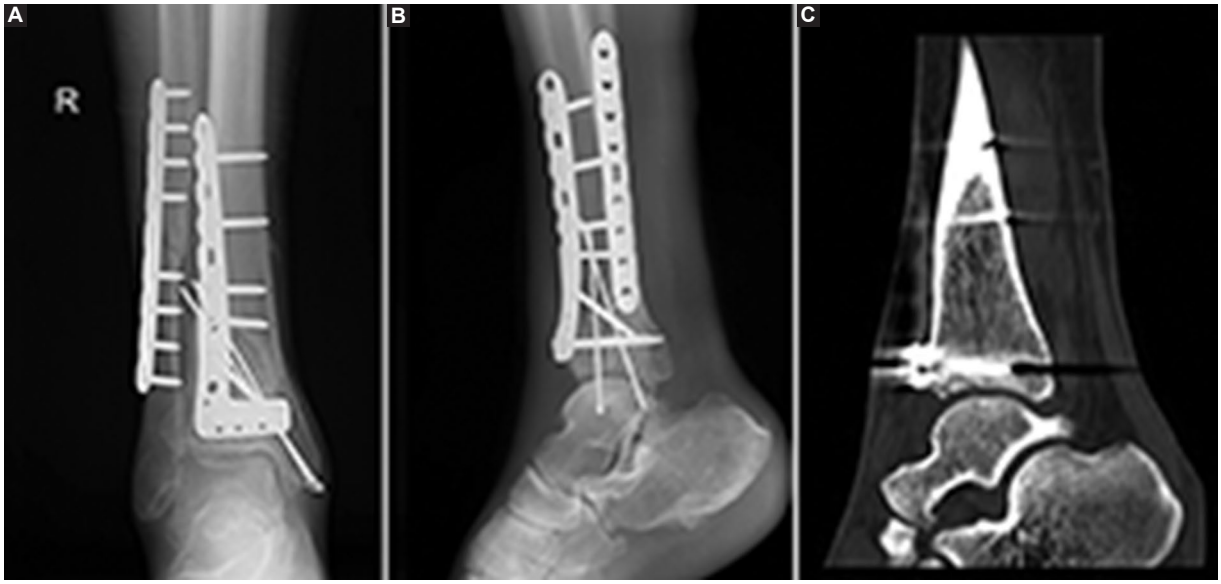

Figure 6. *Imaging findings at final follow-up.* **A:** *complete healing of the fracture, no loosening of the internal fixation, good lower limb force lines on orthogonal X-ray, and no internal or external deformity.* **B:** *lateral x-ray lower extremity lines of force without anterior-posterior angulation.* **C:** *computed tomography scan shows a flat articular surface.*

One patient developed partial skin necrosis at the edge of the anterior tibial incision. This was successfully treated with debridement and dressing changes, and the wound healed without further complications. All other patients experienced successful flap viability and no infections, implant necrosis, or osteomyelitis (Fig. 5).

Fracture reduction and fixation and healing

Postoperative anteroposterior (AP) and lateral X-rays of the ankle joint demonstrated successful surgical outcomes (Fig. 6). These X-rays revealed restoration of the distal tibial articular surface to a flat contour, realignment of the ankle joint and restoration of the lower limb weight-bearing line, and anatomical reduction and restoration of length in the fibula fracture. Utilizing the Burwell-Charnley radiologic criteria, 17 cases achieved anatomical reset (94.4%, 17/18), 1 case achieved reset possible, and no cases fell into the poor reset category. Furthermore, postoperative fracture healing was evaluated according to the Merchant scoring system, with results showing

Table 2. Ankle function was evaluated according to the criteria such as Tornetta in 18 patients up to the last follow-up

Evaluation criteria	Burwell-Charnley radiological evaluation	Merchant bone healing evaluation	Tornetta ankle functional evaluation
Clinical outcome	No. of patients	No. of patients	No. of patients
Excellent	17	15	15
Good		1	1
Moderate	1	1	1
Poor	0	1	1

15 cases achieving an excellent outcome (83.3%, 15/18), 1 case categorized as good, 1 case fair, and 1 case poor.

Eighteen patients were evaluated for ankle function according to the Tornetta et al. criteria by the time of the final follow-up, among which 15 were excellent, 1 was good, 1 was acceptable, and 1 was poor, with an excellent rate of 88.9% (16/18) (Table 2).

Discussion

Emergency soft-tissue debridement and antibiotic application

Adequate debridement is crucial for the successful treatment of open fractures. The risk of infection increases with the severity of the open wound. Type I fractures have the lowest risk (0-2%), followed by type II (2-10%) and type III (10-50%)[8]. Open Pilon fractures often involve skin and soft tissue injuries. The distal tibia has a poor blood supply, and the thin soft tissues are prone to complications. These complications include skin and soft-tissue necrosis, traumatic infections, and osteomyelitis. These complications are lengthy and expensive to treat, and can lead to some of the worst functional outcomes of all open skeletal injuries[9]. Healthy skin acts as a barrier to microorganisms and secretes fatty acids that limit bacterial colonization. When the skin is injured, this barrier is breached, increasing the risk of deeper tissue contamination and potentially severe tissue necrosis.

While the ideal treatment protocol for open tibial fractures remains under debate, all experts agree on the importance of irrigation and debridement[10]. Early debridement is critical. As early as 1997, the British Orthopaedic Association and the British Association of Plastic, Reconstructive and Aesthetic Surgeons recommended performing the first debridement within 6 h of injury[11]. Multiple studies support the concept of a “golden window” for debridement. Patients who undergo debridement within 6 h of admission have lower infection rates[12]. Kreder and Armstrong found a 25% increase in infection risk for open tibial fractures in children when debridement was delayed beyond 6 h[13]. Antibiotics play a role in managing open fractures, but they are primarily used therapeutically rather than preventively. Gustilo and Anderson found that 70% of open wounds were already contaminated with bacteria at the time of injury[14]. A randomized trial by Patzakis and Wilkins showed a significant reduction in infection rates when antibiotics were administered within 3 h of injury (4.7%) compared to delayed administration (7.4%)[15].

Accelerated rehabilitation surgery concept for stage I wound coverage and strong internal fixation

Open Pilon fractures, although representing only 1% of all lower extremity fractures, pose significant challenges due to their complexity[16]. These high-energy injuries often involve comminuted fractures, severe soft tissue damage, and potential complications such as infection and bone exposure[17]. Conventionally, open Pilon fractures were treated with various surgical options, each with limitations. Incisional internal fixation, while restoring limb alignment, may compromise soft-tissue blood supply[18]. Minimally invasive plate internal fixation prioritizes soft-tissue preservation but may not achieve optimal anatomical reduction for all fractures[19]. External fixation, though useful for temporary stabilization, can lead to deformity and stiffness[20].

Recent advancements have revolutionized open Pilon fracture treatment. Early and thorough debridement minimizes infection risk and allows for definitive surgery, aligning with the concept of “total repair” in

trauma management[21,22]. The ERAS protocol, a multimodal approach, emphasizes reducing anxiety, minimizing complications, and promoting faster recovery[23]. Following thorough debridement, early internal fixation and soft-tissue reconstruction facilitate bone healing and functional restoration[24,25]. VSD, also known as negative pressure wound therapy (NPWT), effectively manages open wounds by removing excess exudate, promoting blood flow, reducing tissue edema, protecting the wound bed, and enhancing granulation tissue growth[26,27]. For certain open Pilon fractures (Gustilo type III), achieving early fracture stabilization and soft-tissue coverage in a single surgery is ideal for reducing infection, restoring blood flow, and promoting healing[28]. This approach aligns with the concept of minimizing reconstructive procedures and their associated complications[29]. Our department adheres to the principles of early debridement, single-stage surgery, and NPWT for open Pilon fractures. This approach has yielded excellent clinical outcomes, including reduced infection rates, improved anatomical reduction, faster recovery, and minimized patient burden.

Conclusion

The characteristics of Pilon fractures dictate difficult and specific clinical management, and the acute management of open Pilon fractures remains a serious challenge for orthopedic surgeons. Multiple factors, including fracture severity, size of the trabecular defect, adequacy of debridement, timing of initial treatment, antibiotic use, and other variables in open fractures, contribute to the potential for infection and require prompt attention and treatment. Debridement of all open fractures according to the historical 6-h time window reduces the risk of infection, early administration of appropriate antibiotics has been shown to be a key factor in the reduction and treatment of open fractures, and early internal fixation and coverage of the trauma can be achieved only by ensuring that debridement is complete. The results of our study show that safe management can be obtained by intensive debridement, antibiotics, strong internal fixation, negative pressure closed drainage, and reduction of the calf incision with significant clinical results.

Limitations

There are some limitations of this study: (1) This was a retrospective study conducted at a single center with a relatively small number of participants, which may introduce bias into the results; (2) We excluded patients with Gustilo type IIIC fractures, potentially limiting the generalizability of our findings; and (3) the follow-up period was relatively short. Long-term follow-up is necessary to assess the durability of the treatment outcomes.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from the patient. This retrospective study was approved by the Ethics Committee of the Affiliated Zhongshan Hospital of Dalian University (No.6, Jiefang Street, Zhongshan District, Dalian). All patients agreed and signed informed consent forms.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

A retrospective evaluation of delayed diagnosis and misdiagnosis in skeletal muscle ion channelopathy patients

Evaluación retrospectiva del diagnóstico tardío y del diagnóstico erróneo en pacientes con canalopatía iónica del músculo esquelético

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Abstract

Objective: *Skeletal muscle ion channelopathies are a rare genetically inherited orphan disease. Due to the unique characteristics of the symptoms of the disease, misdiagnosis of patients leads to irreversible losses. This study aims to raise awareness on this issue.* **Methods:** *35 patients with a definitive diagnosis of skeletal muscle ion channelopathy were included in the study. The diagnoses of all patients were confirmed by gene analysis. Demographic and clinical characteristics of the patients were examined. After a definitive diagnosis was made, mimic symptoms and misdiagnoses were evaluated separately.* **Results:** *It was determined that 30 of the patients included in the study had multiple different diagnoses until they got the correct diagnosis. It is thought that due to delayed diagnosis or misdiagnosis, patients experience physical and mental loss, are exposed to ineffective drugs, and their daily lives are adversely affected, as well as serious cost losses.* **Conclusions:** *It is stated that the names of misdiagnoses for imitation symptoms have changed with aging, and drug treatments are applied for each diagnosis. It is stated that health authorities should pay attention to this situation to reduce this.*

Keywords: *Channelopathy. Mimic symptoms. Delay in diagnosis. Primary diagnosis.*

Resumen

Objetivo: *La canalopatía iónica del músculo esquelético es una enfermedad huérfana rara que se hereda genéticamente. Debido a las características únicas de los síntomas de la enfermedad, el diagnóstico erróneo de los pacientes conduce a pérdidas irreversibles. Este estudio pretende concienciar sobre esta cuestión.* **Métodos:** *Se incluyeron en el estudio 35 pacientes con diagnóstico definitivo de canalopatía iónica del músculo esquelético. El diagnóstico de todos los pacientes se confirmó mediante análisis genético. Se examinaron las características demográficas y clínicas de los pacientes. Una vez realizado el diagnóstico definitivo, se evaluaron por separado los síntomas mímicos y los diagnósticos erróneos.* **Resultados:** *Se determinó que 30 de los pacientes incluidos en el estudio tuvieron múltiples diagnósticos diferentes hasta que obtuvieron el diagnóstico correcto. Se cree que, debido al retraso en el diagnóstico o a los diagnósticos erróneos, los pacientes experimentan pérdidas físicas y mentales, están expuestos a fármacos ineficaces y su vida cotidiana se ve afectada negativamente, además de graves pérdidas de costes.* **Conclusiones:** *Los diagnósticos erróneos realizados por síntomas mímicos cambian con la edad del paciente, es decir, se realizan diferentes diagnósticos según la edad del paciente, y se aplican tratamientos farmacológicos para cada diagnóstico. Se afirma que las autoridades sanitarias deberían prestar atención a esta situación para reducirla.*

Palabras clave: *Canalopatía. Síntomas mímicos. Retraso en el diagnóstico. Diagnóstico primario.*

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Introduction

Skeletal Muscle Ion Channelopathies (SMICs) are a rare neurological disease affecting the motor structure and causing non-dystrophic, abnormal cell functioning due to gene mutations encoding voltage-gated cell ion channels. In congenital SMICs, mutations develop in the genes encoding the skeletal muscle sodium channel (SCN5A), skeletal muscle calcium channel (CACNA1S), skeletal muscle potassium channel (KCNJ2 and KCNJ18), cation channels, and voltage-gated skeletal muscle chloride (CLCN1) anion channel. Numerous mutations of each of these genes have been described, and many sub-diagnoses exist. It is primarily autosomal dominant. Its diagnosis is made by examination, blood biochemistry examination, electromyography (EMG), and gene analysis[1]. Its classic diseases include myotonia congenita, paramyotonia congenital, hyperkalemic periodic paralysis, and various sodium channel myotonia. The gene locations in SMICs are CLCN1 Cytogenetic location: 7q34 (long arm 34 of chromosome 7), SCN4A Cytogenetic location: 17q23.3, CACNA1S Cytogenetic location: 1q32.1, KCNJ2 Cytogenetic location: 17q24.3, KCNJ18 Cytogenetic location: 17p11.

Clinical response to the disease

The most prominent symptom in the SMICs clinic is myotonia, also defined as a warming phenomenon with delayed relaxation after voluntary contraction. This symptom occurs in 100% of patients. Musculoskeletal symptoms such as persistent weakness, widespread pain, cramping, stiffness, difficulty grasping, painful awakening, warming phenomenon, myalgia, and non-inflammatory pain sensation in the joints are common. In addition to these symptoms, generalized and diffuse symptoms such as difficulty chewing, swallowing, climbing ramps, and overhead work can be seen to varying degrees. Symptoms are episodic and fluctuate depending on triggering factors. Myotonia decreases or disappears after several consecutive warm-up exercises. Symptoms are aggravated at rest, in the cold, and by certain foods[2,3]. Inflammatory Spondyloarthritis, Fibromyalgia (FM), rheumatoid arthritis (RA), idiopathic inflammatory myopathy (IIM), epilepsy, myasthenia gravis (MG), juvenile idiopathic arthritis (JIA), Cervical Spondylotic Myelopathy, Neurogenerative Disease, disc hernia (DH), Vitamin Deficiency are examples of diseases that mimic this disease.

In many diseases overlapping similar complaints, poor differential diagnosis, data collection problems, and inability to synthesize information have led to misdiagnosis[4,5]. Symptoms of the disease usually begin in the first 20 years of life. SMICs are estimated to occur in approximately 1 in 100,000 people worldwide[6]. In defining SMICs, the level of muscle-derived creatine kinase (CK) in plasma may vary from normal to several times higher. Significant abnormalities in blood parameters due to SMICs are not expected. Although changes were observed in the muscle biopsy, it was observed that it did not provide sufficient differential information[7]. Drug therapy in SMICs is symptomatic. It has been reported that there is a rapid change in symptoms and a decrease in the disease burden with correct and regular physical activity, medical rehabilitation, motivation, education, environmental conditions, and nutrition[8]. Mexiletine, phenytoin, and carbamazepine are used in the symptomatic treatment of SMICs.

In this study, the SMICs clinic aims to analyze the patient's misdiagnoses until a definitive diagnosis is made and to raise awareness about SMICs. In addition, the fact that there is no similar study on this subject shows the originality of the study.

Methods

Ethical aspects of the research

Before the study, local ethics committee approval was obtained from the Health Sciences Gazi Yaşargil Training and Research Hospital (No: 306, Date: December 30, 2022). The study group was informed about the purpose and content of the study. Those who agreed to participate in the study signed an "informed consent form" and were included. The demographic characteristics of all patients were recorded.

Participants in the study and processes

Patients admitted to the Neuromuscular Diseases Unit of Health Sciences Gazi Yaşargil Training and Research Hospital between 2013 and 2022 were evaluated by a 30-year Physical Medicine and Rehabilitation specialist and a 15-year Neuromuscular Diseases physician.

- All patients had symptoms of myotonia
- Only patients with mutations in genes encoding the skeletal muscle chloride channel (CLCN1)

– Demographic information on misdiagnosed patients and patients who received diagnostic
– They were included in the study on condition that they received medication treatment

The study included 35 patients; 5 patients were SMICs diagnosed at the onset of their complaints, so only their demographic characteristics were used. 30 patients were examined by more than one physician on different dates until they received the main diagnosis, non-SMICs diagnoses were made, and drug treatment was initiated for the diagnosis. This led to multiple rheumatologic and neurologic misdiagnoses. The misdiagnosis information documents of the patients were obtained by reviewing the notification given by the patient, archival data, and the registry system. Diagnoses made after the main diagnosis was confirmed were investigated. As a result, no other diagnosis other than FM symptoms and changes in plasma vitamin levels was found. FM and vitamin deficiency can be seen in every individual, the reason for inclusion was that the complaints of 30 patients were attributed to FM and vitamin deficiency, and medication was given for a long time, which caused a delay in diagnosis and was therefore included in the misdiagnosis group. CK levels were irregularly mildly elevated.

EMG

It has an important role in detecting the natural activities of the neuromuscular system. A scientifically standardized acquisition protocol has been established. Compound muscle action potential (CMAP) amplitudes are recorded before and after the acquisition[9]. SMICS is evaluated according to the detection of myotonic discharges by needle EMG. All patients underwent EMG, performed in centers licensed by the Ministry of Health and by certified physicians. The physician performing the EMG procedure used short and long exercise tests for diagnostic accuracy. All patients underwent EMG for biceps, fine motor skills, quadriceps, and anterior tibial muscles by a blinded assessor with maximum sensitivity to universal standardized guidelines. Concentric needle EMG was performed. Findings were interpreted in favor of myopathy. Gene molecular analysis was recommended for specific diagnosis and further interpretation. Gene analysis was performed by authorized gene analysis units licensed by the Ministry of Health.

According to the result of gene analysis, among the patients suspected of the SMIC diagnosis, those who returned from patients whose diagnosis was confirmed by the gene center were included in the study in the assessments made. Some of our 52 patients had chloride, and some had sodium channel mutation disorders. The number of patients with a chlorine channel disorder was higher. The gene mutation demographics were not considered necessary because the characteristics of the symptoms did not differ due to the mutation.

Analysis of the data

The SPSS 22.0 package program was used for the data analysis. The measurable variables were expressed as mean ± standard deviation, and the categorical variables were expressed as numbers and percentages.

Findings

When Table 1 was examined, the patients' median age and standard deviation were 29.00 ± 11.95 (min = 16; max = 52). The mean and standard deviation of the visual analog scale (VAS) were 3.77 ± 1.24. 15 (42.9%) patients were female, and 20 (57.1%) were male. Of the patients, 12 (34.3%) are currently smoking, 2 (5.7%) have smoked in the past, and 21 (60%) have never smoked. When the diagnosis was examined after the confirmation by the genetic analysis, the symptoms of SMICs were detected in 6 (17.1%) relatives having different affinities; of these, those who received misdiagnoses and treatment for the diagnosis were included in the study. There was a diagnosis of SMICs in 5 members of the same family, the oldest of whom was 52. It has been determined that 30 (85.7%) patients were misdiagnosed or diagnosed until the primary diagnosis was made, and only 5 (14.3%) patients were correctly diagnosed. All of the patients could walk, and they stated that they were tired. It was determined that 6 (17.1%) patients had inflammatory spondyloarthritis, 30 (85.7%) patients had FM, 4 (11.4%) patients had RA, 7 (20%) patients had IIM, 6 (17.1%) patients had epilepsy, 4 (11.4%) patients had MG, 5 (14.3%) patients had JIA, 3 (8.6%) patients were cervical spondylotic myelopathy, 4 (11.4%) patients were motor neuron disease (MND), and 30 (85.7%) patients were disc herniation and vitamin deficiency (Table 2).

Discussion

SMICs are a group of rare neuromuscular disorders caused by gene mutation and primarily affecting

skeletal muscle. In these patients, it has been observed that the number, severity, age of onset, and course of symptoms are different in family members with the same gene mutation. Misdiagnoses have been reported in many genetic neuromuscular diseases affecting the musculoskeletal system[10]. According to the VAS, patients with myopathy have been reported to experience an unpleasant pain style[11]. Within the scope of this study, all patients had signs of myotonia when evaluated under appropriate conditions. Significantly different clinical findings were found among family members with the same gene analysis result. Although SMICs sub-diagnoses have many different mutations, widespread similarity within different mutations in the same mutation was seen in clinical problems due to the wide symptom network. This may cause serious problems in genotype-phenotype correlation in SMIC patients. Due to the low prevalence of the disease, establishing standard diagnostic criteria can be an important obstacle for physicians.

FM

The etiology of FM is not completely known, and many accusatory factors have been proposed. Symptoms such as multiple tender points, body fatigue, fatigue, and chronic pain have been reported. FM has been described as affecting approximately 2% of the population[12]. The current criteria for defining FM was established by the American College of Rheumatology (ACR) in 1990[13].

It has been observed that it mimics SMICs or secondary FM develops accordingly. It was analyzed that 30 (85.7%) patients admitted to the neuromuscular center were misdiagnosed with myalgia-FM. In one study, 2 (3.2%) of 63 patients diagnosed with FM were reported to have myotonic myopathy[14].

Inflamatory spondyloarthritis

The prototype of inflammatory spondyloarthritis is ankylosing spondylitis. It is a chronic disease and the cause is unknown. Most symptoms are sacroiliac joint involvement, early onset, body stiffness, musculoskeletal pain, and limitation of movement. The establishment of diagnostic and follow-up criteria by the International Spondyloarthropathy Assessment Society for modified features has facilitated patient identification. The drug response of SPA is successful[15]. 6 (17.1%) patients with confirmed SMIC were misdiagnosed as having SPA and were exposed to prolonged drug therapy. There are similarities at the symptom level in the clinic of SPA and SMIC. In some studies, it has been found that SPA and myopathies mimic each other, misdiagnoses have been experienced, and long-term treatments have been applied at the case level[16,17].

RA

RA is a synovial disease with late-onset, predominantly symmetrical, small joint involvement, morning stiffness, fatigue, muscle weakness, and chronic features. Changes compatible with RA develop in the laboratory and joint radiologic evaluation. Classification criteria for RA were developed by the ACR/European League Against Rheumatism in 2010[18]. It was learned that 4 (11.4%) patients were misdiagnosed with RA and were treated with non-steroidal, steroid, non-biologic, and biologic disease-modifying antirheumatic drugs for a long time until the primary diagnosis was made.

In a study, 25 (26%) of 96 patients with myotonic symptoms were misdiagnosed with musculoskeletal rheumatic diseases such as arthritis, chronic fatigue syndrome, FM, RA, and degenerative diseases[19]. One study found that 1 in 26 patients diagnosed with dysferlinopathy had been treated for arthritis long before diagnosis[20].

IIM

IIM is a group of rare autoimmune inflammatory and heterogeneous diseases characterized by joint, muscle inflammation, skin, gastrointestinal, respiratory, and cardiac involvement. These patients may develop loss of strength in the proximal muscles, atrophy, difficulty in overhead work, pain, fever, and in most cases, symptoms of active arthritis. The diagnosis is determined using patient assessment, diagnostic criteria, elevated CK, other muscle enzyme levels, supportive or excluded laboratory parameters, EMG, and muscle histopathology. Response to immunotherapy is good unless there is an underlying malignancy or other cause[21].

It was noticed that 7 (20%) of our patients who were identified as SMIC were identified as IIM and used long-term disease-modifying non-biological and biological disease-modifying antirheumatic drugs. In

some studies, it has been reported that myopathies with primary muscle involvement mimic each other and it has been stated that IIM unknowingly mimics myopathies with muscular dystrophy by applying long-term treatments. In one study, 15 (57.7%) of 26 patients with Limb-Girdle Muscular Dystrophy were misdiagnosed as inflammatory myopathy before the primary diagnosis and 13 (86.7%) of them were given cortisone treatment before the diagnosis; some received immunosuppressive therapy[20].

Epilepsy

In some recent studies, it has been reported that the diagnoses of epilepsy and SMIC are frequently confused, and long-term antiepileptic treatments are used[22]. When the expected improvement could not be achieved with the treatments, it was found that 6 (17.1%) patients were misdiagnosed with epilepsy in the control examination. A study conducted by Ramos-Maqueda et al. found that 8 of 50 patients with cardiac canalopathy were mistakenly diagnosed with epilepsy before definitive diagnosis[23].

MG

MG belongs to autoimmune neuromuscular diseases with unknown neuromuscular synaptic causes. In MG, muscle focalization and weakness with movement are increased; complaints of impaired vision, swallowing, and speech are common, and patients often complain of fluctuations in muscle strength within 24 h. In cases without ocular involvement or with predominantly proximal involvement, it has been confused with other neuromuscular diseases[24].

In 4 (11.4%) patients admitted to the neuromuscular center with a diagnosis of MG, SMIC was diagnosed when the criteria were evaluated appropriately in patients admitted due to uncertainty in the course, lack of response to medication, and suspicion of diagnosis. Neshuku et al. reported that 4 of 31 misdiagnosed patients were diagnosed with genetic myopathy in a 20-year MG database search[25].

JIA

JIA is a systemic chronic rheumatic diagnosis of unknown etiology with early onset. It manifests with clinical symptoms such as pain, limitation of movement, weakness of musculoskeletal tissue, impaired balance control, fatigue, and motor clumsiness[26]. It was found that 5 (14.3%) patients were treated with medication for a long time with the diagnosis of JIA until adulthood. In the evaluation, it was determined that these were SMIC patients.

Since such diagnostic confusion may occur in some studies, it was concluded that it would be practical to use all diagnostic tests together and to bring the diagnosis to mind to minimize misdiagnosis and diagnostic delay[27].

Spinal spondylotic myelopathy (SSM)

SSM presents with complaints such as a change in muscle tone due to pressure on the spinal cord caused by degeneration of cervical anatomical tissues, disc herniation, congenital malformation, atrophy, loss of strength, decrease in muscle dexterity, loss of sensation, neuropathic pain, change in tendon reflex, and sphincter disorder. The basic diagnosis is made by questioning the examination, imaging, EMG, and differential diagnosis method[28]. It was learned that 3 (8.6%) patients with SMIC were diagnosed with spinal stenosis and myelopathy at some point. Robles et al. A patient with SSM was found to have been treated for a long time and with multiple stages of treatment; the diagnosis was incorrect. The patient was diagnosed with amyotrophic lateral sclerosis[29].

MND

MND is a group of progressive neurological disorders characterized by the degeneration of voluntary muscles in the forebrain, upper and lower brain neurons, and spinal cord. This group includes diseases such as amyotrophic lateral sclerosis, hereditary spastic paraparesis, and spinal muscular atrophy. The pathophysiology has not yet been fully elucidated and is mostly focused on genetic mutations. It may have an adult or congenital onset. General symptoms include decreased dexterity, weakness in voluntary muscles, tone disturbance, balance problems, fatigue, and physical and mental problems that make swallowing, speaking, breathing, and activities of daily living difficult. Diagnosis is mainly based on history and examination. Auxiliary methods such as laboratory analysis, EMG, imaging, cerebrospinal fluid analysis, and genetic analysis can be applied[30].

Table 1. Descriptive analysis regarding the patients

Socio-demographic and clinical characteristics regarding the patients		
Age	29.00 ± 11.95 (min: 16; max: 52)	
Visual analog scale score	3.77 ± 1.24	
	n	%
Gender		
Female	15	42.9
Male	20	57.1
Smoking status		
Still Using	12	34.3
Used in the Past	2	5.7
Never Used	21	60.0
SMICs defined family history		
yes	6	17.1
No	29	82.9
Correct diagnosis receiving status		
Yes	5	14.3
No	30	85.7
Walking status		
Walking	35	10.00
Can Not Walk	0	0.0
Tiredness		
Yes	35	100.0
No	0	0.0
Inflammatory		
Misdiagnosed	6	17.1
Spondyloarthritis		
Undiagnosed	29	82.9
Fibromyalgia		
Misdiagnosed	30	85.7
Undiagnosed	5	14.3
Rheumatoid arthritis		
Misdiagnosed	4	11.4
Undiagnosed	31	88.6
Idiopathic		
Misdiagnosed	7	20.0
Inflammatory myopathy		
Undiagnosed	28	80.0
Epilepsy		
Misdiagnosed	6	17.1
Undiagnosed	29	82.9
Myasthenia gravis		
Misdiagnosed	4	11.4
Undiagnosed	31	88.6
Juvenile idiopathic		
Misdiagnosed	5	14.3
Arthritis		
Undiagnosed	30	85.7
Cervical spondylotic		
Misdiagnosed	3	8.6
Myelopathy		
Undiagnosed	32	91.4
Neurodegenerative		
Misdiagnosed	4	11.4
Disease		
Undiagnosed	31	88.6
Disc herniation		
Misdiagnosed	30	85.7
Undiagnosed	5	14.3
Vitamin deficiency		
Misdiagnosed	30	85.7
Undiagnosed	5	14.3
Total	35	100.0

(Continues)

Table 1. Descriptive analysis regarding the patients *(continued)*

In a study conducted in the United States, it was noted that approximately half of patients diagnosed with chronic inflammatory demyelinating polyradiculoneuropathy, a neurologic disorder, who subsequently applied the 2010 diagnostic criteria of the Federation of European Neurological Societies were misdiagnosed, resulting in a significant loss of time in correct diagnosis and exposure to costly treatments. In the United Kingdom, 68% of patients initially diagnosed with chronic inflammatory demyelinating polyradiculoneuropathy were misdiagnosed when re-examined[31].

DH

DH symptoms are manifested by dermatomal pain, motor loss, atrophy, and sensory changes at the level of compression of the nerve tissue. Physical examination and imaging tools are utilized for diagnosis[32]. When we re-examined 30 (85.7%) patients diagnosed with DH, we did not find any compatible findings to support the DH clinic. Madani et al. re-examined 202 patients diagnosed with lumbar DH and found that 146 (72.3%) patients had sacroiliac joint dysfunction disease[33].

It was reported that 3 patients who were followed up for a long time with a diagnosis of DH were reported to have amyotrophic lateral sclerosis in the analysis performed due to worsening of the clinical course[34].

Table 2. Crossover data intended to patient-related variables

Variable	Sub-variable	Female (%)	Male (%)	Total (%)
Cigarette	Still using	3 (25.0)	9 (75.0)	12 (100.0)
	Used in the past	1 (50.0)	1 (50.0)	2 (100.0)
	Never used	11 (52.4)	10 (47.6)	21 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Family history of channelopathy defined	Yes	2 (33.3)	4 (66.7)	6 (100.0)
	No	13 (44.8)	16 (55.2)	29 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Inflammatory	Yes	1 (16.7)	5 (83.3)	6 (100.0)
Spondyloarthritis	No	14 (48.3)	15 (51.7)	29 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Fibromyalgia	Yes	14 (46.7)	16 (53.3)	30 (100.0)
	No	1 (20.0)	4 (80.0)	5 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Rheumatoid arthritis	Yes	4 (100.0)	0 (0.0)	4 (100.0)
	No	11 (35.5)	20 (64.5)	31 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Idiopathic Inflammatory Myopathy	Yes	6 (85.7)	1 (14.3)	7 (100.0)
	No	9 (32.1)	19 (67.9)	28 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Epilepsy	Yes	2 (33.3)	4 (66.7)	6 (100.0)
	No	13 (44.8)	16 (55.2)	29 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Myasthenia gravis	Yes	4 (100.0)	0 (0.0)	4 (100.0)
	No	11 (35.5)	20 (64.5)	31 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Juvenile idiopathic arthritis	Yes	2 (40.0)	3 (60.0)	5 (100.0)
	No	13 (43.3)	17 (56.7)	30 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Cervical spondylotic myelopathy	Yes	0 (0.0)	3 (100.0)	3 (100.0)
	No	15 (46.9)	17 (53.1)	32 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Motor neuron disease	Yes	2 (50.0)	2 (50.0)	4 (100.0)
	No	13 (41.9)	18 (58.1)	31 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Disc herniation	Yes	14 (46.7)	16 (53.3)	30 (100.0)
	No	1 (20.0)	4 (80.0)	5 (100.0)

(Continues)

Table 2. Crossover data intended to patient-related variables *(continued)*

Variable	Sub-variable	Female, n (%)	Male, n (%)	Total, n (%)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Vitamin deficiency	Yes	14 (46.7)	16 (53.3)	30 (100.0)
	No	1 (20.0)	4 (80.0)	5 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Correctly diagnosed	Yes	1 (20.0)	4 (80.0)	5 (100.0)
	No	14 (46.7)	16 (53.3)	30 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)

Vitamin deficiency

Vitamin deficiency has been shown to cause neurological symptoms such as pelvic and shoulder muscle weakness, fatigue, skeletal muscle pain, atrophy, muscle cramps, loss of muscle strength, muscle tetany, and impaired balance and movement mimicking ataxia[35,36]. It was found that 30 (86%) patients who were diagnosed late received many vitamin deficiency treatments, especially vitamin D and B vitamins, at different times for their current complaints. In laboratory evaluation, some vitamins were low in all patients, but there were no findings that would mimic the SMIC clinic during the examination. In conclusion, although the treatment did not pose a risk for the patient, it caused a delay in diagnosis.

Conclusion

SMICs are heterogeneous, have no specific owner due to a lack of information about them, and have been referred to as orphan diseases. Inherited SMICs are a group of early-life diseases that are rarely seen and diagnosed under physical and neurological evaluation, laboratory tests, EMG, biopsy, and genetic guidance. International bodies have been unable to define criteria to facilitate diagnosis and treatment because the disease is so different. Despite these difficulties, scientific training, intensive research, advances in gene analysis, inventions in medical technology, and increased awareness have made it easier to reach the correct diagnosis in parallel. Frequent review of the patient in combining the initial and final values will help to reach the truth. Going to the first diagnosis that comes to mind with 1 or 2 symptoms reported by the patient does not permanently repair the damage caused by the wrong diagnosis. During the process, the patient may take many medications and experience emotional exhaustion. This can lead to physical, mental, emotional, social, and economic losses. Considering the prevalence of SMIC included in this study and the prevalence of misdiagnosed diseases, there is a significant rate.

As a result, the majority of SMIC patients are misdiagnosed, different diagnoses are made according to the ageing process, and training specialized health cadres in this field can lead to earlier diagnosis.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of Humans and Animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the Institutional Ethics Committee.

Confidentiality, Informed Consent, and Ethical Approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the Use of Artificial Intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Hyperbaric oxygen and metformin treatment in ovarian torsion preserves ovarian reserve

El tratamiento con oxígeno hiperbárico y metformina en la torsión ovárica preserva la reserva ovárica

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Abstract

Objective: *Ovarian torsion is a gynecological emergency that reduces ovarian reserve in reproductive-aged women. This study aimed to evaluate the effects of metformin and hyperbaric oxygen therapy (HBOT) on ovarian reserve after ovarian torsion.* **Methods:** *Forty female Wistar-Albino rats were divided into five groups: control, torsion/detorsion (T), torsion/detorsion + metformin (TM), torsion/detorsion + HBOT (THBO), and torsion/detorsion + metformin + HBOT (TMHBO). Rats in the experimental groups underwent 2 h of unilateral ovarian torsion followed by detorsion. Metformin (50 mg/kg/day) and HBOT (100% oxygen at 2.4 atm for 2 h/day) were administered for 14 days post-detorsion. Serum AMH levels, tissue AMH expression, and ovarian follicle counts were evaluated.* **Results:** *In the torsion group, ovarian histology was disrupted, follicle numbers decreased, TUNEL-positive cells increased, and both serum and tissue AMH levels were reduced. The TM, THBO, and TMHBO groups demonstrated improvements in follicle numbers, TUNEL-positive cells, and AMH levels compared to the torsion group. Among them, TMHBO exhibited the best numerical outcomes, but no significant superiority was observed among TM, THBO, and TMHBO groups.* **Conclusions:** *Both metformin and HBOT were effective in preserving ovarian reserve following ovarian torsion. These therapies may have potential as protective treatments in gynecological emergencies involving ovarian torsion.*

Keywords: *Ovarian torsion. Metformin. Hyperbaric oxygen therapy. Ovarian reserve.*

Resumen

Objetivo: *La torsión ovárica es una emergencia ginecológica que afecta la reserva ovárica en mujeres en edad reproductiva. Este estudio evaluó los efectos de la metformina y la terapia de oxígeno hiperbárico (TOH) en la reserva ovárica tras una torsión ovárica.* **Métodos:** *Cuarenta ratas Wistar-Albino hembras se dividieron en cinco grupos: control, torsión/destorsión (T), torsión/destorsión + metformina (TM), torsión/destorsión + TOH (TTOH) y torsión/destorsión + metformina + TOH (TMTOH). Los grupos experimentales fueron sometidos a torsión ovárica unilateral durante 2 horas, seguida de destorsión. Se administraron metformina (50 mg/kg/día) y TOH (oxígeno al 100%, 2.4 atm, 2 h/día) durante 14 días. Se midieron los niveles séricos y tisulares de hormona antimulleriana y el recuento de folículos ováricos.* **Resultados:** *En el grupo de torsión, la histología ovárica estaba alterada, el número de folículos disminuyó, las células TUNEL positivas aumentaron y los niveles de hormona antimulleriana se redujeron.*

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TM, TTOH y TMTOH mejoraron estos parámetros en comparación con el grupo T. Aunque TMTOH mostró los mejores resultados numéricos, no se observó superioridad significativa entre los grupos tratados. **Conclusiones:** *La metformina y la TOH demostraron ser eficaces para preservar la reserva ovárica tras una torsión ovárica, lo que destaca su potencial terapéutico en estas emergencias ginecológicas.*

Palabras clave: *Torsión ovárica. Metformina. Terapia de oxígeno hiperbárico. Reserva ovárica.*

Introduction

Gynecological emergencies such as ovarian torsion, which occurs when the ovary, fallopian tube, or both rotate completely or partially around the vascular axis, can occur at rates ranging from 2-5% to 7-4%[1,2]. Risk factors for ovarian torsion include ovarian cysts, polycystic ovary syndrome, previous ovarian torsion episodes, and previous pelvic surgeries[3]. Since there is no specific clinical, laboratory, or radiological finding of ovarian torsion and patients with the condition are typically admitted late, the torsion observed during surgery is used to make a definitive diagnosis[4]. Immediate adnexal detorsion is the recognized treatment for ovarian torsion.

Detorsion should be performed as soon as possible before ovarian torsion causes a serious decrease in follicle reserve or loss of the ovary[5]. However, this intervention causes reperfusion injury after detorsion in ovaries that have suffered ischemic damage due to torsion. Thus, ovarian torsion and detorsion give rise to ischemia-reperfusion (I/R) damage, which leads to biochemical, histological, and morphological changes in the ovarian tissue[6]. During the reperfusion period, the entry of molecular oxygen into the cell rapidly causes the formation of reactive oxygen species (ROS). Excessive production of ROS causes lipid peroxidation, DNA damage, apoptosis, and protein dysfunction[7]. Therefore, in addition to surgical treatment in ovarian torsion, antioxidant and anti-inflammatory treatment is also recommended to prevent the resulting I/R damage[8]. Numerous pharmacological interventions (such as curcumin, lipoic acid, melatonin, vitamin C, lycopene, erdosteine, methylprednisolone, and verapamil) have been studied to prevent I/R injury in ovarian torsion[9-16]. However, new treatments that provide good protection against inflammation and oxidative stress and minimize adverse effects are desired.

The use of 100% oxygen at pressures greater than one atmosphere is known as hyperbaric oxygen therapy (HBOT), and it has been used in medicine for more than 30 years[17]. Increasing the partial oxygen pressure in the tissues is the goal of HBOT. Thus, by boosting the synthesis of numerous growth factors and cytokines, elevated tissue oxygen levels promote angiogenesis. Due to this effect, HBOT is used in the treatment of decompression sickness, carbon monoxide poisoning, diabetic foot, osteomyelitis, and ischemic wounds[18]. HBOT is known to be an effective treatment method in ischemia-reperfusion injury and has anti-inflammatory and antioxidant effects[19].

A biguanide agent, metformin, is used as a first-line drug in the treatment of type 2 diabetes[20]. In addition to its antidiabetic effect, metformin has been shown to have antioxidant, anti-inflammatory, and antiproliferative properties[21,22]. Metformin protects the heart, brain, and testes from I/R damage[23-25]. It has also been reported that metformin can increase ovulation in women[26], and improve ovarian I/R damage[27].

In the clinical evaluation of fertility in women, the number of follicles in the ovaries and the levels of anti-Müllerian hormone (AMH) are important. Ovarian reserve is measured using AMH secreted from preantral ovarian follicles[28]. Detorsion surgery has been shown to reduce AMH[29]. This situation shows that conservative treatment of ovarian torsion alone cannot protect the ovarian reserve. In this context, new treatment approaches aimed at overcoming I/R damage in ovarian torsion are needed. The aim of this study was to evaluate the effects of HBOT and metformin treatment on the preservation of ovarian reserve in I/R damage resulting from ovarian torsion and detorsion in rats.

Methods

Animals

This experimental study was conducted at the Department of Gynecology and also at the Department of Histology and Embryology, Faculty of Medicine, Erciyes University, between December 2021 and June 2022. Ethical approval was obtained from the ethics committee of the Faculty of Medicine, Erciyes University, and the study was conducted in accordance with the World Animal Rights Declaration. The G power program was used to calculate the sample size of the study. According to the one-way ANOVA

test analysis with 95% confidence (1-α), 95% test power (1-β), and d = 0.5 effect size, the number of samples to be taken in each group was determined as seven. Considering the possibility of losing 10% of the rats during surgical interventions, eight rats per group were included in the study. Eight-week-old female Wistar-Albino rats weighing 180-260 g, obtained from the Erciyes University Experimental Applications and Research Center, were used in the study. The rats were kept in a room with 12 h of light and 12 h of darkness, 25 ± 2 °C, and a humidity rate of around 40-50%, and were fed a balanced diet and unlimited water.

The 40 female Wistar-Albino rats included in the study were randomly divided into five groups, each containing eight rats. Control Group: No procedure was applied to this group. Torsion/detorsion group (T): The rats in this group were subjected to unilateral ovarian torsion for 2 h, and then the ovary was detorsioned and returned to its anatomical position. Torsion/detorsion + metformin group (TM): The rats in this group were subjected to unilateral ovarian torsion for 2 h, and then the ovary was detorsioned and returned to its anatomical position. Four hours after the detorsion procedure and daily for the following 13 days, the rats were treated with 50 mg/kg oral metformin (glucophage 50 mg tablet; Merck Pharmaceutical Industry Inc., Istanbul, Turkey). Torsion/detorsion + hyperbaric oxygen therapy group (THBO): The rats in this group were subjected to unilateral ovarian torsion for 2 h, and then the ovary was detorsioned and returned to its anatomical position. Four hours after the detorsion procedure and daily for the following 13 days, the rats were treated with HBOT by breathing 100% O_2 at 2.4 atmospheres pressure for 2 h in a hyperbaric chamber. Torsion/detorsion + metformin + hyperbaric oxygen therapy group (TMHBO): The rats in this group were subjected to unilateral ovarian torsion for 2 h, and then the ovary was detorsioned and returned to its anatomical position. HBOT and metformin were administered to rats 4 h after the detorsion procedure and for the next 13 days. HBOT was applied in a hyperbaric chamber at 2.4 atmospheres of pressure with 100% O_2 inhalation for 2 h. Metformin was administered by oral gavage at 50 mg/kg/day. On the 14th day of the study, all rats were sacrificed, and tissue samples and blood were collected.

Surgical procedure

Before the operation, each rat was given 50 mg/kg cefazolin sodium intramuscularly as a prophylactic. All rats were given 50 mg/kg ketamine (Ketalar; Parke Davis, Eczacibasi, Istanbul, Turkey) and 7 mg/kg xylazine hydrochloride (Rompun; Bayer AG, Leverkusen, Germany) intraperitoneally to induce general anesthesia. The rat was placed in the dorsal position. The operation area was shaved, cleaned, and sterilized with 10% povidone-iodine. The surgical field was covered with sterile compresses. After opening the abdomen by making a 2.5 cm midline laparotomy incision under sterile conditions, the large intestines were gently separated, and the left ovary was made visible. The ovary was rotated 720 degrees and fixed to the abdominal side wall with 4.0 Vicryl sutures. After 2 h of waiting, the ovary was separated from the abdominal side wall, and detorsion was carried out. The abdominal incision was closed with 3.0 Vicryl suture. Following this procedure, cefazolin sodium was administered intramuscularly to the rats at a dose of 50 mg/kg daily for 3 days. None of the rats died following the surgery procedure[30].

Histopathological examination

Ovarian tissues were fixed in 10% formaldehyde solution for 48 h and then embedded in paraffin blocks after routine histological procedures. Serial sections of 5 μm thickness were taken with a microtome. Sections were stained with Hematoxylin and Eosin (H&E) and Masson Trichrome (MT) and evaluated histopathologically. Furthermore, primordial, primary, preantral, secondary, and tertiary follicles were counted under a light microscope (Olympus® Inc. Tokyo, Japan)[30].

Immunohistochemical analysis

AMH staining was performed immunohistochemically to evaluate ovarian reserve. Sections taken on slides with Poly-L-lysine were stained according to the procedure recommended by the Avidin-Biotin Peroxidase Complex (ABC) (TP-125- HL, Thermo Ultravision Detection System, Fremont, USA) kit manufacturer. Deparaffinized sections were washed with phosphate buffered solution (PBS, pH 7.4) (Afg Bio-science 729350) for 3 × 5 min. To block tissue endogenous peroxidase activity, sections were incubated with 3% H_2O_2 prepared in methanol for 12 min. The sections were incubated in 10% normal goat serum at room temperature for 10 min to prevent non-specific antigenic binding and were then incubated with AMH primary antibody (1:150; anti-AMH Antibody, sc-1667529,

Santa Cruz Biotechnology, Oregon, ABD) at 4°C overnight. The slides were then incubated with ready-to-use biotinylated secondary antibody at room temperature for 15 min. Following this, the sections were incubated with Streptavidin Peroxidase conjugate at room temperature for 15 min, and the staining process was terminated after applying DAB (3,3'-diaminobenzidinetetrahydrochloride) (DAB Plus substrate system, Thermo Scientific, Fremont, USA) substrate for 5 min. Sections counterstained with Gill hematoxylin were covered with a coverslip. To evaluate AMH expression in ovarian tissue, images obtained from an Olympus BX 51 light microscope were analyzed using the Image J software program[30].

TUNEL assay for apoptosis

Terminal Deoxynucleotide-Transferase (TdT)-mediated dUTP Nick End Labeling (TUNEL) method was applied for apoptosis. ApopTag® Fluoresce In Situ Apoptosis Detection Kit (EMD Millipore, Darmstadt, Germany) was used for staining, and staining steps were performed according to the kit procedure. A 5 μm sections taken on polylysine-coated slides were deparaffinized and washed 3 times with PBS. Slides were incubated with proteinase K for 15 min and then washed with distilled water. Slides were treated with 3% H_2O_2 for 10 min to minimize endogenous peroxidase activity. Then, the slides were washed with PBS 3 times for 5 min and were then incubated with TdT at 37 °C in a humid and dark environment for 1 h. Slides were counterstained with 4',6-diamidino-2-phenylindole (DAPI) to visualize nuclei. All procedures were performed in a humidity chamber. The TdT step was omitted for the negative control. Slides were evaluated using a fluorescent microscope (Olympus BX51, Tokyo, Japan). After the immunofluorescent staining procedure, positively stained apoptotic cells in the obtained slides were counted using the Image J software program[31].

Enzyme-linked immunosorbent assay (ELISA)

Serum AMH levels were analyzed by the ELISA method. Serum AMH levels were measured using an ELISA kit (Rat ELISA kit, 201-11-1246, Baoshan District, Shanghai, China) according to the manufacturer's instructions. The quantities were determined at 450 nm in a micro ELISA reader (BioTek ELx800)[32].

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows 24.0 program. One-way Analysis of Variance (ANOVA) was used for comparisons between control and experimental groups in normally distributed variables, and the Tukey test was used for *post hoc* analysis. For statistical analysis results, a $p < 0.05$ was considered significant[32].

Results

Histological findings

The ovaries in the control group showed normal histological structure. In the torsion group, the general structure of the ovary was irregular, and there was hemorrhage, edema, and inflammation. Irregularity in the structures of follicles at different maturation stages, an increase in granulosa cells with pyknotic nuclei in secondary and tertiary follicles, and an increase in the number of atretic follicles were observed in the torsioned ovary. There was a significant improvement in the follicular structures of the ovary in the TM, THBO, and TMHBO groups compared to the torsion group (Fig. 1).

The mean follicle numbers are given in table 1. It was determined that the primordial, primary, preantral, secondary, and tertiary follicle numbers in the torsioned ovarian tissue were significantly lower than the follicle numbers in the control group. The follicle numbers in the TM, THBO, and TMHBO groups were significantly improved compared to the follicle numbers in the torsion group. However, no significant difference was found between the follicle numbers in the TM, THBO, and TMHBO groups.

Immunohistochemical findings

AMH expression in ovarian tissue is given in table 2 and figure 2. AMH expression was observed in primary, preantral, secondary, and tertiary follicles in both control and experimental groups. In addition, AMH expression in tertiary follicles was lower than in other follicles. AMH expression in all follicles in the

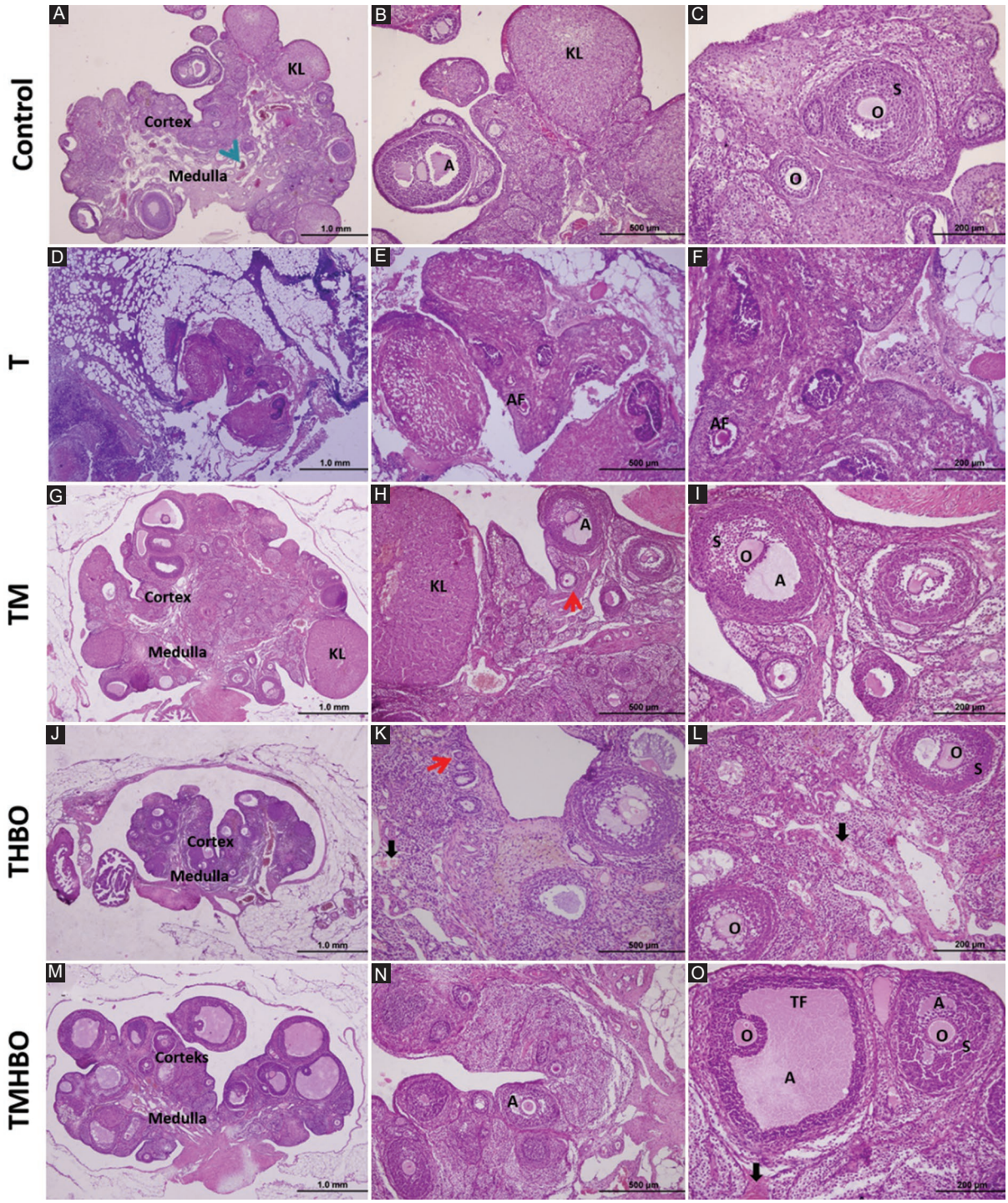

Figure 1. *Ovarian section view of control and experimental groups. Control group* **(A-C)**, *T: torsion/detorsion group* **(D-F)**; *TM: torsion/detorsion+metformin group* **(G-I)**; *THBO: torsion/detorsion+hyperbaric oxygen therapy group* **(J-L)**; *TMHBO: torsion/detorsion+metformin+hyperbaric oxygen therapy group* **(M-O)**. *S: secondary follicle; TF: tertiary follicle; PA: preantral follicle; primary follicle (red arrow), oocyte* **(O)**, *atretic follicle* **(AF)**, *antrum* **(A)**, *zona pellucida (green arrow), hemorrhage (black arrow). Hematoxylin & Eosin staining. Scale bars: 1.0 mm* **(A, D, G, J, M)**; *500 µm* **(B, E, H, K, N)**; *200 µm* **(C, F, I, L, O)**.

torsion group was significantly lower than in the control group. AMH expression in TM, THBO, and TMHBO groups was significantly higher than in the torsion group. Although the greatest numerical improvement was in the TMHBO group, it was not significantly different from the TM and THBO groups.

Table 1. Comparison of follicle numbers of control and experimental groups

Follicle types	Control	T	TM	THBO	TMHBO	p
Primordial Follicle	154.25 ± 18.40[a]	41.00 ± 9.44[b]	78.00 ± 12.60[c]	80.50 ± 8.29[c]	94.25 ± 10.68[c]	0.001
Primary Follicle	77.63 ± 7.59[a]	27.63 ± 10.96[b]	61.75 ± 12.36[c]	67.25 ± 11.74[ac]	71.38 ± 6.02[ac]	0.001
Preantral Follicle	50.88 ± 7.60[a]	26.00 ± 7.19[b]	45.00 ± 10.82[a]	49.63 ± 9.25[a]	49.75 ± 10.55[a]	0.001
Secondary Follicle	27.13 ± 5.22[a]	8.50 ± 2.77[b]	20.88 ± 3.56[c]	19.63 ± 3.58[c]	22.13 ± 5.46[ac]	0.001
Tertiary Follicle	12.50 ± 2.44[a]	4.50 ± 2.33[b]	7.38 ± 1.92[bc]	7.75 ± 1.90[c]	9.38 ± 1.84[c]	0.001

One way ANOVA. Different letters in the row indicate statistically significant difference.
T: torsion/detorsion group; TM: torsion/detorsion + metformin group; THBO: torsion/detorsion + hyperbaric oxygen therapy group; TMHBO: torsion/detorsion + metformin + hyperbaric oxygen therapy group. "The same letters on the same line indicate similarity between groups and different letters indicate the difference between groups."

Table 2. Anti-mullerian hormone (AMH) expression in follicles of control and experimental groups

Follicle types	Control	T	TM	THBO	TMHBO	p
Primary Follicle	157.70 ± 22.79[a]d	123.84 ± 23.47[bc]	144.11 ± 22.74d[c]	137.15 ± 16.27[c]	158.85 ± 26.53[a]	0.001
Preantral Follicle	159.89 ± 23.31[ac]	129.10 ± 24.6[b]	172.18 ± 14.09[c]	142.05 ± 13.86[ab]	172.71 ± 24.58[c]	0.001
Secondary Follicle	154.10 ± 24.40[a]	122.41 ± 23.42[b]	131.94 ± 24.92[b]	129.37 ± 25.00[b]	164.11 ± 24.17[a]	0.001
Tertiary Follicle	121.09 ± 18.55[a]	115.48 ± 14.96[a]	127.46 ± 29.76[a]	119.61 ± 18.34[a]	154.82 ± 28.02[b]	0.001

One-way ANOVA. Different letters in the row indicate a statistically significant difference.
AMH: anti-mullerian Hormone; T: torsion/detorsion group; TM: torsion/detorsion + metformin group; THBO: torsion/detorsion + hyperbaric oxygen therapy group; TMHBO: torsion/detorsion + metformin + hyperbaric oxygen therapy group. "The same letters on the same line indicate similarity between groups and different letters indicate the difference between groups."

TUNEL findings

TUNEL-positive cells were observed in the cortex and medulla layers of the ovary of all control and experimental groups. There was also an increase in TUNEL-positive cells in tertiary and secondary follicles. The highest number of apoptotic cells among all experimental groups was in the T group. The number of TUNEL-positive cells in the ovary tissues of the torsion group was statistically significant when compared with the number of TUNEL-positive cells obtained from the control, TM, and TMHBO groups. However, there was no statistical difference in the number of TUNEL-positive cells between the T and THBO groups (Table 3 and Fig. 3).

Biochemical findings

The mean AMH level of the torsion group was 7.89 ± 0.30 pg/mL, which was significantly lower than the mean AMH level of the control group of 9.65 ± 1.06 pg/mL. The mean AMH level of the TM group was 10.77 ± 0.55 pg/mL, the mean AMH level of the THBO group was 9.95 ± 0.41 pg/mL, and the mean AMH level of the TMHBO group was 11.73 ± 0.94 pg/mL, which were significantly improved compared to the T group. In addition, the mean AMH levels of the TM and TMHBO groups were significantly higher than the mean AMH levels of the control group (Table 4).

Discussion

This experimental study focused on the effects of metformin and HBOT on damage to torsioned ovarian tissue. In the torsion group, it was determined that the histology of follicular structures was impaired, the number of follicles decreased, the number of TUNEL-positive cells increased, and the serum AMH level and tissue AMH expression decreased. Metformin and HBOT given for treatment purposes improved all these damages. Metformin and HBOT were not superior to each other, but the best results were obtained in the TMHBO group.

Ovarian torsion is one of the emergency gynecological surgeries that causes ischemic cell damage in the ovary. Reversing torsion is the current treatment used to preserve fertility in young patients. However, reperfusion of ischemic tissue causes excessive ROS production, thus developing reperfusion damage and eventually I/R damage occurs[33]. I/R damage causes

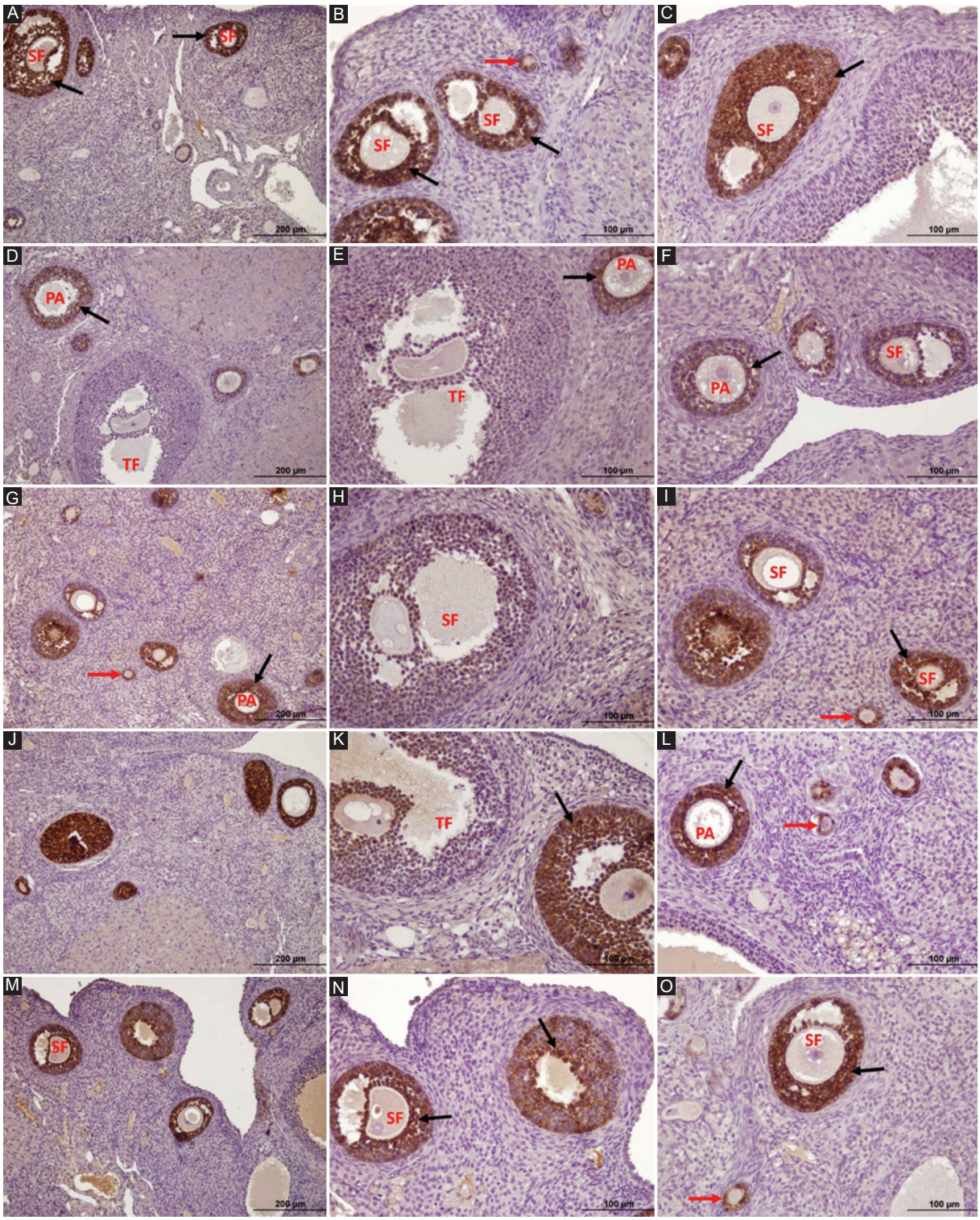

Figure 2. *Immunohistochemical staining for anti-Mullerian hormone in ovarian sections of control and experimental groups. Control group* **(A-C)***; T: torsion/detorsion group* **(D-F)***, TM; torsion/detorsion+metformin group* **(G-I),** *THBO; torsion/detorsion+hyperbaric oxygen therapy group* **(J-L)***; TMHBO; torsion/detorsion+metformin+hyperbaric oxygen therapy group* **(M-O)***. SF: secondary follicle; TF: tertiary follicle; PA: preantral follicle; primary follicle (red arrow). Black arrow: AMH-positive cells. Scale bars: 200 µm* **(A, D, G, J, M)***; 100 µm* **(B, C, E, F, H, I, K, L, N, O)**.

morphological and biochemical changes in the ovarian tissue. Moreover, different I/R techniques have been used to better understand the damage that develops as a result of ovarian torsion. It has been reported that 2 h of ischemia time is sufficient to induce experimental I/R injury in the ovaries[34]. In our

Table 3. Number of TUNEL positive cells in the control and experimental groups

Positivity of the cells	Control	T	TM	THBO	TMHBO	p
Number of TUNEL (+) cells	0.69 ± 0.11[a]	1.69 ± 1.23[b]	1.00 ± 0.93[a]	1.09 ± 1.01[ab]	0.83 ± 0.78[a]	0.001

One-way ANOVA. Different letters in the row indicate a statistically significant difference.
T: torsion/detorsion group: TM: torsion/detorsion + metformin group; THBO: torsion/detorsion + hyperbaric oxygen therapy group; TMHBO: torsion/detorsion + metformin + hyperbaric oxygen therapy group. "The same letters on the same line indicate similarity between groups and different letters indicate the difference between groups."

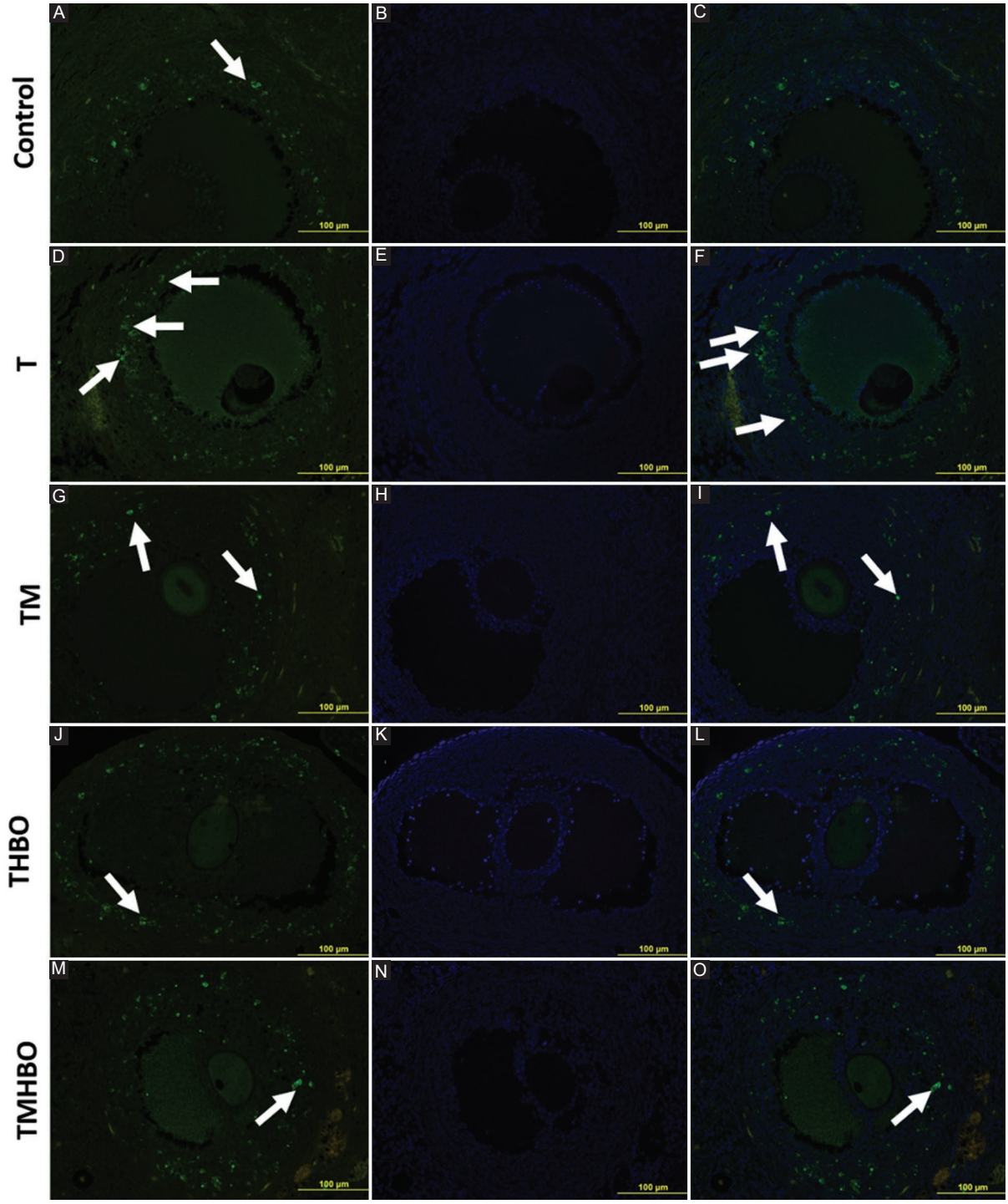

Figure 3. *TUNEL staining in the ovary sections of the control and experimental groups. Control group* **(A-C)***; T: torsion/detorsion group* **(D-F)***; TM: torsion/detorsion+metformin group* **(G-I);** *THBO: torsion/detorsion+hyperbaric oxygen therapy group* **(J-L)***; TMHBO: torsion/detorsion+metformin+hyperbaric oxygen therapy group* **(M-O)***. Arrows: TUNEL-positive cells. Scale bars: 100 µm.*

Table 4. Comparison of serum Anti-mullerian hormone (AMH) levels in the control and experimental groups

Serum AMH levels	Control	T	TM	THBO	TMHBO	p
AMH, pg/ml	9.65 ± 1.06[a]	7.89 ± 0.30[b]	10.77 ± 0.55[cd]	9.95 ± 0.41[ac]	11.73 ± 0.94[d]	0.001

One-way ANOVA. Different letters in the row indicate a statistically significant difference.
T: torsion/detorsion group; TM: torsion/detorsion + metformin group; THBO: torsion/detorsion + hyperbaric oxygen therapy group; TMHBO: torsion/detorsion + metformin + hyperbaric oxygen therapy group. "The same letters on the same line indicate similarity between groups and different letters indicate the difference between groups."

study, 2 h of ischemia were created. Different reperfusion times were studied to reveal the tissue effects of I/R damage. Yurtcu et al.[34] used a 2-h reperfusion period, Hortu et al.[35] used a 3-h reperfusion period, Sahin Ersoy et al.[36] used a 24-h reperfusion period, and Karakas et al.[37] used 14 14-day reperfusion period. We believed that a longer reperfusion period would be more appropriate because the purpose of our study was to assess the impact of I/R injury on ovarian reserve. Therefore, the reperfusion period in our study was 14 days.

The pool of follicles and serum AMH levels are used to assess ovarian function and reserve during the fertile period. AMH secreted from the granulosa cells of preantral follicles is an indirect marker reflecting the growing follicle pool[38]. The levels of serum AMH rise during childhood and adolescence, peaking at age 18, and then fall as the ovarian reserve gradually runs out[28]. As a measure of ovarian reserve, serum AMH levels are superior to those of age, LH, FSH, and estradiol[29,39,40]. Eken et al.[41] observed a significant decrease in the number of primordial, preantral, and antral follicles after ovarian torsion. Mohammadi et al.[42] determined that torsion-detorsion decreased the number of follicles at each stage, such as antral, graafian, and preantral, and also increased the number of atretic bodies. Sakin et al.[43] observed that after 3 h of ischemia and reperfusion, the number of primordial, primary, secondary (pre-antral), and tertiary (antral) follicles decreased significantly compared to the control group. The researchers also determined that the number of atretic follicles increased and serum AMH levels decreased in the torsion group. Erimsah and Cetinkaya[44] showed that I/R injury in the ovary decreased AMH expression in follicles. In our previous study, hemorrhage, edema, and inflammation, an increase in histopathological score, a decrease in follicle numbers, and a decrease in AMH expression were observed in the ovarian tissue after 2 h of torsion. In addition, an increase in Hsp70, NF-κß, CD31, COX-2, Beclin-1, LC-3, and p62 expressions was determined after ovarian torsion[30]. In the current study, AMH expression was observed in primary, preantral, secondary, and tertiary follicles, but AMH expression in tertiary follicles was lower than in other follicles. AMH expression in all follicles and serum AMH levels in the torsion group were significantly lower than in the control group. It was also determined that the number of primordial, primary, preantral, secondary, and tertiary follicles decreased, and the number of atretic follicles and TUNEL-positive cells increased in the T group of rats. Our study results reaffirm previous study results showing that ovarian torsion negatively affects ovarian reserve.

It has been reported that ovarian reserves decrease after ovarian torsion/detorsion and that surgical detorsion alone is ineffective in preserving ovarian reserves[45]. To avoid I/R damage and maintain ovarian reserves, antioxidants and anti-inflammatory were applied in this experimental study. Clinical approval for the use of these agents has not yet been granted, despite their demonstrated experimental benefits. Consequently, research efforts persist in the pursuit of safe and effective medications aimed at mitigating I/R damage in the ovary. Metformin, one of the primary drugs used in the treatment of patients with type 2 diabetes, has been shown to have anti-inflammatory and antioxidant effects[46]. Asghari et al.[47] showed that metformin protects testicular I/R injury in rats. Wang et al.[48] reported that metformin reduces inflammation and prevents apoptosis of renal tubular epithelial cells in a renal I/R rat model study. Palomba et al.[26] observed that metformin use in patients with polycystic ovaries improves ovulation capacity. Topcu et al.[2] documented that metformin improves estradiol levels, tissue oxidative system parameters, and histopathological score in their studies where they applied 250 mg/kg and 500 mg/kg of metformin against ovarian I/R injury. Karakas et al.[37] showed that 50 mg/kg metformin administration for 14 days protects ovarian reserve. Dayangan Sayan et al.[27] showed that 500 mg/kg metformin applied after ovarian torsion improved histopathological score, apoptosis levels, and biochemical oxidant/antioxidant levels. In our

study, 50 mg/kg metformin was applied for 14 days against I/R injury in the ovaries. After metformin administration, improvements were observed in the number of follicles, TUNEL positive cell count, and AMH expression in the ovarian tissue and serum AMH levels. Our results show that metformin has a protective effect on ovarian reserve in I/R injury.

HBOT provides 100% oxygen at environmental pressures greater than 1 atmosphere. HBOT has anti-inflammatory and antioxidant effects and is used for the treatment of ischemia-reperfusion injury. Yu et al.[49] applied HBOT to patients with ovarian cysts after laparoscopic ovarian cystectomy. At the end of the study, it was determined that the serum AMH, estradiol levels, and antral follicle count of patients in the HBOT group were higher than the control group, and serum FSH and LH levels were lower. Ma et al.[19] showed that HBOT reduced follicular apoptosis, improved oocyte maturation, fertilization, and blastocyst formation in aged mice, and improved age-related serum AMH levels. In the study of Cagli et al.[50] evaluating premature ovarian failure, determined that primodial, primary, secondary, and tertiary follicle counts and serum AMH levels decreased compared to control after Cyclophosphamide application. Researchers observed that HBOT provided improvement in all these parameters. Bulutlar et al.[51] documented that HBOT applied to rats after ovarian torsion improved 8-hydroxy-2'-deoxyguanosine, malondialdehyde, AMH, neutrophilic infiltration, vascular occlusion, follicular cell damage, and edema. HBOT, which has been clinically approved, can last up to 120 min at a pressure of three atmospheres. However, for typical therapeutic uses, 1.8-2.8 atmosphere pressure is typically applied for 60-90 min[18,52]. In the current study, HBOT was applied in a hyperbaric chamber at 2.4 atmospheres pressure for 2 h/day for 14 days, with 100% O_2 inhalation. HBOT applied after torsion provided improvement in follicle numbers, AMH expression in follicles, and serum AMH levels. Our results show that HBOT is a treatment protocol that can be successfully applied in preserving ovarian reserve.

To our knowledge, there is no study in which HBOT and metformin were applied together in ovarian torsion. However, combined steroid and HBOT significantly improves hearing thresholds in patients with idiopathic sudden sensorineural hearing loss[53], demonstrating the potential of combining therapies to enhance clinical outcomes. Our study is the first study in which HBOT and metformin were applied together in ovarian torsion. According to this study, metformin and HBOT improved the damage caused by torsion both histologically and biochemically, but the individual effect of any of them is not better than using both of them. In the TMHBO group, where metformin and HBOT were applied together, there was a numerically greater improvement in follicle counts, follicular AMH expression, and TUNEL-positive cell count, but they were not significantly different from the groups that received only metformin and only HBOT. The highest serum AMH levels were in the TMHBO group and were significantly higher than the control, torsion, and THBO groups.

The strength of our study is the evaluation of the effects of HBOT and metformin on ovarian reserve. There are some limitations in our study, in that which sample size was small. We think that our results are promising for larger sample clinical studies. Another limitation is the lack of studies on metformin and HBOT to determine the optimum dose.

Conclusion

In this research, the impact of metformin and HBOT administered following ovarian torsion on ovarian reserve was assessed. The findings indicated that both metformin and HBOT, whether utilized independently or in combination, enhanced the follicular pool within the ovaries as well as serum levels of AMH. Given that this investigation was conducted on animal models, it is essential for our results to be validated through clinical studies involving larger sample sizes.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethıcal consıderatıons

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The

procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study. This study was approved by the Erciyes University Animal Research Ethics Committee (Date: November 03, 2021, No: 21/224).

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Factors influencing the knowledge, attitude, and belief practice of nurses with sepsis and septic shock

Factores que influyen en el conocimiento, la actitud, la práctica y las creencias de las enfermeras sobre la sepsis y el choque séptico

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Abstract

Objective: *The aim of this study was to investigate the current awareness status of nurses on the "Treatment Guidelines for Sepsis and Septic Shock."* **Methods:** *According to the "International Guidelines for Management of Sepsis and Septic Shock 2021," a self-made questionnaire on nursing knowledge related to sepsis and septic shock was used to evaluate nurses' level of knowledge-attitude-belief-practice (KAP) in sepsis and septic shock, and to explore the influential factors on their awareness level.* **Results:** *The awareness rate of nurses was 46.67% toward the treatment guidelines for sepsis and septic shock. Nurses' mastery rate was < 60.00%; and 85.00% of nurses scored 10-18 points using the sepsis and septic shock-related questionnaire. The power order of related factors affecting the KAP level of nurses on sepsis and septic shock was listed as follows: years of service > guideline-related training duration > guideline-related training or not > professional title > degree of education. The years of service had the most significant impact on nurses' level of KAP in sepsis or septic shock (r = 0.521).* **Conclusion:** *Nurses have poor awareness of the "Treatment Guidelines for Sepsis and Septic Shock." The findings suggest that guidelines- and standards-based training with longer duration should be carried out to improve the KAP level of nurses.*

Keywords: *Nurse. Infectious shock. Sepsis. Knowledge-attitude-belief-practice.*

Resumen

Objetivo: *El objetivo de este estudio fue investigar el estado actual de conocimiento de las enfermeras sobre las "Directrices para el tratamiento de la sepsis y el shock séptico".* **Métodos:** *De acuerdo con las "Directrices internacionales para el tratamiento de la sepsis y el shock séptico 2021", se utilizó un cuestionario elaborado por nosotros mismos sobre los conocimientos de enfermería relacionados con la sepsis y el shock séptico para evaluar el nivel de conocimientos, actitudes, creencias y prácticas (KAP) de las enfermeras en materia de sepsis y shock séptico, y para explorar los factores que influyen en su nivel de conocimiento.* **Resultados:** *El índice de conocimiento de las enfermeras sobre las directrices terapéuticas para la sepsis y el shock séptico fue del 46.67 %. El índice de dominio de las enfermeras fue < 60.00 %; y el 85.00 % de las enfermeras obtuvieron una puntuación de entre 10 y 18 puntos en el cuestionario relacionado con la sepsis y el shock séptico. El orden de importancia de los factores relacionados que afectan al nivel de KAP de las enfermeras sobre la sepsis y el shock séptico se enumeró de la siguiente manera: años de servicio > duración de la formación relacionada con las directrices > formación relacionada con las directrices o no > título profesional > grado de educación. Los años de servicio tuvieron el impacto más significativo en el nivel de KAP de las enfermeras en sepsis o shock séptico (r = 0.521).*

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Conclusiones: *Las enfermeras tienen baja conciencia de las pautas de tratamiento de la sepsis y del choque séptico. Se recomienda formación a largo plazo basada en pautas para mejorar los niveles de CACP de las enfermeras.*

Palabras clave: *Enfermeras. Choque séptico. Sepsis. Conocimientos, actitudes, prácticas y creencias.*

Introduction

Sepsis and septic shock are two clinical syndromes characterized by systemic infection-induced organ dysfunction, both of which have been accepted to be major causes of death in critically ill patients in the Infectious Disease Department, Emergency Department, and Intensive Care Unit (ICU). It has been reported that the morbidity and mortality of septic shock were 8.2% and 60.1%, respectively, significantly higher than those of severe infection[1]. The high mortality of septic shock has long been a challenge in clinical practice[2]. In October 2002, the European Society of Intensive Care Medicine, the Society of Critical Care Medicine, and the International Forum on Infections jointly launched a global initiative, surviving sepsis campaign (SSC), in Barcelona, Spain, calling on healthcare professionals, health institutions, and government organizations worldwide to attach great importance to sepsis. SSC proposed an action goal of reducing the mortality rate of sepsis patients by 25% within 5 years. In 2004, experts in critical care and infectious diseases from 11 international organizations jointly developed the "Guidelines for the Treatment of Sepsis and Infectious Shock."[3] In 2021, it was revised and renamed the "International Guidelines for Management of Sepsis and Septic Shock 2021"[4] (hereinafter referred to as the guidelines). The guidelines are international programmatic documents, supported by evidence-based medicine, aimed at raising global awareness of sepsis and septic shock, and striving to improve prognosis. The guidelines have been gradually popularized in China recently, leading to significant changes in the control concepts and treatment principles for sepsis in clinical practice. Nurses are important participants and practitioners in the implementation of the guidelines, suggesting that it is particularly important for nurses in the Infectious Disease Department, Emergency Department, and ICU to understand and master the Guidelines. It has been reported that nurses' knowledge-attitude-belief-practice (KAP) toward the guidelines have a direct impact on the treatment and nursing practices for patients with sepsis[5]. Therefore, this study was performed to investigate the current status of KAP toward septic shock among nurses in the Infectious Disease Department, Emergency Department, and ICU, and explore specific measures to play a positive role of nurses in SSC nursing practice, so as to provide theoretical reference for the nursing of patients with sepsis and septic shock clinically.

Subjects and methods

Subjects of study

Using convenience sampling, this study enrolled 240 nurses in the Infection Department, Emergency Department, and ICU of Peking University People's Hospital. Inclusion criteria: (1) nurses received training in critical care in hospitals; and (2) nurses worked in the department for at least 2 years. This study was approved by the Ethics Committee of Peking University People's Hospital, and informed consent was provided from the respondents. All data collected were strictly confidential for the purpose of this study only.

Methods of study

A self-made questionnaire on nursing-related knowledge that nurses should be aware of was developed in this study based on the Guidelines. The questionnaire consisted of three parts: (1) general data: age, gender, years of service, years of service in the infectious disease department/emergency department/ICU, degree of education, professional title, awareness of the guidelines, receiving guideline-related training on sepsis and septic shock or not, guideline-related training duration, etc. (2) Questionnaire on knowledge that should be mastered by nurses in the treatment of septic shock: four major dimensions of fluid resuscitation, anti-infection treatment, mechanical ventilation, and other monitoring (e.g., vital signs, lactate, and blood glucose). Each dimension respectively consists of 11, 8, 4, and 5 items, with each item scoring 1 point for correct answers and 0 points for incorrect or no answers. The total score is the sum of each item. The

respondents with higher scores might have better knowledge mastery. The researchers were responsible for questionnaire distribution, explanation of the purpose of the survey to the respondents, and questionnaire collection the next day. The respondents were informed to truthfully fill out the questionnaire anonymously. A total of 250 questionnaires were distributed and 246 were collected, including 240 valid questionnaires.

A total of 40 copies of the questionnaire were distributed in the pilot survey. As shown in the analysis of reliability and validity of the questionnaire, the item-content validity index (CVI) was 0.754 ~ 1.00, the scale-level CVI/average was 0.858, and the scale-level CVI/universal agreement was 0.846; besides, the Cronbach's α of the total questionnaire was 0.854, and that of each dimension ranged between 0.886~0.962; the split-half coefficient of the total questionnaire was 0.693, and that of each dimension ranged between 0.827 ~ 0.934; additionally, the test-retest reliability of the total questionnaire was 0.932 ($p < 0.001$). It supported that the self-made questionnaire had good content validity and internal consistency.

Statistical analysis

Data analysis in this study adopted Statistical Package for the Social Sciences 25.0 statistical software. Measurement data that met the normal distribution were expressed by mean±standard deviation ($x \pm s$), and inter-group comparison used an independent sample t-test. In univariate analysis, linear correlation analysis was used to calculate the Pearson correlation coefficient for measurement data, and rank correlation analysis was used to calculate Spearman's rank correlation coefficient for clarifying the correlation between rank variables. In addition, multiple regression analysis was employed for multivariate analysis. $p < 0.05$ was considered to have a statistically significant difference.

Results

Baseline data of the respondents

This study included 240 female nurses, with an average age of 25.9 ± 4.8 years old (22 ~ 43 years). Their average years of service in nursing and years of service in the department were 7.42 ± 4.36 and 2.96 ± 1.55 years, ranging between 1~20 and 1-18 year(s), respectively. In terms of the degree of education, there were 44 nurses with vocational school degrees, 166 with college degrees, and 30 with bachelor's degrees or above. Besides, as for professional titles, there were 22 nurses, 202 nurse practitioners, and 16 supervisor nurses or above.

Table 1. Nurses' awareness of relevant content of the Guidelines (n = 240)

Items	Number of awareness	Awareness rate (%)	Sequence
Fluid resuscitation and fluid therapy	240	100.00	1
Antibiotic therapy	210	87.50	2
Mechanical ventilation	200	83.33	3
Use of vasopressors and cardiotonic drugs	190	79.17	4
Pathogenic diagnosis and control of infection sources	182	75.83	5
Bicarbonate therapy	180	75.00	6
Glucose control	168	70.00	7
Use of glucocorticoids	158	65.83	8
Use of blood products	150	62.50	9
Use of sedatives, analgesics, and muscle relaxants	142	59.17	10
Renal replacement therapy	140	58.33	11

Nurses' awareness of relevant content of the guidelines

Among all respondents, 130 nurses were aware of the content of the guidelines, with an awareness rate of 54.17%. A survey was further conducted on the 11 treatment items mentioned in the guidelines. The results showed that only 112 nurses (46.67%) believed that all 11 items were related to the treatment of sepsis and septic shock, while the remaining respondents had varying degrees of cognitive misunderstandings. Furthermore, according to the survey on the ways in which nurses were aware of the guidelines, only 8.93% (10/112) received relevant training; 44.64% (50/112) reviewed the guidelines; 41.07% (46/112) only heard and never reviewed; and 5.36% (6/112) were aware through other channels. Nurses' awareness of the relevant content of the guidelines is shown in table 1.

Table 2. Nurse's mastery of guideline-related knowledge

Dimensions	Total score	Score	Accuracy (%)
Fluid resuscitation	11	7.67 ± 1.72	59.65
Anti-infection	8	5.23 ± 1.22	55.34
Mechanical ventilation	4	1.89 ± 0.72	48.77
Other monitoring	5	2.11 ± 1.03	29.33

Table 3. Nurse's mastery of septic shock-related knowledge

Score range	Number of respondents	Proportion (%)
1~9	6	5.00
10~18	102	85.00
19~28	12	10.00

The score of nurses on the KAP questionnaire for sepsis and septic shock

The average score of the respondents was 15.30 ± 4.22 points (26 ~ 5 points). The total accuracy rate of the four dimensions of knowledge that nurses in the Infectious Disease Department, Emergency Department, and ICU of our hospital should master in the treatment of sepsis and septic shock was < 60% (Table 2). In addition, concerning nurses' mastery of relevant knowledge, the score ranged between 10 and 18 points in the majority of nurses (85.00%) (Table 3).

Correlation analysis of nurses' mastery of septic shock-related knowledge

This study further carried out a univariate analysis of the influential factors of sepsis and septic shock-related knowledge mastery among nurses in the Infectious Disease Department, Emergency Department, and ICU. The score of the questionnaire was positively correlated with nurses' age, years of service, professional title, guideline-related training or not, and guideline-related training duration. It showed the strongest correlation with the years of service in the department (r = 0.53, t = 4.102, p < 0.001; Table 4).

Table 4. Analysis of factors influencing nurses' mastery of guidelines

Factors	*r*-value	*t/Z*	p-value
Age	0.31	3.454	< 0.001
Years of service	0.29	3.231	< 0.001
Years of service in the department	0.53	4.102	< 0.001
Degree of education	0.32	3.231	< 0.001
Professional title	0.35	3.122	< 0.001
Guideline-related training or not	0.43	4.512	< 0.001
Guideline-related training duration	0.44	4.642	< 0.001

Multiple linear regression analysis of nurses' mastery of knowledge related to sepsis and septic shock

$$Y = 5.833 + 0.521X_1 + 0.322X_2 + 0.418X_3 + 0.442X_4 + 0.355X_5$$

Using knowledge-related scores of the respondents as the dependent variable and variables with statistically significant differences in univariate analysis as independent variables, a stepwise regression analysis was performed to further explore factors affecting the mastery of septic shock-related knowledge among nurses in the Infectious Disease Department, Emergency Department, and ICU. The assignment of variables with statistically significant differences in univariate analysis was as follows: degree of education: primary school and below = 1, middle school = 2, vocational school = 3, college and above = 4; professional title: primary = 1, intermediate = 2, senior = 3; and guideline-related training or not: yes = 1, no = 2. All other variables were included as continuous variables. The stepwise regression was used to include and exclude independent variables (α_{entry} = 0.05, and $\alpha_{removal}$ = 0.1) to eliminate influential factors with interactive effects. Age and years of service were excluded during the inclusion and exclusion of variables. The determination coefficient was R^2 = 0.699 in the regression model, indicating that nurses' years of service in the department, degree of education, and other independent variables could explain 69.9% of nurses' mastery of knowledge related to sepsis and septic shock (F = 356.73, p < 0.001). It suggested that the dependent variable of mastery of sepsis and septic shock-related knowledge among nurses in the Infectious Disease

Table 5. Multiple linear regression model for influential factors

Variables	Standard error	Partial regression coefficient	p	95% confidence interval	Variance inflation factor
Constant	5.833	-	< 0.001	-	-
Years of service in the department	1.323	0.521	< 0.001	0.465~1.322	1.002
Degree of education	1.319	0.332	< 0.001	0.165~0.422	1.057
Guideline-related training or not	1.520	0.418	< 0.001	0.355~0.512	1.064
Guideline-related training duration	1.612	0.442	< 0.001	0.248~0.731	1.055
Professional title	1.192	0.355	< 0.001	0.121~0.440	1.087

Department, Emergency Department, and ICU had a good fit with the five independent variables. Furthermore, the Durbin-Watson index was 1.995, indicating no correlation among independent variables in the model. As indicated by the significance test results, the five independent variables should be retained considering the presence of statistically significant differences in the model (all $p < 0.05$). Moreover, four independent variables had VIF values of far < 10, suggesting no collinearity between individual variables. The fitted multiple linear regression equation (I) was:

$$Y = 5.833 + 0.521X_1 + 0.322X_2 + 0.418X_3 + 0.442X_4 + 0.355X_5$$

According to the partial regression coefficients in the model, the power order of related factors affecting the KAP level of nurses on sepsis and septic shock was as follows: years of service in the department > guideline-related training duration > guideline-related training or not > professional title > degree of education (Table 5).

Discussion

Sepsis and septic shock, with a mortality of up to 28.6%[6], are a high concern globally in Critical Care Medicine and are also nursing challenges worthy of in-depth research[7,8]. Patients with septic shock have relative or absolute hypovolemia in general and may further suffer from injuries of major organs and metabolic disorders due to tissue ischemia and hypoxia resulting from unstable hemodynamics and tissue hypoperfusion[9]. Resuscitation therapy offers a key strategy for circulatory support to improve hemodynamic status and reverse organ dysfunction, exhibiting significant roles in the rescue and treatment of septic shock patients. Nurses are front-line personnel in early identification of critically ill patients at the initial stage of disease onset[10]. Clinical effects may be compromised if nurses are not familiar with septic shock and have a low KAP level. In this study, nurses in the Infectious Disease Department, Emergency Department, and ICU had low awareness of knowledge related to resuscitation therapy for septic shock, with an awareness rate of only 54.17%. It is consistent with the findings of Edwards and Jones[11]. At the same time, only 8.93% (10/112) of the knowledge providers received relevant training, 41.07% of them only heard and never reviewed the guidelines, and the total accuracy of nurses in the infectious diseases department, emergency department, ICU, and other departments in mastering the four dimensions related to this guideline was < 60%. Among them, the accuracy of the' other monitoring' dimension is the lowest, only 29.33%. A study from Switzerland[12] also pointed out that the lack of awareness and knowledge of sepsis reflects the lack of sepsis-specific continuing education. The training and education of septic shock may be affected by many factors, such as insufficient attention, backward training content and methods, insufficient teachers, nurses' own factors, and imperfect training evaluation and feedback mechanism. To improve the quality of training and education of septic shock, it is necessary for medical institutions, training institutions and nurses to work together to strengthen training investment, update training content and methods, improve teachers' strength, stimulate nurses' learning motivation, and improve training evaluation and feedback mechanism.

Foreign research has emphasized the importance of clinical reflection and self-reflection to improve professional abilities[13]. In this study, most nurses in the Infectious Disease Department, Emergency

Department, and ICU had a moderate level of mastery (85.00%), while those with poor mastery accounted for 5.00%. The study of Chua et al.[14] also found that nurses have a general knowledge of sepsis and are confident in identifying and coping with sepsis patients. However, only 52.0% of them could correctly define sepsis. This result underscores the need for systematic and multi-level on-the-job training of knowledge not yet mastered by nurses' care managers and educators. Among the four dimensions of the survey, nurses had the worst mastery of "other monitoring" related knowledge, which, however, is a hot-spot issue of concern in Critical Care Medicine at present. It in turn proposes a requirement for improving nurses' ability to identify and acquire new knowledge.

Furthermore, foreign reports also revealed that factors such as learning duration and years of service might affect the development of nurses' professional abilities[15]. Consistently, in this study, younger and junior nurses as well as those with junior professional titles had significantly lower mastery of the guidelines compared to older and senior nurses as well as those with senior professional titles. It may be explained by the lack of clinical experience, limited opportunities to participate in relevant training, and insufficient proactive learning ability and needs of the former group. This is consistent with the research results of Yuan and Xiaoying[16]. Due to the short working hours, junior nurses have no contact with many new knowledge and new theories, and lack the enthusiasm of active learning[5]. In clinical nursing, only passive monitoring can be achieved, rather than taking the initiative to manage patients, unable to achieve target management, let alone predictive nursing. Due to the lack of relevant knowledge, it seriously affects the early observation and timely and effective nursing of sepsis patients by low-level nurses, which will delay the overall treatment and affect the prognosis. Therefore, younger and junior nurses as well as those with junior professional titles and insufficient work experience in the department should receive more training actively, thereby improving the overall professional and technical level of nursing in the Infectious Disease Department, Emergency Department, and ICU[17]. Therefore, in the training of nurses, there is a need to fully consider the differences in their mastery of existing knowledge and skills among different departments and disease entities. A diversified training model stratified by age, departments, and administrative levels should be adopted when formulating training programs[18]. Meanwhile, nurses in the Infectious Disease Department, Emergency Department, and ICU should also learn actively to improve their understanding and mastery of the guidelines by reviewing the latest professional journals and utilizing abundant online resources[19]. In this way, nurses can make full use of their own value in the nursing practice of the "Guidelines for the Treatment of Sepsis and Infectious Shock."

Without a doubt, this study still has several limitations. It was a single-center study with a smaller sample size, resulting in potential selective bias and poor universality of the results. In the future, multi-center randomized controlled trials with larger sample sizes should be conducted to objectively and effectively evaluate nurses' mastery of the guidelines.

This study has important practical significance for improving nurses' understanding and mastery of sepsis and septic shock treatment guidelines. We identified the key factors affecting nurses' mastery of relevant knowledge, such as service years, education level and training experience, and provided targeted training directions for nursing managers and educators. According to the differences between different departments and disease entities, a hierarchical and diversified training model should be developed. Future research can further explore the optimization of training programs, design refined courses, combine clinical cases and simulation exercises, and improve nurses' practical ability and ability to respond to emergencies. At the same time, multi-center, large-sample randomized controlled trials are important directions for evaluating the effects of different training strategies. With the progress of medical technology and the development of clinical practice, the treatment guidelines will be constantly updated. Future research needs to pay attention to the update of the guidelines, adjust the training content and methods in time, ensure that nurses master the latest clinical knowledge and skills, and provide better nursing services for patients.

Conclusion

Higher requirements have been placed on the knowledge and skills of nurses in the Infectious Disease Department, Emergency Department, and ICU with the development of Critical Care Medicine. However, the present study reveals a relatively low KAP level among nurses toward septic shock at present. Therefore, it is necessary to strengthen continuing education and training of nurses in the Infectious Disease Department, Emergency Department, and ICU, so as to improve their understanding and correct

mastery of knowledge related to resuscitation treatment of septic shock. In addition, outdated and/or incorrect concepts, knowledge, and practices should be updated and corrected among nursing staff in a timely manner.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the Institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Factors influencing the outcome of pregnancy and the clinical effects of emergency cervical cerclage in singleton and twin pregnancies

Factores que influyen en el resultado del embarazo y efectos clínicos del cerclaje cervical de urgencia en embarazos únicos y gemelares

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Abstract

Objective: *This study aimed to analyze pregnancy and perinatal outcomes in singleton and twin pregnancies undergoing ultrasonography (USG)-indicated and clinically indicated cervical cerclage.* **Methods:** *The study population included pregnant women with a cervical length of < 15 mm as determined by transvaginal ultrasonography between 16 and 27 weeks of gestation or a cervix < 4 cm open as observed through USG measurement, who subsequently underwent emergency cervical cerclage. The study compared pregnancy and perinatal outcomes between the two groups.* **Results:** *A comparison of the data according to USG (n = 18, 37%) or clinical (n = 31, 63%) indication revealed that the weeks of cerclage, weeks to delivery, and duration of pregnancy were similar between the groups (p = 0.509, p = 0.095, p = 0.090, respectively). In pregnancies involving a single fetus (n = 36, 73%) and those involving two fetuses (n = 13, 27%), the week of cerclage, the week of delivery, and the duration of pregnancy exhibited no statistically significant differences (p = 0.344, p = 0.309, p = 0.762, respectively).* **Conclusions:** *In both singleton and twin pregnancies, emergency cerclage between 16 and 27 weeks of gestation in patients with cervical shortening or dehiscence has been demonstrated to prolong the gestation period under appropriate conditions by experienced specialists.*

Keywords: *Emergency cerclage. Singleton pregnancy. Twin pregnancy. Perinatal outcomes.*

Resumen

Objetivo: *Analizar los resultados perinatales y del embarazo en gestaciones únicas y gemelares tras un cerclaje cervical indicado por ecografía y por indicación clínica.* **Métodos:** *La población del estudio incluyó mujeres embarazadas con una longitud cervical de menos de 15 mm determinada por ecografía transvaginal entre las 16 y 27 semanas de gestación o con el cuello uterino abierto de menos de 4 cm medido por ecografía, que posteriormente se sometieron a cerclaje cervical de emergencia. El estudio comparó los resultados perinatales y del embarazo entre los dos grupos.* **Resultados:** *La comparación de los datos según la indicación ecográfica (n = 18, 37%) o clínica (n = 31, 63%) reveló que las semanas de cerclaje, las semanas hasta el parto y la duración del embarazo fueron similares entre los grupos (p = 0.509, p = 0.095 y p = 0.090, respectivamente). En los embarazos con feto único (n = 36, 73%) y con dos fetos (n = 13, 27%), la semana del cerclaje, la semana del parto y la duración del embarazo no mostraron diferencias estadísticamente significativas (p = 0.344, p = 0.309 y p = 0.762, respectivamente).* **Conclusiones:** *Tanto en los embarazos con feto único como en los gemelares se ha dem-*

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ostrado que el cerclaje de urgencia entre las 16 y 27 semanas de gestación en pacientes con acortamiento o dehiscencia cervical prolonga el periodo de gestación, en condiciones adecuadas y por especialistas experimentados.

Palabras clave: *Cerclaje de emergencia. Embarazo único. Embarazo gemelar. Resultados perinatales.*

Introduction

The term "preterm delivery" (PTD) is used to describe a birth that occurs before the 37th week of gestation. One of the most significant contributors to perinatal morbidity and mortality is preterm labor and the subsequent complications that arise from it[1]. Four primary etiological factors have been identified as contributing to the pathogenesis of PTD: maternal or fetal hypothalamic-pituitary-adrenal activation, infection, decidual hemorrhage, and pathologic uterine distension[2].

As defined by the American College of Obstetricians and Gynecologists, cervical insufficiency (CI) is characterized by cervical dilatation that occurs in the second trimester without concurrent uterine contractions and membrane rupture[3,4]. CI is an important cause of PTD, accounting for 1% of all pregnancies and 8% of recurrent second-trimester losses[5].

The diagnosis of CI is based on obstetric history or measurement of cervical length (CL) by transvaginal ultrasonography (TVU). It is important to prolong the gestation period in pregnant patients diagnosed with CI[3]. CL screening is a reliable method for identifying patients at risk of spontaneous PTD. A CL value of 25 mm or less, as determined by TVU in the second trimester of pregnancy, is indicative of a short cervix[6].

There are two principal treatment modalities for CI: surgical and conservative. The conservative treatment approach involves a wait-and-see approach, the administration of progesterone, and the use of a pessary. In surgical treatment, the cerclage procedure may be performed either transvaginally or transdominally[7]. The recent introduction of perioperative therapies has considerably enhanced the safety and efficacy of emergency cervical cerclage. Moreover, evidence indicates that emergency and prophylactic cervical cerclage are similarly effective when antibiotics and tocolytics are used in an appropriate manner[8].

At present, there is a paucity of evidence-based guidelines that can definitively determine whether conservative treatment or cervical cerclage is more effective for patients with CI. Consequently, the absence of standardized guidelines and sufficient evidence-based medical evidence results in physicians diagnosing and treating patients based on their personal experience. This can result in not only inconsistent procedures but also the administration of an excessive degree of uniformity in treatment or the delay of the most appropriate treatment option[9]. In twin pregnancies with a cervix length of < 15 mm or a dilated cervix of > 10 mm, the use of cerclage has been demonstrated to be an effective method for reducing the incidence of PTD and prolonging the gestational period[10].

Although there is more information about cerclage in singleton pregnancies, the efficacy of cerclage in multiple pregnancies is still unclear. Therefore, in this study, we aimed to evaluate the perioperative management, maternal, antenatal, and neonatal outcomes of singleton and twin pregnancies undergoing emergency cervical cerclage in the second trimester in a tertiary center. We also investigated the effect of indications for emergency cerclage on obstetric outcomes.

Methods

This study was conducted in the Department of Obstetrics and Gynecology, Faculty of Medicine, Selcuk University, between March 1, 2023, and June 30, 2024. The study was designed in accordance with the principles set forth in the Declaration of Helsinki and received approval from the Selcuk University, Faculty of Medicine Local Ethics Committee (Ethics Committee number: 2023/162) before its commencement. The data pertaining to patients who underwent follow-up and treatment at our clinic were obtained prospectively.

A total of 49 patients who underwent emergency cerclage for cervical shortness or cervical dilatation and whose treatment and delivery took place in our hospital were included in the study. CL was measured using a Voluson E6 (GE Medical Systems, Milwaukee) transvaginal probe with an empty bladder without compression of the anterior cervix, with the image covering at least 50% of the screen. A sagittal section was taken, and the distance between the internal and external os was measured linearly with equal

thickness of the anterior and posterior lips of the cervix. The study population consisted of all pregnant women with a TVU-measured CL of < 15 mm between 16 and 27 weeks of gestation or a USG-measured cervical opening of < 4 cm who underwent emergency cervical cerclage. The flow chart for patient selection is given below (Fig. 1).

Patients who were diagnosed with CI between 16 and 27 gestational weeks and underwent emergency cerclage were included in the study. In addition, absence of vaginal bleeding, negative active labor contractions, absence of rupture of membranes, negative vaginal and urine cultures, absence of clinical or laboratory findings of chorioamnionitis, and CL < 15 mm were accepted as inclusion criteria in this group. In contrast, exclusion criteria were vaginal bleeding, onset of active labor contractions, CL more than 15 mm or cervical opening more than 4 cm, premature rupture of membranes, culture positivity, or clinical or laboratory positivity.

Transvaginal cerclage was performed by experienced specialists (G.O. and A.P.) under spinal anesthesia or sedoanalgesia in the inverted trendelenburg position using an allis clamp in cases with prolapsed membranes and pushing it slightly upward with gauze. In the procedure, cerclage was performed using the McDonald technique using a Mersilene tape suture. The cervical image of a 24w3d pregnant patient with CI before and after cervical cerclage is given in figure. 2.

The patients were initially hospitalized upon the diagnosis of cervical shortness. The results of the vaginal and urine cultures were negative before the performance of the procedure. Intravenous antibiotics and prophylactic indomethacin were initiated during the course of hospitalization. A combination of ceftriaxone (1 g every 24 h), clarithromycin (500 mg every 12 h), and metronidazole (500 mg every 8 h) was employed as the antibiotic regimen. As reported in the study by Oh et al.[11] Cervical cerclage was determined to be the optimal course of action following a comprehensive evaluation of the clinical and laboratory results over a minimum of 48 h, particularly in patients exhibiting indications of inflammation on ultrasound (enhanced echogenicity of sludge and amniotic membrane, dense particles in amniotic fluid).

All pregnancy follow-ups after the procedure until delivery were performed by the maternal fetal medicine unit. Progesterone treatment was added to all cases after the cerclage procedure. Progesterone 200 mg every 24 h intravaginally was recommended until 36 weeks of gestation. The cerclage suture was removed at 37 weeks of gestation. The mode of delivery was decided according to obstetric indications.

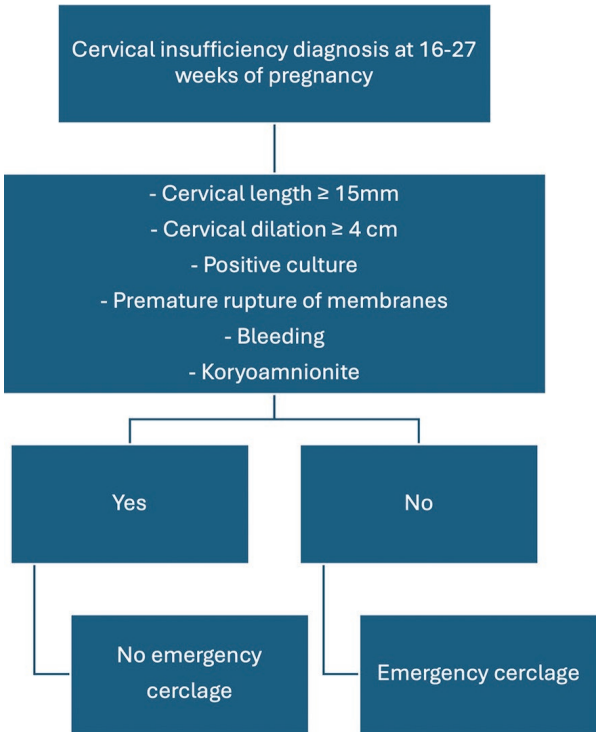

Figure 1. *Patients undergoing emergency cerclage.*

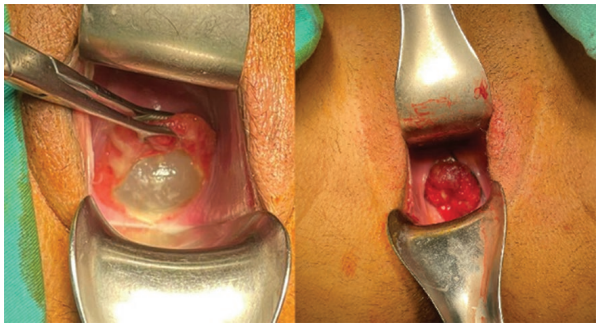

Figure 2. *Emergency cerclage images before and after.*

A comparative analysis was conducted on clinical follow-up, laboratory parameters, pregnancy outcomes, the interval between cerclage and delivery, and neonatal outcomes in singleton and twin pregnancies across the two groups. Furthermore, the obstetric and perinatal outcomes of patients who underwent cerclage for the indications of cervical patency or shortness were also compared between the two groups.

Statistics

The analyses were evaluated using the Statistical Package for Social Sciences (SPSS) 22 package

program (SPSS, Inc., Chicago, IL). Descriptive data were presented as absolute and relative frequencies for categorical variables and as means ± standard deviations for continuous variables. A χ^2 analysis (Pearson χ^2) was employed to ascertain the significance of the observed differences in categorical variables between the groups. The compliance of continuous variables with a normal distribution was evaluated using the Kolmogorov-Smirnov test. A Student's t-test was employed to facilitate a comparison between groups. The level of statistical significance was accepted as $p < 0.05$ in the analyses.

Results

A total of 49 patients were included in the study. As indicated by the criteria for cerclage application, (n = 18, 37%) were deemed eligible based on ultrasound findings, whereas (n = 31, 63%) met the criteria based on clinical assessment. The results of the comparison of demographic and obstetric characteristics between the two groups are presented in table 1. While cerclage education was more prevalent in singleton pregnancies, USG indication was more common in twin pregnancies. The mean time to delivery was 13.6 ± 4.0 weeks in patients who underwent cerclage according to USG indication and 11.4 ± 4.9 weeks in the group who underwent cerclage according to clinical indication (p = 0.095). The incidence of preterm premature rupture of membranes (PPROM) was 25.8% in the cerclage group with clinical indication and 11.1% in the group with USG indication (p = 0.278).

A comparison was also conducted between the data of patients included in the study with regard to singleton and twin pregnancies. Of the patients included in the study, 13 were identified as having twin pregnancies, representing 27% of the total sample, whereas 36 were identified as having singleton pregnancies, representing 73% of the total sample. The demographic and obstetric data of the groups are presented in table 2. The mean time to delivery was 12.4 ± 5.2 weeks in singleton pregnancies and 12.0 ± 2.9 weeks in twin pregnancies (p = 0.762). The incidence of PPROM-related complications was 19.4% in singleton pregnancies and 23.1% in twin pregnancies (p = 0.781).

A comprehensive analysis of all cases revealed that the earliest cerclage procedure was conducted at 16 gestational weeks, whereas the latest was performed at 27 weeks (mean: 21.7 ± 2.3 weeks; minimum: 16 weeks; and maximum: 27 weeks). In the present

Table 1. Comparison of demographic and obstetric characteristics of groups based on indication

Data	Indication for USG (n = 18) Mean ± SD	Clinical indication (n = 31) Mean ± SD	p*
Age	27.4 ± 4.5	28.3 ± 5.9	0.559
Gravida	1.9 ± 0.9	2.0 ± 1.4	0.092
Parity	0.2 ± 0.5	0.5 ± 1.0	0.131
Abortus	0.2 ± 0.4	0.4 ± 1.0	0.194
Cerclage week	21.6 ± 3.0	22.2 ± 2.2	0.509
Birth week	35.4 ± 3.3	33.4 ± 5.0	0.095
Elapsed time (week)	13.6 ± 4.0	11.4 ± 4.9	0.090
Number of fetuses (n)			
Singleton (%)	10 (55.5)	26 (83.9)	0.049**
Twin (%)	8 (44.5)	5 (16.1)	
PPROM			
Yes (%)	2 (11.1)	8 (25.8)	0.278**
No (%)	16 (88.9)	23 (74.2)	
Cerclage EFW mean (g)	395.3 ± 154.7	498.1 ± 197.9	0.095
Birth EFW mean (g)	2476.1 ± 711.1	2235.4 ± 809.8	0.222

*Student's t-test. **χ^2 analysis.
PPROM: premature preterm early rupture of membrane; SD: standard deviation, EFW: estimated fetal weight, g: gram.

Table 2. Comparison of groups based on the number of fetuses of the patients

Data	Singleton pregnancy (n = 36) Mean ± SD	Twin pregnancy (n = 13) Mean ± SD	p*
Age	28.2 ± 5.7	27.2 ± 4.2	0.544
Gravida	1.9 ± 1.4	1.2 ± 0.4	0.008
Parity	0.5 ± 1.0	0.0 ± 0.0	0.005
Abortus	0.4 ± 1.0	0.1 ± 0.3	0.063
Cerclage week	22.2 ± 2.4	21.4 ± 2.8	0.344
Birth week	34.5 ± 5.0	33.4 ± 2.3	0.309
Elapsed time (week)	12.4 ± 5.2	12.0 ± 2.9	0.762
Cerclage EFW mean (g)	493.5 ± 193.6	380.2 ± 152.3	0.053
Birth EFW mean (g)	2499.7 ± 1040.8	2101.5 ± 484.6	**0.025**
Cervical dilatation			
Yes (%)	26 (72.3)	5 (38.5)	0.007**
No (%)	10 (27.7)	8 (61.5)	
PPROM			
Yes (%)	7 (19.4)	3 (23.1)	0.781**
No (%)	29 (81.6)	10 (76.9)	

*Student t-test. **χ^2 analysis was applied.
PPROM: premature preterm early rupture of membranes; SD: standard deviation; EFW: estimated fetal weight; g: grams.

study, three patients underwent cerclage between 24 and 27 weeks of gestation. Of these, three were singleton pregnancies, and cerclage was performed subsequent to the detection of cervical patency. All three cases reached the full term after the cerclage procedure was performed. A total of 62 fetuses were evaluated for perinatal outcomes, as detailed in table 3.

Among the fetuses (n = 3, 4.8%) were lost as postnatal exitus, and there was no intrauterine exitus. The rate of neonatal intensive care unit (NICU) hospitalization requirement was (n = 27, 43.5%). All of these hospitalizations were due to prematurity and newborn transient tachypnea. The mean length of stay in the new NICU unit in the neonatal period was calculated as 13.6 ± 16.5 days.

Table 3. Patients' neonatal results

Perinatal outcomes, n (%)	Media ± SD
NICU	
Yes, n (%)	27 (43.5)
No, n (%)	35 (56.5)
Mortality	
Yes, n (%)	3 (4.8)
No, n (%)	59 (95.2)
APGAR 1 min	5.4 ± 1.8
APGAR 5 min	7.3 ± 1.9
Hospitalization duration (days)	13.6 ± 16.5

n: number of cases, SD: standard deviation; NICU: newborn intensive care unit; min: minute.

Discussion

In our study, an emergency cerclage procedure was performed in a total of 49 patients with singleton and twin pregnancies with cervical shortness or cervical dehiscence. Similar results were found in both singleton and twin pregnancies that underwent emergency cerclage, and the results showed that the emergency cerclage procedure can be recommended up to the 27th gestational week in pregnancies threatened by cerclage failure.

Detection of a short cervix or cervical dilatation in the second trimester of pregnancy may be a sign of miscarriage or preterm labor. Cervical cerclage is known to be effective in patients with a history of premature birth and a short cervix[12]. Emergency cervical cerclage is recommended in patients with clinically detected cervical patency in the second trimester, but labor has not started, and there is no evidence of infection or bleeding[13,14]. Consequently, CL measurement during the second trimester of pregnancy is a crucial and readily achievable procedure for all pregnant women. By measuring the length of the cervix, it is possible to implement treatment strategies that may prolong the gestation period in pregnancies with a high risk of PTD.

The present study demonstrates that emergency cerclage in patients with cervical shortness and cervical dilatation can be an effective method for prolonging the gestation period. Furthermore, comparable success rates in singleton and twin pregnancies suggest that cerclage may also be a viable option for multiple pregnancies.

Ultrasonographic changes are detected before cervical changes are detected by examination. In most pregnant patients with CL 10-25 mm by TVU in the second trimester, the cervix feels long and closed on physical examination. Cervical effacement and dilatation are usually not detected until CL ≤ 10 mm by TVU. In one study, only one-third of patients with CL < 11 mm had cervical dilatation ≥ 1 cm on physical examination[15]. All these data emphasize the importance of second-trimester CL measurement.

Some conditions need to be specifically ruled out in patients with cervical shortening or dilatation. The first condition to be ruled out is active labor and vaginal infections. First of all, risk factors should be eliminated with intensive follow-up of these pregnant women[16]. Normal cervical ripening occurs over days to weeks, whereas cervical change in labor occurs over minutes to hours. A short or dilated cervix may be the first clinical sign of impending preterm labor triggered by subclinical inflammation[17]. A history of placental abruption or bleeding from placenta previa should be excluded through physical examination and ultrasound imaging. These conditions have the potential to cause biochemically mediated cervical ripening, which may result in second-trimester pregnancy loss or extremely PTD[18]. Infections that may cause PTD should be excluded through the implementation of appropriate diagnostic procedures, including transabdominal amniocentesis, urine culture, and complete urinalysis. In a study, the incidence of intraamniotic infection resulting from amniocentesis was found to be approximately 20-50% in patients with a dilated cervix of ≥ 2 cm on routine digital or speculum examination[19]. In the present study, cerclage was performed in all cases after the exclusion of infection according to the results of laboratory tests and the

absence of infection according to the results of physical examinations.

The management of patients diagnosed with CI is still controversial. Different opinions have been reported regarding progesterone treatment, which is one of the treatments for CI. In a study comparing emergency cerclage and bed rest for CI, emergency cerclage was shown to significantly increase mean gestational age and perinatal survival in both singleton and twin pregnancies[20,21]. In another study, overall survival after emergency cervical cerclage was 74%, fetal survival 88%, and neonatal survival 90%. Singleton and twin pregnancies showed similar survival and prolonged the gestation period by 52 and 37 days, respectively[21]. In our study, the mean time to delivery was 12.4 ± 5.2 weeks in patients who underwent cerclage in singleton pregnancies with USG indication and clinical indication in the second trimester and 12.0 ± 2.9 weeks in patients who underwent cerclage in twin pregnancies. In addition, fetal survival was 100%, and neonatal survival was 95.2% in our study. We found that emergency cerclage had a favorable effect on pregnancy and neonatal outcomes in both singleton and twin pregnancies. We think that this may be related to the exclusion of other causes of cervical shortness with perioperative examinations of the patients before cerclage, as well as anti-inflammatory and antibiotic treatment.

A study was conducted on patients with intra-amniotic infection/inflammation, as detected by amniocentesis, who were treated with antibiotics (ceftriaxone, clarithromycin, and metronidazole). The results demonstrated that approximately 60% of patients exhibited successful treatment outcomes following the regression of the intra-amniotic inflammatory process or infection. Furthermore, 75% of patients exhibited complete resolution of the infection or inflammation[11]. In our study, all patients with cervical dilatation but prolapsed amniotic membranes or with cervical shortness but no dilatation who had evidence of inflammation on USG findings were started on antibiotherapy, similar to the literature. The lack of amniotic fluid sampling to prove intra-amniotic infection/inflammation is one of the limitations of our study.

Rupture of membranes during the cerclage procedure or in the immediate post-operative period is uncommon in history-based cerclage but is of concern in emergency cerclage. In the absence of perioperative rupture, the risk of PPROM at < 34 gestational weeks may not differ according to the indication for cerclage[22]. In our study, the PPROM (< 32 weeks) complication rate was 25.8% in the cerclage group and 11.1% in the USG indication group according to clinical indication, and no statistically significant difference was observed.

The majority of clinicians avoid performing cerclage after 24 weeks of gestation due to the fact that the majority of data on the efficacy of this procedure are derived from pregnancies that are < 24 weeks in duration. In addition, there is a potential risk of rupture of the fetal membranes, which could result in premature delivery of the baby. Both the SMFM and the International Society of Ultrasound in Obstetrics and Gynecology recommend emergency cerclage in singleton pregnancies with no previous history of spontaneous PTD but with a very short CL (≤ 10 mm) before 24 weeks[23,24]. The findings of our study indicate that emergency cerclage performed by experienced specialists until the 27th week of gestation has a similar effect on prolonging the gestation period. Similarly, the efficacy of cerclage in twin pregnancies remains a topic of debate. However, the findings of our study indicate that cerclage is as effective in twin pregnancies with a short or dilated cervix as in singleton pregnancies. The prospective design of our study, the inclusion of both singleton and twin pregnancies, and the comparison of patients with cervical shortness and cervical dilatation within a single study represent the study's key strengths.

It should be noted that our study is subject to a number of limitations. The present study is limited by its single-center design, the relatively small number of patients included, the absence of a control group, and the exclusion of intraamniotic infection.

Conclusions

In both singleton and twin pregnancies, emergency cerclage between 16 and 27 weeks of gestation in patients with cervical shortening or dehiscence has been demonstrated to prolong the gestation period under appropriate conditions by experienced specialists. Nevertheless, each case should be considered on an individual basis, and the potential risks associated with the procedure should be carefully evaluated.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. Approval was obtained from the Selcuk University Faculty of Medicine Local Ethics Committee (Ethics Committee number: 2023/162, date: March 28, 2023). The consent of the patients was taken before the writing of the manuscript. The study is in accordance with the Declaration of Helsinki.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ARTÍCULO ORIGINAL

Traducción y adaptación cultural al español de la escala IKDC-Subjetiva y la Escala de Actividad de Tegner

Translation and cultural adaptation into spanish of the IKDC-Subjective knee form and Tegner Activity Scale

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Resumen

Objetivo: *Realizar la traducción y adaptación cultural al idioma español de las escalas IKDC-Subjective Knee Form (IKDC-Subjetiva) y Tegner Activity Scale (TAS). Son escalas subjetivas muy relevantes y muy utilizadas, pero no se dispone de su versión en español.* **Métodos:** *Se siguió la metodología ISPOR basada en diez etapas: 1) preparación, 2) traducción directa (dos traducciones del inglés al español), 3) reconciliación (unificación de las dos versiones españolas), 4) traducción inversa (traducción de la versión unificada española al inglés), 5) revisión de la traducción inversa (comparación con la escala original), 6) armonización, 7) prueba de comprensión (valoración de la comprensibilidad con 10 pacientes y 10 médicos), 8) revisión, 9) corrección de errores y 10) informe definitivo.* **Resultados:** *Se ha realizado la traducción y adaptación cultural al idioma español de las escalas IKDC-Subjetiva y TAS. Al comparar la traducción inversa al inglés y la versión original inglesa se observó una completa equivalencia conceptual en todos los ítems. Las pruebas de comprensión de ambas escalas mostraron que todos los ítems presentaban «comprensibilidad clara».* **Conclusiones:** *Al aplicar las escalas IKDC-Subjetiva y TAS a pacientes de habla española es recomendable utilizar la versión en español presentada en este artículo.*

Palabras clave: *Traducción. Adaptación transcultural. IKDC. Tegner. Español.*

Abstract

Objective: *To perform a translation and cultural adaptation into Spanish of the IKDC-Subjective Knee Form and Tegner Activity Score (TAS). They are very relevant and widely used subjective scales, but their Spanish version is not available.* **Methods:** *The ISPOR guide methodology was followed. It is structured in ten stages: 1) preparation, 2) forward translation (two translations from English to Spanish), 3) reconciliation (unification of the two Spanish versions), 4) back translation (translation of the Spanish unified version into English), 5) back translation review (comparison with the original scale), 6) harmonization, 7) cognitive debriefing (assessment of the scale comprehensibility: 10 patients and 10 doctors), 8) review of cognitive debriefing, 9) proofreading, and 10) final report.* **Results:** *The IKDC-Subjective scale and TAS have been translated and culturally adapted into Spanish. When comparing the back translation into English and the original English version, a complete conceptual equivalence was observed in all the items. The comprehension tests of both scales showed that all the items were "clearly comprehensible".* **Conclusions:** *It is recommended to use the current Spanish versions of the IKDC-Subjective knee form and the TAS when applying these scales to Spanish-speaking patients.*

Keywords: *Translation. Cross-cultural adaptation. IKDC. Tegner. Spanish.*

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Introducción

Los resultados reportados por los pacientes, conocidos como PROM *(Patient-Reported Outcome Measure),* son muy importantes para valorar su percepción subjetiva del dolor, la funcionalidad, la calidad de vida y el nivel de actividad en relación a una patología o intervención[1]. Usar escalas traducidas y adaptadas culturalmente siguiendo un método sistemático y validado permite emplear el idioma, los términos y las expresiones más comprensibles para la población a la que se dirige[2].

Existen diversas escalas subjetivas usadas en el ámbito de la patología de rodilla[1]. La *International Knee Documentation Committee Subjective Knee Evaluation Form* (IKDC-Subjetiva) fue creada por un comité internacional de expertos en rodilla en el año 2000[3]. Este PROM específico de rodilla consta de 10 preguntas divididas en tres apartados (síntomas, actividad deportiva y funcionalidad). La IKDC-Subjetiva ha sido validada para una amplia variedad de patologías de rodilla[4,5]. Por otro lado, la *Tegner Activity Scale* (TAS) valora el máximo grado de actividad deportiva o laboral (niveles 0-10) que realiza el paciente[6]. Aunque inicialmente fue diseñada para patología ligamentosa de la rodilla, también ha sido validada para otras lesiones de esta articulación[7,8].

Las escalas IKDC-Subjetiva[9-13] y TAS[14-16] se han traducido a diversos idiomas. A pesar de ser escalas muy utilizadas, no se dispone de una traducción al idioma español realizada siguiendo un método sistemático y validado, y menos aún una adaptación cultural a nuestra población. El objetivo de este estudio fue realizar la traducción y adaptación cultural al idioma español de las escalas IKDC-Subjetiva y TAS.

Métodos

El Comité Ético de Investigación Clínica de nuestro hospital aprobó la realización de este estudio.

Para llevar a cabo la traducción y adaptación transcultural al español se utilizaron las versiones originales de las escalas IKDC-Subjetiva[3] y TAS[6]. Se siguieron la sistemática y las directrices propuestas por la guía ISPOR *(Principles of Good Practice for the Translation and Cultural Adaptation Process for PROMs)*[2], en la que se distinguen 10 etapas (Fig. 1):

1) Preparación: se solicitó permiso al autor (Tegner) para usar su trabajo (TAS), se le invitó a participar en el presente proyecto y nos proporcionó la última versión de la escala. Para el uso de la escala IKDC-Subjetiva, la American Orthopaedic Society for Sports Medicine autoriza su empleo con fines académicos. Durante esta etapa se asignaron las distintas funciones dentro del grupo de trabajo. El autor principal (OP) y el segundo autor (DGM) fueron los guías para la ejecución del trabajo y los mediadores en las discrepancias.
2) Traducción directa: se realizaron dos traducciones independientes del inglés al español para cada escala, para lo cual se contó con dos traductores nativos españoles, uno con experiencia clínica y nivel avanzado de inglés (OP), y el otro con certificado oficial de traducción, pero ajeno a la práctica clínica.
3) Reconciliación: las dos traducciones directas al español de cada escala fueron unificaron por una persona independiente nativa española y con nivel avanzado de inglés (YL), basándose en las recomendaciones recogidas en la guía ISOQOL TCA-SIG[17].
4) Traducción inversa: la versión unificada en español se tradujo de nuevo al inglés por un tercer traductor oficial, nativo inglés y ajeno a la práctica clínica.
5) Revisión de la traducción inversa: los dos autores principales observaron las similitudes y diferencias entre la escala obtenida tras la traducción inversa y la escala original. Se valoró la concordancia de cada ítem entre las dos versiones para aceptarlo como cognitivamente equivalente. En caso de discrepancias, se consultaría a los autores originales su grado de acuerdo respecto a la concordancia.
6) Armonización: la resolución de las discordancias entre las traducciones la realizaron los dos autores principales. Se evaluó la equivalencia conceptual de cada ítem.
7) Prueba de comprensión: se seleccionaron 10 pacientes que acudieron a la consulta externa de la unidad de rodilla de forma consecutiva. Los criterios de inclusión fueron los siguientes: edad > 18 años, patología de rodilla, idioma nativo español y sin deterioro cognitivo. Se les informó sobre el estudio, aceptaron participar y firmaron el consentimiento informado. Los autores principales aplicaron las escalas a estos 10 pacientes, valorando de forma dicotómica la comprensibilidad de cada ítem (claro/confuso) y registrando sus sugerencias para mejorar la

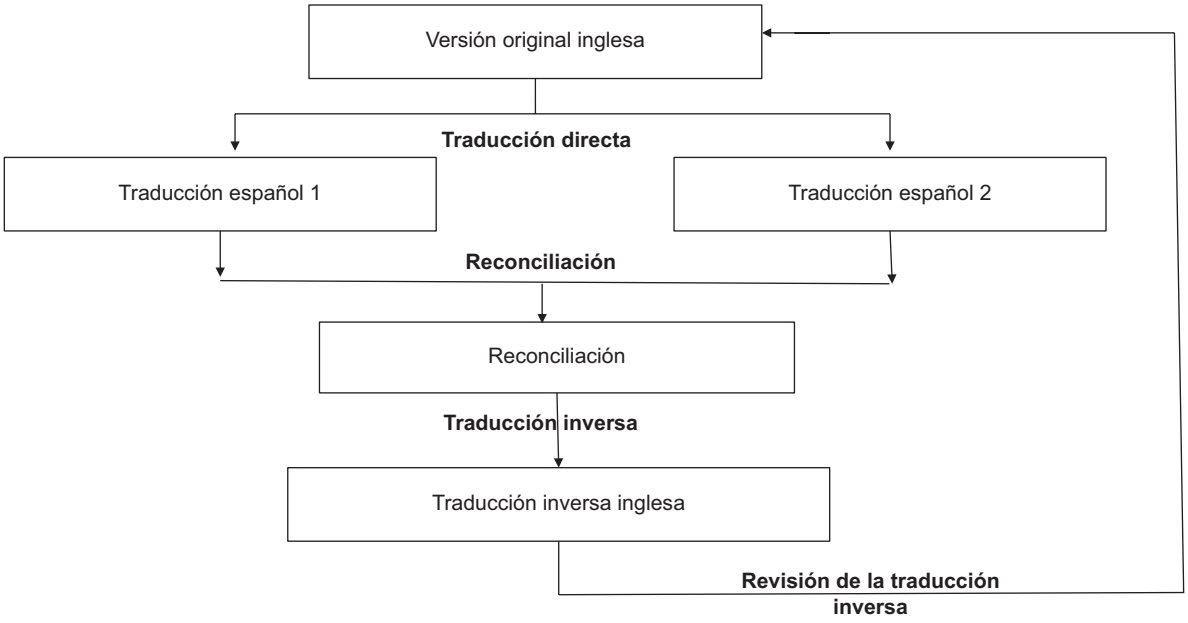

Figura 1. *Resumen esquemático del procedimiento de traducción y adaptación cultural de las escalas siguiendo la metodología propuesta en la guía ISPOR[2].*

comprensibilidad. Por otro lado, se seleccionaron al azar cinco médicos de cirugía ortopédica y traumatología y cinco de medicina física y rehabilitación con idioma nativo español. Mediante un ejercicio de simulación de relación médico-paciente, los autores aplicaron la escala a los médicos. Los autores les interrogaron sobre la comprensibilidad de los ítems (claro/confuso), registraron los aciertos y errores al aplicar la escala, y anotaron sus sugerencias para mejorar la comprensibilidad.

8) Revisión de la prueba de comprensión: los autores principales revisaron los resultados. Para aceptar un ítem como «comprensibilidad clara» es necesaria una tasa de comprensión del 80% o más[18].
9) Corrección de pruebas: se corrigieron los errores, las discrepancias o la falta de concordancia en las traducciones.
10) Informe definitivo: elaboración definitiva de la escala traducida y adaptada culturalmente al idioma español. Redacción del presente trabajo para exponer la metodología seguida y la escala definitiva.

Resultados

Siguiendo la metodología propuesta por la guía ISPOR[2] se obtuvieron las traducciones con adaptación transcultural de las escalas IKDC-Subjetiva (véase Material Suplementario 1) y TAS (véase Material Suplementario 2). Las distintas versiones de las escalas IKDC y TAS (versión original en inglés, traducciones directas en español, versión reconciliada en español y traducción inversa en inglés) se exponen en el Material Suplementario 3 y 4, respectivamente.

Al comparar la traducción inversa al inglés y la versión original se observaron un muy alto grado de similitud y una completa equivalencia conceptual en todos los ítems (Material Suplementario 3 y 4).

Las pruebas de comprensión de las dos escalas se realizaron a 10 pacientes que acudieron a consulta externa de la unidad de rodilla y a 10 médicos (cinco de cirugía ortopédica y traumatología y cinco de medicina física y rehabilitación). Todos los ítems fueron catalogados como «comprensibilidad clara» por el 100% de los pacientes y de los médicos a los que se aplicaron las escalas.

Discusión

El resultado más importante de este trabajo es que hemos realizado la traducción y adaptación cultural al idioma español de las escalas IKDC-Subjetiva y TAS. Para ello, hemos seguido la metodología propuesta por la guía ISPOR[2]. Disponer de una escala traducida y adaptada transculturalmente siguiendo un método sistemático y validado aporta múltiples ventajas. Para el médico, le permite disponer de una

escala fiable y en su idioma de forma rápida, sin tener que realizar traducciones propias. Estas traducciones informales[15], a menudo realizadas de manera no planificada mientras se aplica la escala al paciente, consumen tiempo y requieren esfuerzo. Además, al estar realizadas sin seguir una metodología sistemática, pueden introducir sesgos o errores. En cuanto a la investigación, permite el uso homogéneo de una escala, facilitando la comparación entre estudios. Finalmente, para el paciente, la escala tiene el idioma, los términos y las expresiones más comprensibles para él[2].

Las escalas IKDC-Subjetiva y TAS han sido traducidas a diversos idiomas, pero hasta ahora no se disponía de una versión oficial en español. Al revisar los artículos con traducciones a otros idiomas se puede observar que en la mayoría se ha seguido una metodología sistemática muy similar a la usada por nosotros. Al igual que otros autores, creemos que es clave seguir unas guías estructuradas al realizar una traducción y adaptación cultural (como la guía ISPOR[2] o la de Beaton[19]), con el fin de homogeneizar el proceso de traducción, garantizar un nivel de calidad y limitar los errores.

En nuestro estudio, la etapa de reconciliación se realizó según la guía ISOQOL (International Society for Quality of Life Research). De los 10 ítems de la escala IKDC, ocho presentaron concordancia exacta y uno mostró diferencias leves que no afectaban la comprensión del parámetro. Al referirse a la pregunta 4 («¿Cuán rígida o hinchada ha estado su rodilla?»), el traductor no médico usó la gradación «ninguno, suave, moderado, bastante o extremo», y el médico «nada, leve, moderado, mucho, extremo». En la pregunta 7 hubo diferencias relevantes. Fue traducida por el traductor no médico como «¿Cuál es el máximo nivel de actividad que puede realizar sin sentir que la rodilla cede?» y por el traductor médico como «¿(…) sin sentir la rodilla inestable?». En ambos casos se consideró que la traducción médica refleja de forma más correcta y precisa la información original.

Por otro lado, de los 11 ítems de la escala TAS, cinco presentaron concordancia exacta y seis mostraron diferencias leves. La mayor parte de las diferencias se debieron a las diversas formas de mencionar un deporte. En cada caso se seleccionó la opción considerada más comprensible para la población diana. Por ejemplo, *running on even surface* fue traducido por un traductor de forma literal como «correr en superficie desigual», mientras que el otro lo tradujo como «correr en terreno irregular». Consideramos que era mejor traducción y adaptación la segunda opción. Otra diferencia fue que el término *work,* que aparece en varios parámetros, fue traducido por un traductor como «actividad» y por otro como «trabajo». Se decidió usar el segundo término, ya que se consideró más específico para referirse a «actividad laboral». Se ha usado el título de la escala dado por el traductor médico, «Escala de actividad de Tegner», en lugar del título del traductor no médico, que fue «Puntuación de la escala de Tegner».

Creemos que es importante destacar que en este estudio no solo se realizó una traducción literal, sino también una adaptación cultural. Por ejemplo, la actividad laboral «cuidador de renos» no es aplicable a nuestra sociedad; en su lugar, se usó el término «granjero de grandes mamíferos». Al traducir la escala IKDC al árabe, Ahmed et al.[11] también remarcaron la importancia de realizar una correcta adaptación cultural. Defendieron que la adaptación es necesaria para lograr una equivalencia excelente con la versión original, adoptando los hábitos, la forma de vivir y la manera de expresarse de la sociedad a la que se dirige. Tigerstrand et al.[12], en su traducción al sueco, cambiaron el término *basketball* por *handball* o *floorball,* ya que consideraron que eran deportes más comunes en su país y con similares requerimientos para la rodilla. Asimismo, en la traducción al indonesio, el término *skiing* fue sustituido por «bádminton».

Finalmente, en este estudio se compararon la traducción inversa al inglés realizada por nuestro equipo y la versión original inglesa, y se encontró un muy alto grado de similitud y una completa equivalencia conceptual en todos los ítems. Esta revisión de la traducción inversa permitió comprobar que el procedimiento de traducción se había realizado correctamente y que podíamos usar la versión española. Posteriormente, se realizaron las pruebas de comprensión para asegurar que las escalas eran entendibles tanto para los médicos como para los pacientes. En ambas escalas, el 100% de los ítems fueron catalogados como «comprensibilidad clara».

Conclusiones

Se ha realizado la traducción y adaptación cultural al idioma español de las escalas IKDC-Subjetiva y TAS. Es recomendable utilizar estas dos versiones cuando se quiera utilizar las escalas IKDC-Subjetiva y TAS en población de habla hispana.

Financiamiento

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Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

Consideraciones éticas

Protección de personas y animales. Los autores declaran que los procedimientos seguidos se conformaron a las normas éticas del comité de experimentación humana responsable y de acuerdo con la Asociación Médica Mundial y la Declaración de Helsinki.

Confidencialidad, consentimiento informado y aprobación ética. Los autores han seguido los protocolos de confidencialidad de su institución, han obtenido el consentimiento informado de los pacientes, y cuentan con la aprobación del Comité de Ética. Se han seguido las recomendaciones de las guías SAGER, según la naturaleza del estudio.

Declaración sobre el uso de inteligencia artificial. Los autores declaran que no utilizaron ningún tipo de inteligencia artificial generativa para la redacción de este manuscrito.

Material suplementario

El material suplementario se encuentra disponible en DOI: 10.24875/CIRU.23000460. Este material es provisto por el autor de correspondencia y publicado *online* para el beneficio del lector. El contenido del material suplementario es responsabilidad única de los autores.

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ORIGINAL ARTICLE

Clinical effect analysis of different treatment schemes for children with ulnar and radial double fractures

Análisis del efecto clínico de diferentes esquemas de tratamiento para niños con fracturas dobles cubital y radial

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Abstract

Objective: *The objective of the study is to evaluate the safety and efficacy of three different treatment methods for pediatric ulnar and radial double fractures.* **Methods:** *120 children with ulnar and radial double fractures were included in the study. According to the different treatment plans, children were divided into three groups: manual reduction, splint external fixation, double elastic intramedullary fixation, and double plate fixation. Surgical indicators, radiological results, clinical efficacy, and complications were evaluated and compared among the groups.* **Results:** *The average hospital stay and operation time were significantly longer in the double plate internal fixation group compared to the other two groups. The double elastic intramedullary nailing group showed a higher fracture healing rate at 3 months compared to the other groups. There were no significant differences in clinical efficacy among the three groups. Complications were observed in all groups but did not show significant statistical differences.* **Conclusion:** *Double elastic intramedullary nailing fixation demonstrated favorable outcomes in terms of surgical indicators and fracture healing rates for pediatric ulnar and radial double fractures.*

Keywords: *Pediatric fractures. Ulnar and radial fractures. Treatment methods. Double elastic intramedullary nailing. Clinical outcomes.*

Resumen

Objetivo: *Evaluar la seguridad y eficacia de tres métodos de tratamiento diferentes para las fracturas dobles cubital y radial pediátricas.* **Métodos:** *Se incluyeron en el estudio 120 niños con fracturas dobles de cúbito y radio. Según los diferentes planes de tratamiento, los niños se dividieron en tres grupos: reducción manual, fijación externa con férula, fijación intramedular doble elástica y fijación con doble placa. Se evaluaron y compararon entre los grupos indicadores quirúrgicos, resultados radiológicos, eficacia clínica y complicaciones.* **Resultados:** *La estancia hospitalaria promedio y el tiempo de operación fueron significativamente más prolongados en el grupo de fijación interna con doble placa en comparación con los otros dos grupos. El grupo de clavo intramedular elástico doble mostró una mayor tasa de curación de la fractura a los 3 meses en comparación con los otros grupos. No hubo diferencias significativas en la eficacia clínica entre los tres grupos. Se observaron complicaciones en todos los grupos pero no mostraron diferencias estadísticas significativas.* **Conclusión:** *La fijación con clavo intramedular elástico doble demostró resultados favorables en términos de indicadores quirúrgicos y tasas de curación de fracturas pediátricas dobles cubital y radial.*

Palabras clave: *Fracturas pediátricas. Fracturas cubital y radial. Métodos de tratamiento. Clavado intramedular elástico doble. Resultados clínicos.*

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Introduction

Forearm fractures are the most common injury in children. In particular, forearm shaft fractures are one of the most common injuries in children[1]. Forearm double bone fracture accounts for 3.4% of children's fractures, and upper limb long bone fracture accounts for 26.6%[2]. In most children under the age of 10, forearm fractures can be effectively treated by closed reduction and splinting or gypsum because it has a considerable potential of bone remodeling, although in the case of children over the age of 10, conservative treatment is still a viable option. However, due to the reduced ability of mature bone remodeling, the potential of plaster to repair fracture is low in children aged 10 and in older teenagers[3]. If conservative treatment does not maintain reduction, internal fixation may be needed. It is well known that malunion occurs at a high rate with poor reconstruction of forearm diaphysis fractures[4]. Angular or rotational deformities can result in significantly reduced forearm pronation, especially in older children with bone remodeling potential[5]. Therefore, surgical treatment is required for open fractures with obvious soft tissue injury, unstable fractures with compartment syndrome, and fractures with unacceptable alignment after closed reduction.

At present, there is much debate in the field of pediatric orthopedic surgery. Manual reduction splint external fixation has the advantages of simple operation, low pain, and quick healing, but some unstable fractures have the risk of redisplacement after reduction[6]. Open reduction plate internal fixation can achieve anatomic reduction, but the surgical dissection is large, the incision scar obviously destroys the blood supply of the fracture end, it is easy to cause delayed fracture union or non-union. Closed reduction flexible intramedullary nailing has the advantages of convenient operation, improved appearance, short operation time, stable blood supply to the fracture end, and convenient secondary removal[7]. Closed reduction flexible intramedullary nailing, as a pediatric orthopedic surgical technique, has many advantages, but it also has some drawbacks, such as the requirement for high technical skills and the risk of inadvertent injury to surrounding tissues, nerves, or blood vessels during the nailing process.

The objective of this retrospective cohort study was to evaluate the safety and effectiveness of three different treatment methods, namely manual reduction splint external fixation, double elastic intramedullary nailing, and double steel plate internal fixation, in the management of ulnar and radial double fractures in children aged 3-14 years.

Methods

Study population

The clinical data of 120 children with ulnar and radial double fractures treated by three treatment schemes, including manual reduction and splint external fixation, double elastic intramedullary pin fixation, and double plate fixation, were collected from January 2016 to December 2019 in the Department of Orthopedics of Pediatric Trauma, Zhongshan Hospital affiliated with Dalian University. There were 78 males and 42 females aged from 3 to 14 years old, with an average of 10.6 ± 2.8 years old, and the time from injury to operation was 1-7 days, with an average of 3.5 days. According to different treatment methods, they were divided into 3 groups: manual reduction splint external fixation group (48 cases, Group A). Forty patients (Group B) were treated with double elastic intramedullary nailing fixation. Thirty-two patients (Group C) were treated with double plate fixation. The study was retrospective and was grouped according to the type of surgery. In the sample size calculation, we set the significance level to 0.05, which is the probability threshold for accepting or rejecting the null hypothesis. The effect size was estimated based on previous research and practical considerations. We aimed to detect a moderate effect size and thus chose 0.3 as the effect size. To ensure that the study has the power to detect a true effect, we set the statistical power to 0.8. According to the sample size calculation formula for correlation analysis, we calculated that a minimum sample size of 30 is required.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (i) 3~14 years old; (ii) the fracture was a transverse short oblique or comminuted double fracture of 1/3 of the radius and ulnar bone, either closed or open; (iii) after closed reduction, there were still more than 10 angular or more than 30 rotational deformities; and (iv) The treatment time was 7 days.

The exclusion criteria were as follows: (i) pathological fracture and forearm fracture; (ii) patients with neurovascular injury; (iii) associated wrist fracture dislocation or combination with fractures in other parts; and (iv) incomplete clinical data or loss during

follow-up. This retrospective study was approved by the Ethics Committee of the Affiliated Zhongshan Hospital of Dalian University (No. 6, Jiefang Street, Zhongshan District, Dalian). Informed written consent was obtained from all patients or their guardians.

Surgical method

Gimmick reset splint external fixation (Group A): Intravenous or general anesthesia, limb outreach in the C arm fluoroscopy stage and assistant traction elbow confrontation, easy traction with the forearm and wrist, correct rotating shift, and adoption of the folding roof reset correct before and after the shift. See the fracture under the C arm X-ray perspective, matched to the line. The forearm cotton pads were placed on the dorsal small splint for counter fixation, and then, external fixation was placed on the neutral elbow and wrist splint (Fig. 1, typical case).

Double elastic intramedullary nailing fixation group (Group B): the reduction and fixation under the C-arm fluoroscopy with positioning of the proximal ulna into the needlepoint; the selection of the ulnar olecranon for the lateral incision, ca. 1 cm long, is apart from the epiphyseal plate, 1.5 cm into the needle, and is suitable for the medullary cavity. A mouth opener was inserted into the vertical bone cortex at the lateral proximal end of the Lister tuberosity and gradually tilted 40°~60°. After penetrating the cortex, the head of the nail was inserted into the medullary cavity with a needle holder, and the elastic intramedullary nailing was rotated 180° and gradually advanced along the medullary cavity. Under C-arm fluoroscopy, the fracture end was reduced by a Traditional Chinese osteopath, the fracture end was continued to be advanced to the radial head, and elbow flexion was performed at 90° neutral positions with external fixation of the elbow and wrist plaster (Fig. 2, typical case).

Double plate internal fixation group (Group C): conventional radial dorsal and ulnar approaches were adopted with two incisions of approximately 6-8 cm in length. Reconstruction plate screws were used for fixation. After elbow flexion at the 90° neutral position, external plaster of the elbow and wrist was applied with intravenous antibiotics for 3 days (Fig. 3, typical case).

Intraoperative and post-operative follow-up evaluation

After the operation, the affected limb was suspended with an elbow band, and external fixation was performed with plaster for 4-6 weeks. The tightness of external fixation was adjusted and strengthened in a timely manner in the outpatient clinic every week. Relevant indices were recorded.

Imaging evaluation

After 2 weeks, 4 weeks, 6 weeks, 8 weeks, and 12 months, the outpatient department regularly made follow-up visits and took films. We tentatively defined a fracture healing time over 3 months as “delayed healing” and a fracture healing time over 6 months as “non-healing”[8]. The fracture healing standard was the appearance of a bridging callus in three directions of the bone cortex, which was observed on the anteroposterior and lateral X-ray radiographs without tenderness at the fracture site. The fracture healing rate was recorded at 3 and 6 months to evaluate the wrist joint function according to Berton’s healing evaluation standard[9].

Clinical evaluation

There were regular follow-up visits at 2 weeks, 4 weeks, 6 weeks, 8 weeks, and 12 months after the operation, and the functional recovery of the forearm was checked according to the X-ray review. Grace and Eversman scoring criteria[10] are to evaluate the efficacy of forearm function as follows: excellent: fracture healing, with forearm rotation function greater than 90% of normal, 95~100 points; good: fracture healing, with forearm rotation function greater than 80% of normal, 80~94 points; medium: fracture healing, with forearm rotation function more than 60% of the normal, 60~79 points; and poor: non-union of the fracture or forearm rotation less than 60% of normal, 0-59 points. At the past follow-up visit, we tentatively determined that the pronation or supination angle of the affected forearm was < 10° or more than the rotation angle of the uninjured forearm on the opposite side, which could be considered limited forearm rotation of the affected limb.

Surgical complications

The post-operative complications were recorded.

Statistical analysis

SPSS 23.0 software was used for data analysis. Quantitative data were statistically described by

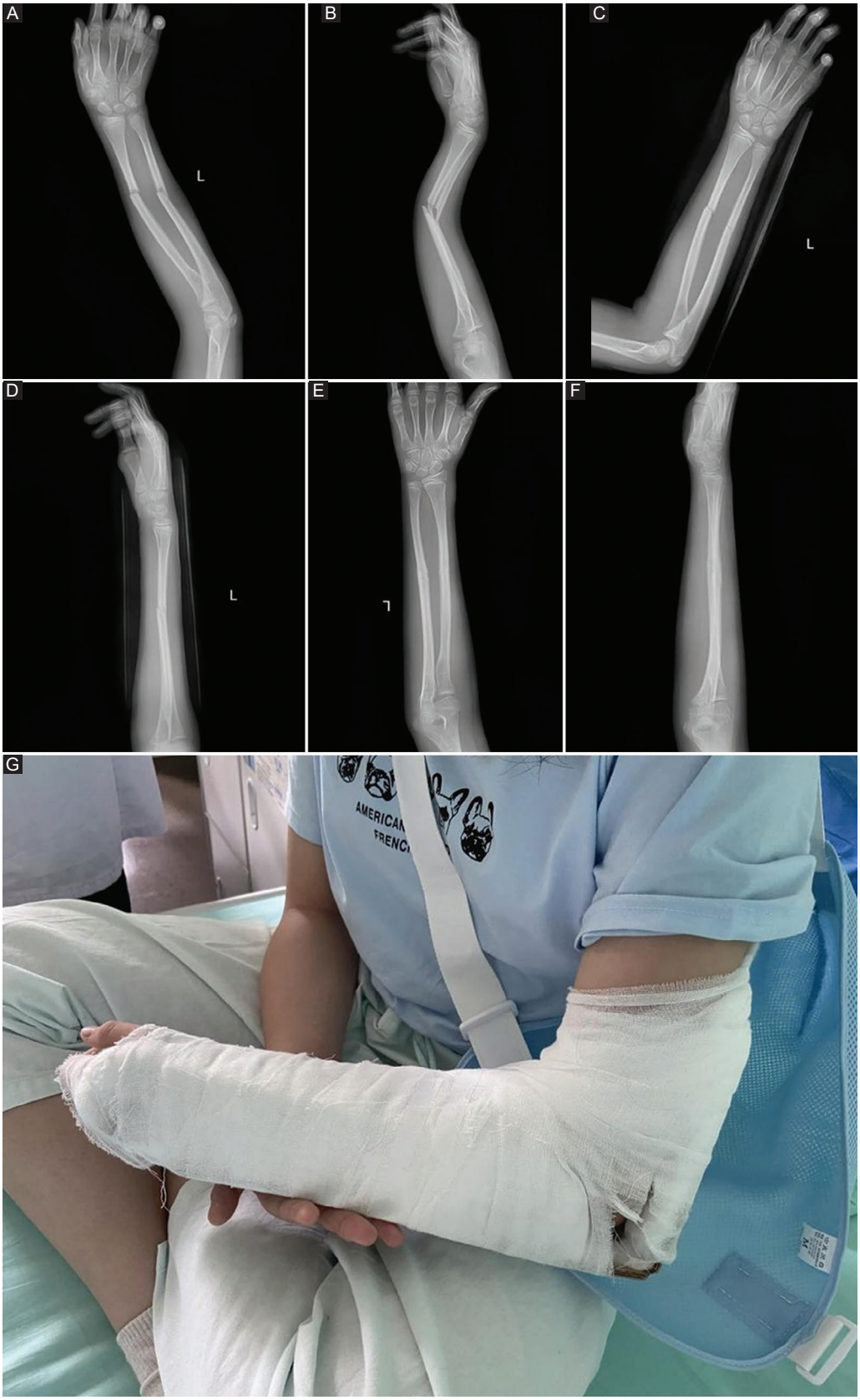

Figure 1. *Female child, 12 years of age, with a running fall causing a double shaft fracture of the left arm.* **A** *and* **B:** *the positive side of the X ray film.* **C** *and* **D:** *after admission, in the C arm machine perspective, with the administration of intravenous anesthesia and reset of the splint by external fixation with the elbow and wrist in neutral position for splint external fixation.* **E** *and* **F:** *splint external fixation for 6 weeks, demolition of the external fixation film and fracture healing;* **G:** *reset cubits. External observation of the wrist in neutral position with splint fixation.*

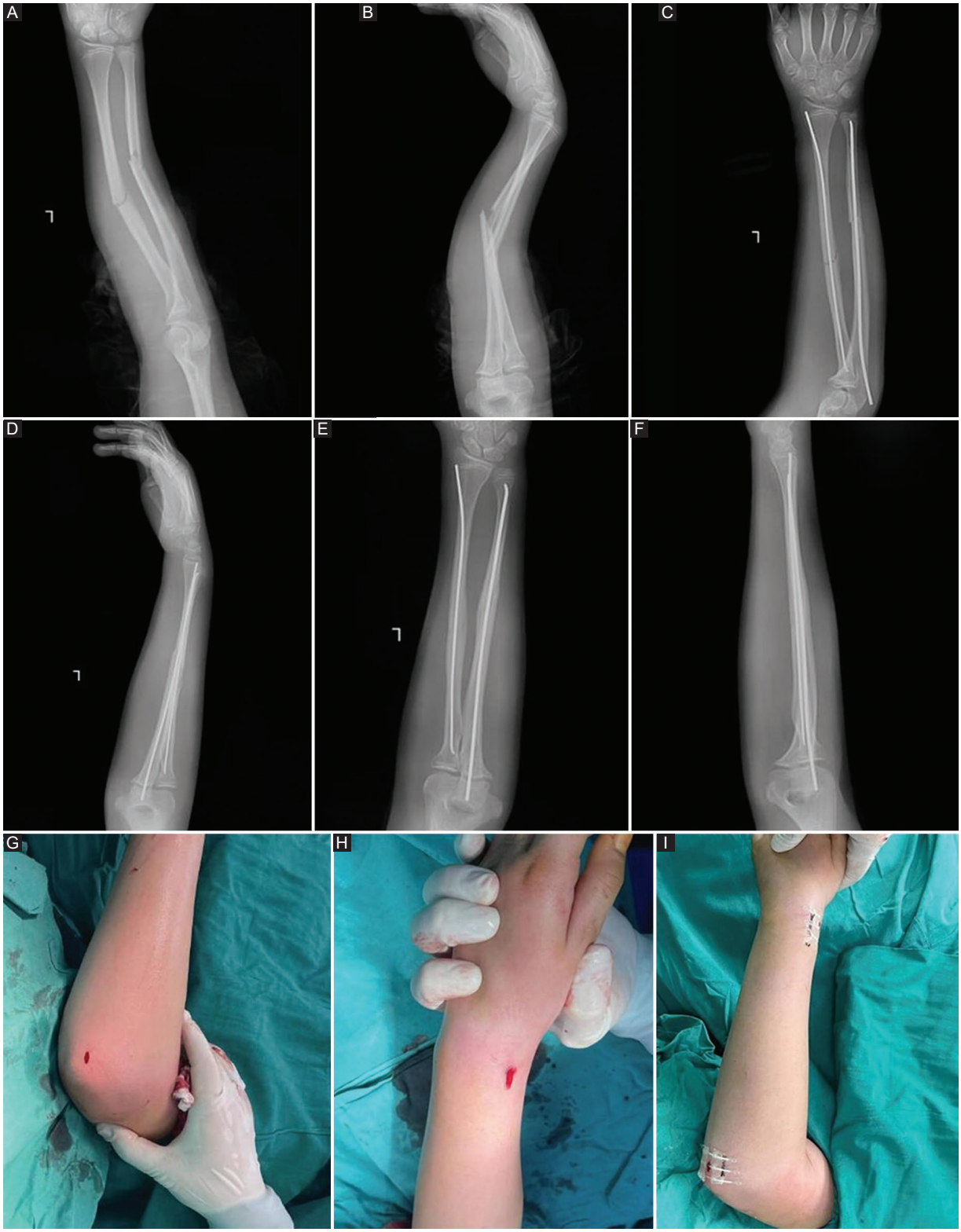

Figure 2. *Fourteen-year-old female child fell while roller skating and sustained a double shaft fracture of the left arm.* **A** *and* **B:** *the positive side of the X ray film.* **C** *and* **D:** *2 days after admission, general anesthesia in the C-arm machine perspective downward with closure by double elastic intramedullary nailing fixation.* **E** *and* **F:** *3 months after the operation, X-ray positive side in fracture healing.* **G-I:** *double elastic intramedullary nailing (post-operative outside view).*

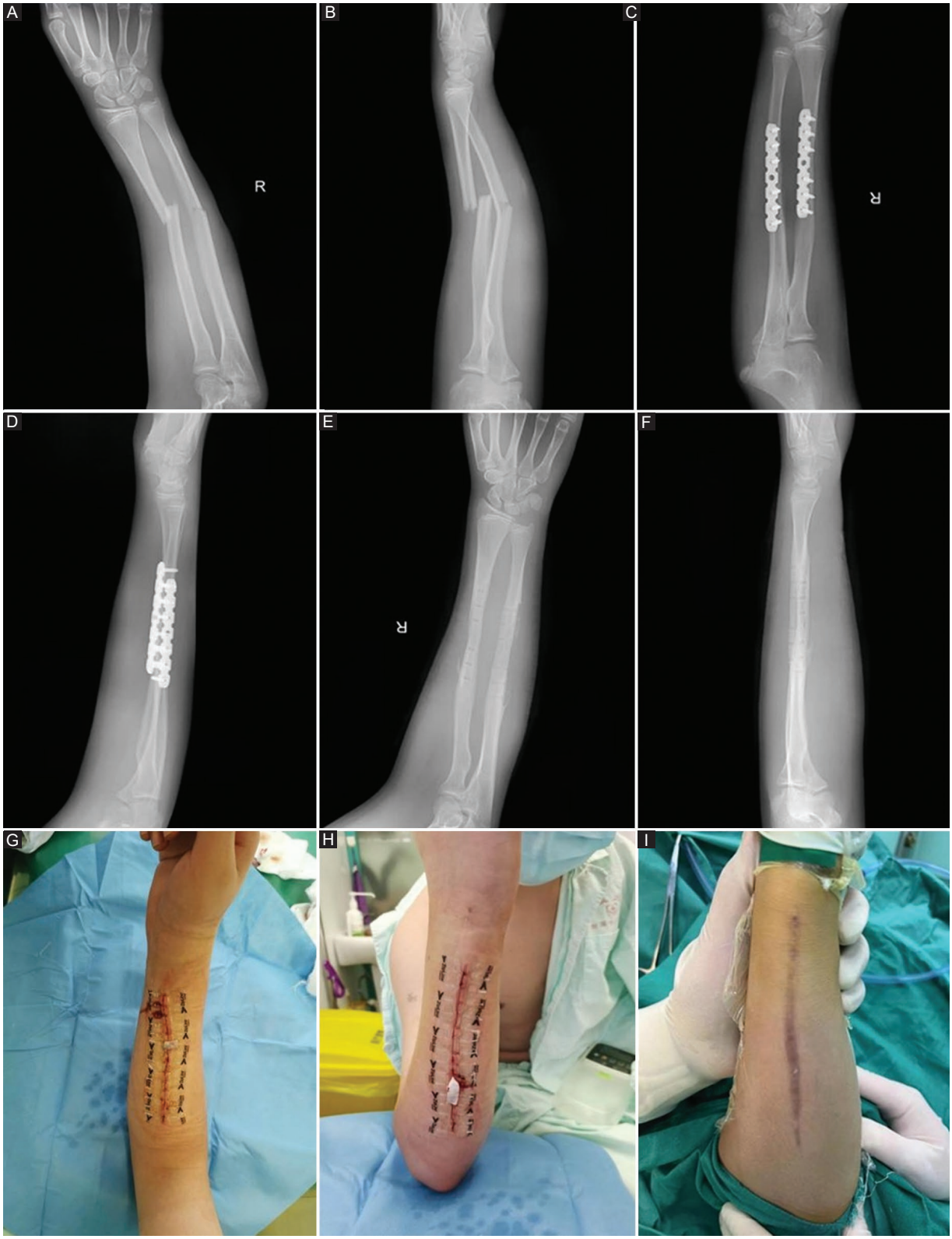

Figure 3. *A 14-year-old male patient suffered a double fracture of the right radial diaphysis caused by a bicycle fall.* **A** *and* **B:** *orthographic and lateral radiographs at the time of injury.* **C** *and* **D:** *on the 2nd day after admission, open reduction and double-plate fixation were performed under general anesthesia.* **E** *and* **F:** *the 2nd year after surgery, he was readmitted to remove the plate internal fixation.* **G-I:** *the scar of the incision before internal fixation and the external observation after operation was removed.*

means ± standard deviation. Differences between the groups were assessed by Student's t-test (two groups) or one-way ANOVA (multiple groups). The count data were expressed as the number of cases/percentage (n/%) and tested by Chi-square test or Fisher exact test. $p < 0.05$ was considered statistically significant.

Results

General Information

There were 75 males and 45 females aged from 3 to 14 years old, with an average of 10.6 ± 2.8 years old. Specific clinical general information for the three groups of patients is presented in Supplementary Table 1. General information did not differ between the three groups and could be used for subsequent comparisons ($p > 0.05$).

Comparison of surgical indicators

Length of hospital stay

There was no significant difference between Group A and Group B ($p > 0.05$). There were statistically significant differences between Groups B and C, and there were statistically significant differences between Groups A and C ($p < 0.05$). Group C had the longest average hospital stay.

Operation time

There was no significant difference between Group A and Group B ($p > 0.05$). There were statistically significant differences between Groups B and C and statistically significant differences between Groups A and C ($p < 0.05$). Group C had the longest average operation time.

Intraoperative blood loss

There was no significant difference between Group A and Group B ($p > 0.05$). There were statistically significant differences between Groups B and C and statistically significant differences between Groups A and C ($p < 0.05$). The average blood loss in Group C was the highest.

Incision length

There was no significant difference between Group A and Group B ($p > 0.05$). There were statistically significant differences between Groups B and C and statistically significant differences between Groups A and C ($p < 0.05$). Group C had the longest average incision length.

Treatment cost

There was no significant difference between Group A and Group B ($p > 0.05$). There were statistically significant differences between Groups B and C and statistically significant differences between Groups A and C ($p < 0.05$). Group C had the highest average treatment cost (Table 1).

Radiological results

Comparison of the fracture union rate 3 months after operation: in Group A, 39 cases had complete fracture union; there were 37 cases of complete union in Group B and 27 cases in Group C. The fracture healing rate of Group B was higher than that of Group A and Group C at 3 months. The difference between Group B and Groups A and C was statistically significant ($p < 0.05$), and there was no significant difference between Group A and Group C ($p > 0.05$) in terms of the number of non-union cases involving ulnar fracture.

Comparison of the fracture union rate 6 months after the operation: there were 47 cases, 40 cases, and 31 cases of fracture union, respectively, among the 3 groups.

Clinical efficacy results

The forearm function of the three groups was evaluated by the Grace and Eversman evaluation criteria at the 3-month follow-up after surgery. The excellent and good rates of Group A, Group B, and Group C were 87.6% (42/48 cases), 97.5% (39/40 cases), and 93.6% (29/32 cases), respectively. According to the Berton healing evaluation standard, the excellent and good rates of Group A, Group B, and Group C were 91.6% (44/48 cases), 95% (38/40 cases), and 93.6% (30/32 cases), respectively. There was no significant difference in the excellent and good rate assessed by the forearm rotation wrist function score among the three groups ($p > 0.05$) (Table 2).

Table 1. Comparison of perioperative data

	Group A	Group B	Group C	χ^2/F value	p
Hospitalization days (day)	3.2 ± 1.2	3.3 ± 1.1	10.6 ± 1.3	6.213	0.001
Operation time (min)	32.1 ± 4.3	35.3 ± 3.5	58.4 ± 5.2	9.942	0.001
Blood loss (mL)	0	5.5 ± 1.1	25.2 ± 9.8	8.652	0.001
Length of incision (cm)	0	1.0 ± 0.3	9.2 ± 1.3	6.431	0.001
Cost of treatment (yuan)	2300 ± 430.3	5000 ± 121.4	18000 ± 200.5	44.252	0.001

Complication results

In Group A, there were 2 children with fracture displacement 2 weeks after surgery, and their families required conservative treatment and finally malunion within the acceptable angle range. There was 1 case of needletail irritation in Group B; 1 case of incision infection in Group C, which was healed by dressing changes; 1 case of delayed healing; and 1 case of refracture, which was healed by iliac bone regrafting. There was no statistical significance in pairings among Groups A, B, and C ($p > 0.05$).

Table 2. Clinical efficacy results of the three groups

Group	Excellent and good rate according to the Berton score (wrist)	Excellent and good rate according to the Grace score
Group A	91. 6% (44/48)	87.6% (42/48)
Group B	95% (38/40)	97.5% (39/40)
Group C	93.6% (30/32)	93.6% (29/32)
χ^2/F value	0.235	0.276
p	0.868	0.967

Discussion

In this study, we conducted a comprehensive evaluation of three different surgical treatment methods for pediatric diaphyseal forearm fractures, focusing on their clinical outcomes and complications. Significant differences were observed among the three groups in terms of surgical indicators, including hospital stay, operation time, intraoperative blood loss, incision length, and treatment cost. Radiographic results also revealed variations in fracture healing rates among the three groups. Furthermore, clinical efficacy assessments demonstrated differences in forearm function evaluations. However, no significant statistical differences were observed in terms of complications.

Forearm fractures in children can be treated with non-surgical methods such as manual reduction splints or plaster external fixation[11]. However, these methods have limitations in achieving anatomical reduction and may result in treatment failure[12]. Surgical intervention is recommended for patients with significant rotation deformities after closed reduction[13,14]. The traditional fixation method is open reduction and plate internal fixation, which can ensure anatomical reduction but has drawbacks such as surgical trauma, increased risk of non-union and infection, and aesthetic concerns[15,16]. Therefore, there is a need for a better fixation method for pediatric forearm shaft fractures.

The application of elastic intramedullary nailing in the fixation of double bone fractures of the forearm in children has shown promising functional and imaging results, making it the preferred method due to its simplicity, minimal damage to the blood supply, esthetic incisions, and easy nail removal[17]. This technique utilizes small incisions and the insertion of elastic nails to provide three-point support within the long bone cavity, maintaining fracture stability[9,18,19]. Closed reduction and elastic intramedullary nailing therapy are designed to cause the foot radius to obtain anatomical reduction that is maintained in the process of healing fracture alignment. Ligier et al.[20] believed that the elasticity of elastic intramedullary nailing could transform shear force into compression force and traction force, thus promoting the formation of early callus. Furlan et al.[21] retrospectively analyzed 175 cases of long bone fracture fixed by elastic intramedullary nailing in 2011, with an average follow-up of 41.3 months. All patients achieved complete union, with an average healing time of 7.5 weeks, and 11 patients (6.3%) had complications. Lu et al.[22] found that elastic intramedullary nail

has multiple advantages of mini-invasiveness, quicker healing, and excellent function recovery in the treatment of both ulna and radius fractures in children. Antabak et al.[23] retrospectively analyzed the efficacy and imaging manifestations of elastic intramedullary nailing for the treatment of double fractures of the forearm diaphysis in children and concluded that elastic intramedullary nailing is an effective technique universally recognized for the fixation of double fractures of the forearm diaphysis in children, which is conducive to the recovery their forearm function. Richter et al.[24] reported that 30 children with forearm fractures were treated with elastic intramedullary nailing, and the results were excellent in 24 cases, good in 5 cases, and moderate in 1 case after 6 months of follow-up. Our study aligns with previous research, demonstrating improved surgical indicators and higher fracture healing rates in the group treated with elastic intramedullary nailing. These findings support the effectiveness of this method in pediatric forearm fractures.

However, it is important to acknowledge the potential complications associated with elastic intramedullary nailing. Although the flexible intramedullary nailing technique has many advantages, such as no injury to the epiphyseal vessels, safety, low infection rate, and convenience for early rehabilitation and exercise, its complications still need to be given attention[25]. Elastic intramedullary nailing can be complicated by wound infection, nerve injury, skin irritation, and refracture, with an average complication rate of approximately 10 to 15%[26]. In our study, we also observed potential complications associated with elastic intramedullary nailing in the treatment of double bone fractures of the forearm in children. Some complications may be attributed to surgeon-related factors, such as poor reduction skills or disruption of the blood supply during open reduction, increasing the risk of delayed union or non-union. Open reduction can also lead to local periosteal destruction, reduced blood supply, and delayed callus formation. Some complications can be attributed to surgical-related factors[27-29].

A single intramedullary nail or open and mixed fixation method has been reported to reduce operative time, fluoroscopy time, and soft tissue dissection. Colaris's study[30] warns against using single-bone fixation in all double-bone fractures of the forearm, as it significantly reduces the operation time. However, this may lead to increased clinical outcomes of redisplacement and may not provide rotational stability. Our study employed experienced traditional Chinese medicine osteosetters who performed closed reduction without compromising the blood supply at the fracture site. Therefore, the duration of surgery and fluoroscopy time should be interpreted in the context of individual surgeon expertise and fracture complexity.

This study has several limitations. First, it adopted a retrospective design, which may introduce recall bias and incomplete information. Second, the sample size was relatively small, which may affect the reliability and generalizability of the results. Third, the study only included data from one hospital, which may limit the generalizability of the findings due to regional and institutional differences. Finally, the study did not consider individual differences and pre-operative conditions that may influence treatment outcomes, which could have an impact on the results.

Conclusions

Double elastic intramedullary nailing fixation shows favorable outcomes in terms of surgical indicators and fracture healing rates for ulnar and radial double fractures in children aged 3 to 14 years. These findings provide important guidance for clinicians in selecting appropriate surgical treatment methods.

Acknowledgments

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Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human and animal subjects. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's

confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

Supplementary data

Supplementary data are available at DOI: 10.24875/CIRU.23000426. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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ORIGINAL ARTICLE

Surgical interventıons to save autogenic dialysis access in aneurysmal arteriovenous fistulas

Intervenciones quirúrgicas para salvar el acceso autogénico de diálisis en las fístulas arteriovenosas aneurismáticas

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Abstract

Objective: *The aim is to share our surgical approaches for the removal of aneurysmatic dilatation by preserving the vascular access pathway in aneurysmatic arteriovenous fistulas (AVF).* **Methods:** *This study includes patients were admitted between September 2017 and May 2022 and were found to have true aneurysms in their upper extremity AVF. Patients were treated with partial aneurysmectomy combined with aneurysmorrhaphy or autologous vein graft interposition after total aneurysmectomy.* **Results:** *Six patients who underwent aneurysmoraphy after partial aneurysmectomy were named Group I. The mean age of the patients was 49, and the aneurysm diameter was 4.1 cm. 14 patients who underwent autologous vein interposition after aneurysmectomy were named Group II. The mean age of the patients was 58, and the aneurysm diameter was 4.4 cm. 13 patients met the need for hemodialysis with new AVF within 31 days (± 4-11 days). Due to the detection of insufficient post-operative flow in 1 patient (flow rate 180-200 mL/min) was taken to dialysis with alternative accesses.* **Conclusion:** *In AVF aneurysms, it is possible to save the vascular access path with surgical treatments applied under elective conditions.*

Keywords: *Arteriovenous fistulas. Aneurysm. Aneurysmectomy. Aneurysmorrhaphy. Graft vein interposition.*

Resumen

Objetivo: *Compartir nuestros abordajes quirúrgicos para la remoción de dilataciones aneurismáticas en fístulas arteriovenosas, preservando la vía de acceso vascular.* **Métodos:** *El estudio incluyó pacientes ingresados entre septiembre de 2017 y mayo de 2022, con aneurismas verdaderos en fístulas arteriovenosas de las extremidades superiores. Los pacientes fueron tratados mediante aneurismectomía parcial combinada con aneurismorrafia o interposición de injerto venoso autólogo después de la aneurismectomía total.* **Resultados:** *Se dividió a los pacientes en dos grupos. El grupo I consistió en 6 pacientes a quienes se realizó aneurismorrafia después de aneurismectomía parcial; la edad promedio fue de 49 años y el diámetro del aneurisma fue de 4.1 cm. El grupo II incluyó 14 pacientes que se sometieron a interposición de injerto venoso autólogo después de la aneurismectomía; la edad promedio fue de 58 años y el diámetro del aneurisma fue de 4.4 cm. Trece pacientes pudieron someterse a hemodiálisis mediante una nueva fístula arteriovenosa dentro de los 31 días (± 4-11 días). En un caso, debido a un flujo posoperatorio insuficiente (180-200 mL/min), se utilizó un acceso alternativo para la diálisis.* **Conclusiones:** *Es posible preservar la vía de acceso vascular en los aneurismas de fístula arteriovenosa mediante tratamiento quirúrgico en condiciones electivas.*

Palabras clave: *Fístulas arteriovenosas. Aneurisma. Aneurismectomía. Aneurismorrafia. Interposición de injerto venoso.*

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Introduction

Chronic kidney disease refers to progressive loss of kidney function, characterized by kidney damage or an estimated glomerular filtration rate of < 60 mL/min/1.73 m^2 for a duration of 3 months or more, eventually leading to the need for dialysis or transplantation[1]. Arteriovenous fistulas (AVFs) created for hemodialysis purposes are considered the optimal vascular access route[2]. Compared to arteriovenous grafts and catheters used for hemodialysis, AVFs have longer patency and lower complication rates[3]. However, AVFs can be associated with life-threatening bleeding resulting from aneurysmal dilatation, which can occur in up to 60% of cases regardless of the duration of use[4] (Fig. 1). In cases where an aneurysm leads to bleeding, surgical approaches or endovascular methods are commonly employed to control the life-threatening bleeding, often resulting in the removal of the AVF[5,6].

In cases of aneurysms arising from AVF procedures, the continuity of the vascular access pathway and prevention of functional loss can be achieved by electively performing partial resection of the excessive wall of the aneurysm while preserving the wall integrity (aneurysmorraphy)[7]. Another surgical approach under elective conditions may involve aneurysmectomy and autologous venous graft interposition to ensure functional continuity of the vascular access pathway[8].

Methods

Patients

In the retrospective study conducted between September 2017 and May 2022, a total of 20 patients were included in the study. Among them, six patients who underwent partial aneurysmectomy with subsequent aneurysmorraphy for maintaining fistula continuity, and 14 patients who underwent aneurysmectomy with autologous venous graft for maintaining fistula continuity, were included in the study.

Patients with central venous obstructive lesions requiring separate treatment and potentially affecting access patency, those with central venous stenosis or occlusion requiring emergency surgery due to aneurysm rupture, and those with pseudoaneurysms were excluded from the study. Surgical repair indications were determined as thinning or erosion of the skin due to aneurysm, inability to meet dialysis needs, or high blood flow (> 1,500 mL/min). Informed consent forms were obtained from all patients and their families before the surgery.

Ethical consideration

This retrospective study was carried out after the approval of the Hatay Mustafa Kemal Universty Tayfur Ata Sökmen Medical Faculty Ethics Committee (Decision number: 15/Date: May 12, 2022). The hospital authority accepted the study results.

Pre-operative examination

Demographic data for all patients and the results of Doppler ultrasound examinations for all patients were retrospectively extracted from hospital records before the surgery. Aneurysms at the arteriovenous access site were defined as having a diameter larger than 20 mm. Temporary dialysis catheters were placed in all patients scheduled for surgery using the contralateral jugular vein.

Surgical procedure

Except for one patient (a 13-year-old male whose family declined regional block application), all patients who underwent aneurysmorraphy after partial aneurysmectomy were operated under regional block. The block procedure was performed under ultrasound guidance by the anesthesia unit. First, the extension of the aneurysm was determined using Doppler ultrasound, and then a skin incision was made. Healthy venous segments were prepared on both boundaries of the aneurysmatic segment. Heparin (100 units/kg) was administered intravenously. Following proximal and distal clamping, the aneurysm sac was longitudinally incised, and the lumen was irrigated with heparinized saline solution. The thrombus-adherent aneurysmal wall was partially resected. To guide aneurysmorraphy and prevent stenosis, arterial diameter measurement was performed, and a sterile dilatation bougie of 10-12 mm was inserted. The venous lumen was reduced and closed using non-absorbable polypropylene sutures of 6-0/13 mm. The clamps were released to restore blood flow. Excess skin was removed by cutting from both sides of the skin incision (Fig. 2). No adjuvant medical treatment was applied to increase the patency of the AVF.

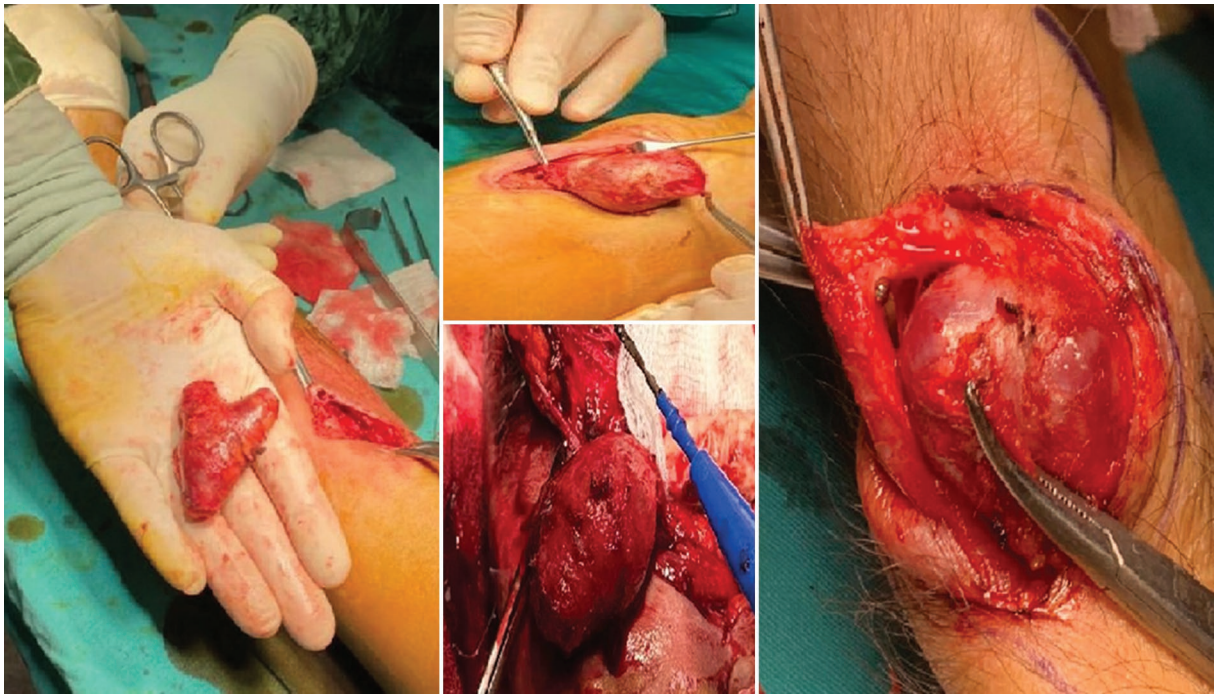

Figure 1. *Huge aneurysmal dilatation of arteriovenous fistulas.*

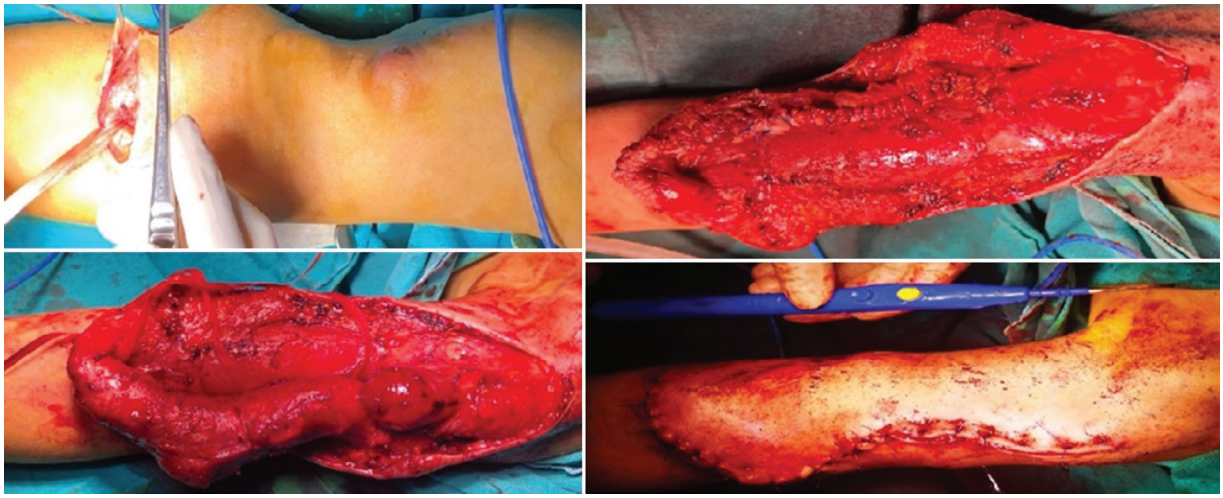

Figure 2. *Preparation of aneurysmatic segment of arteriovenous fistulas and closed skin after skin excision.*

For patients planned for autologous venous interposition after aneurysmectomy, pre-operative evaluation of the great saphenous vein was performed in the operating room conditions using Doppler ultrasound. All patients were operated under general anesthesia. First, the extension of the aneurysm was determined using Doppler ultrasound, and then a skin incision was made. Healthy venous segments were prepared on both boundaries of the aneurysmatic segment. After measuring the aneurysmatic segment with a sterile ruler, the autologous saphenous vein graft was harvested at an appropriate length. No hemoclips were used on the graft side. The branches of the venous graft were ligated using 3-0 silk sutures. Heparin (100 units/kg) was administered intravenously. After clamping, aneurysmectomy was performed. The autologous saphenous graft was anastomosed in the appropriate shape with non-absorbable polypropylene

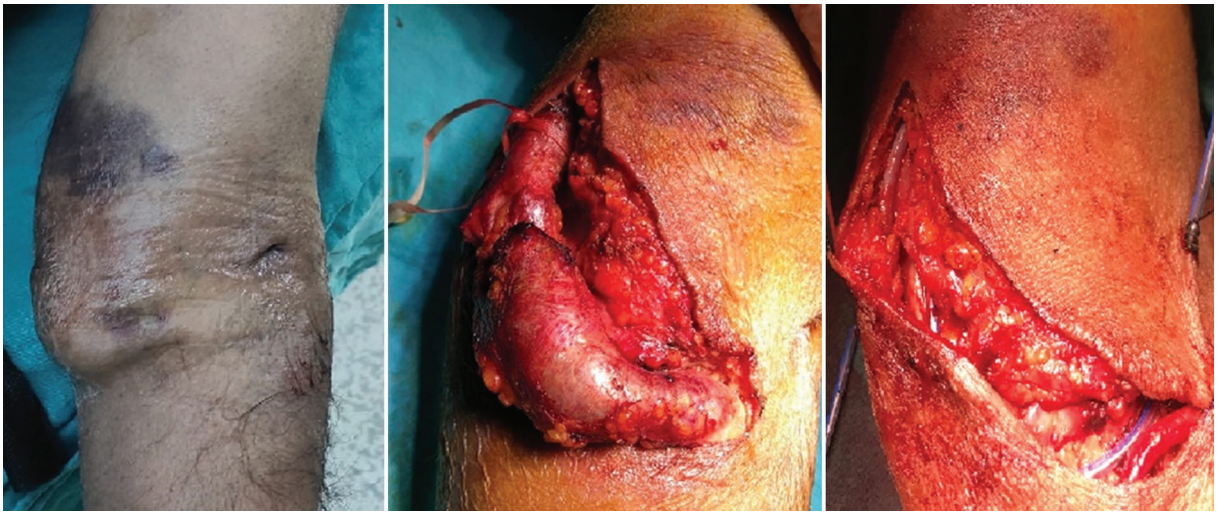

Figure 3. *Autologous venous interposition after aneurysmectomy.*

sutures of 6-0/13 mm in the direction of flow. The clamps were released to restore blood flow. Excess skin was removed by cutting from both sides of the skin incision (Fig. 3). No adjuvant medical treatment was applied to increase the patency of the AVF.

Follow-up

All patients were followed up for a period of 1 month. During this 1-month period, patients underwent hemodialysis with a temporary dialysis catheter. Primary patency was defined as the time from the moment of surgical procedure to the first hemodialysis session occurring within 1 month. Before the first hemodialysis session following the surgical procedure, patients underwent flow measurement using Doppler ultrasound based on clinical memory. In cases where there was suspicion of residual aneurysm or proximal stenosis, intraluminal angiographic imaging was planned.

Statistical analysis

The data were presented as means and standard deviations for continuous variables and as patient counts and percentages for categorical variables. Statistical analysis was performed using IBM Statistical Package for the Social Sciences Statistics version 21.0 software (IBM Corp., Armonk, NY). Comparison of means of continuous variables between the two groups was performed using t-test, and differences were considered significant at a probability level of $p < 0.05$.

Results

In Group I, which consisted of six patients who underwent aneurysmorrhaphy after partial aneurysmectomy, the median age was 49 (13-62 years). The patients had been using the same vascular access for hemodialysis for an average of 13.1 ± 5.2 years. The mean aneurysm diameter in Group I was measured as 4.1 (± 1.8) cm. Five patients in Group I had a history of multiple AVF access pathways. The 13-year-old male patient had a previous AVF access history. One patient, a 37-year-old male, was taken to the emergency operating room due to hemorrhage 2 h after the operation. The bleeding from the aneurysmorrhaphy site was repaired using absorbable polypropylene sutures (6-0/13 mm), and hemostasis was achieved. All Group I patients were able to undergo dialysis through the newly salvaged access pathway for hemodialysis at 30 days. As no findings suggestive of residual aneurysm or proximal stenosis were detected in any of the patients, angiographic imaging was not performed.

In Group II, which consisted of 14 patients who underwent autologous venous interposition after aneurysmectomy, the median age was 58 (49-67 years). The patients had been using the same vascular access for hemodialysis for an average of 9.7 ± 7.6 years. The mean aneurysm diameter in Group II was measured as 4.4 (± 1.7) cm. All Group II patients had a history of multiple AVF access pathways. Two patients, one male, and one female, were taken to the emergency operating room within the first 24 h

postoperatively due to hemorrhage. It was determined that the bleeding was not related to the anastomosis line but originated from the excised surrounding tissues of the aneurysm sac, and hemostasis was achieved. Among the 13 patients in Group II, hemodialysis needs were met with a new AVF within 30 days (± 4-11 days). One patient was switched to alternative AVF routes for dialysis at the 4th week postoperatively due to an ultrasound evaluation indicating a flow rate of 180-200 mL/min. In another patient, upper extremity edema occurred after the surgical procedure, and intraluminal angiographic imaging was performed due to suspicion of proximal stenosis. However, no stenosis or residual aneurysm was found.

Discussion

Chronic kidney failure is being increasingly diagnosed at a high frequency[8]. Hemodialysis, peritoneal dialysis, and kidney transplantation are essential lifesaving interventions for patients diagnosed with chronic kidney failure[9]. The number of patients requiring kidney transplantation is increasing at a faster rate than the number of available donors, resulting in wait times of up to 4 years for kidney transplantation[10,11].

According to the guidelines for the diagnosis and treatment of chronic kidney failure, approximately 65% of diagnosed patients require AVF for hemodialysis[12]. Although AVF is the most commonly preferred method for hemodialysis, complications such as aneurysm formation, neurological disorders, and vascular steal syndrome are known to occur[13].

The occurrence of true or false aneurysmal dilation in AVFs is a frequently observed condition[14-16]. In cases where an aneurysm ruptures and starts bleeding profusely, urgent surgical or endovascular intervention is necessary to manage life-threatening hemorrhage[17]. While endovascular methods may successfully eliminate the aneurysm and maintain the continuity of the vascular access pathway dependent on the presence of a stent graft, they may restrict needle access[5]. Although ligation may be life-saving in situations where hemorrhage poses a threat to life, it can result in permanent loss of vascular access pathway[18]. While there is no standardized treatment method for complications associated with AVFs, guidelines recommend preserving the vascular access pathway[5,18,19]. Various aneurysmorrhaphy techniques, including partial aneurysmectomy and autologous venous graft interposition, aim to eliminate the aneurysm while preserving the vascular access pathway[19,20]. There are studies demonstrating the safety and long-term outcomes of the combination of partial aneurysmectomy and aneurysmorrhaphy[21,22]. However, there are no clinical studies comparing the effectiveness and safety of surgical approaches in the treatment of AVF-related aneurysms. Although there is no standard method selection guideline, it is recommended to preserve the vascular access pathway, and if a suitable autologous venous graft is not identified during intraoperative Doppler ultrasound screening, partial aneurysmectomy, and longitudinal aneurysmorrhaphy with prolene are performed. In cases of upper extremity autologous fistula aneurysms, 20 patients were treated with surgical methods in this study series, and technical success was achieved in all patients at the time of the procedure.

Limitations

Although the short follow-up period and numerical imbalance between the groups included in the study are among the limitations of the study, sharing the results without conducting a comparative analysis between the groups eliminates the statistical flaw.

Conclusion

The diagnosis and treatment guidelines for chronic kidney failure recommend intervention for aneurysmal dilations that arise from the use of AVFs, but there is no standardized treatment method. With this study, we aimed to share the early-term outcomes of the two different approaches we implemented. The medium and long-term follow-up results of the surgical methods we applied will guide us in selecting the appropriate method for the future.

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Conflicts of interest

The authors declare no conflicts of interest in this study.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Multilayer flow modulator stents in aortic aneurysms: an overview based on preliminary experience

Stents moduladores de flujo multicapa en aneurismas aórticos toracoabdominales: una descripción basada en experiencia preliminar

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Abstract

Objective: *Analyze the approach of the multilayer flow modulator (MFM) based on the results obtained in patients treated with Stena MFM® (S-MFM).* **Methods***: It was evaluated 6-month follow-up outcomes of 12 patients (nine men and three females; mean age 60 years, range 34-79 years) underwent aneurysm repair with the S-MFM between July 2022 and December 2022. All patients undergoing S-MFM were patients at high risk of mortality and/or morbidity for open surgical repair and endovascular aneurysm repair, including thoracic Endovascular Aortic Repair (TEVAR) or fenestrated endovascular aortic repair (FEVAR).* **Results:** *The control angiograms confirmed successful patency in the lumen of the main aorta and the branches in all cases. Complete aneurysm thrombosis was detected in all patients on computed tomography angiography at 6-month follow-up. The technical success was 100%, and no case required immediate intervention. Significant complications, such as ruptures, stent migrations, retractions, thrombosis, fractures were not observed.* **Conclusions:** *The present data show the MFM approach may be an attractive alternative for complex aortic aneurysms. While it shrinks the aneurysm sac and protects the side branch blood flow, it reduces mortality and morbidity risks.*

Keywords: *Aortic aneurysm. Multilayer flow modulator. Peripheral arterial diseases.*

Resumen

Objetivo: *Analizar el enfoque del modulador de flujo multicapa basándose en nuestros resultados en pacientes tratados con Stena Multilayer Flow Modulator® (S-MFM).* **Métodos:** *Se evaluaron los resultados del seguimiento a 6 meses de 12 pacientes (9 hombres y 3 mujeres; edad promedio 60 años, rango 34-79 años) sometidos a reparación de aneurisma con S-MFM entre julio de 2022 y diciembre de 2022. Todos los pacientes que recibieron S-MFM eran de alto riesgo de mortalidad o morbilidad para reparación quirúrgica abierta y reparación endovascular, incluyendo reparación aórtica endovascular torácica (TEVAR) o reparación aórtica endovascular fenestrada (FEVAR).* **Resultados:** *Las angiografías de control confirmaron la permeabilidad exitosa en la luz de la aorta principal y las ramas en todos los casos. En el seguimiento de 6 meses, en la angiografía por tomografía computarizada se detectó trombosis completa del aneurisma en todos los pacientes. El éxito técnico fue del 100% y ningún caso requirió intervención inmediata. No se observaron complicaciones importantes, como roturas, migraciones del stent, retracciones, trombosis o fracturas.* **Conclusiones:** *Los datos actuales muestran que el enfoque del modulador de flujo multicapa puede ser una alternativa atractiva para los aneurismas aórticos complejos. Si bien encoge el saco del aneurisma y protege el flujo sanguíneo de la rama lateral, reduce los riesgos de mortalidad y morbilidad.*

Palabras clave: *Aneurisma aórtico. Modulador de flujo multicapa. Enfermedades arteriales periféricas.*

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Introduction

The aortic aneurysm (AA), which is locally caused by weakening and dilation of the aortic wall, remains a major public health problem in the world[1]. Although most patients with aneurysms usually do not have symptoms, the aneurysm can be fatal in up to 80% of cases when the aneurysm ruptures[2]. Currently there is no drug therapy to limit the progression of AA and continues to challenge clinicians around the world[1,3]. Efforts to reduce the clinical problems associated with AA have focused on early detection and subsequently improved surgical management. For more than 40 years, the conventional approach has been open surgical repair, which is replacement of the aneurysmal aortic segment with a synthetic graft, although it is associated with high morbidity and mortality[3].

In recent decades, endovascular aneurysm repair (EVAR) has rapidly become the main treatment option due to the significant reduction in mortality rate and shorter hospital stay, recovery, and return to basic functional capacity compared to open surgical repair[2,4]. In this methodology, the stent grafts are placed within the aneurysmal sac with proximal and distal fixation to healthy arterial segments[3]. Several EVAR approaches, including endovascular thoracic aortic repair (TEVAR), have been validated as safe and feasible strategies for patients with favorable aortic anatomy[5].

Unfortunately, it is not possible to apply EVAR or TEVAR procedures in complex aneurysms involving some important side branches. Treatment options for these conditions have been greatly expanded with windowed EVAR (FEVAR), branched EVAR, and chimney-EVAR. However, their application is hampered by high costs and the need for individual customization, which leads to delays in the manufacture and planning of devices. For this reason, its use is limited and is not particularly suitable for emergencies[6,7].

In this context, the multilayer flow modulator (MFM) has recently been developed and entered clinical practice. The concept is based on hemodynamic principles and stents act as a flow modulator both to maintain side branch perfusion and to reduce the flow velocity vortex and allow thrombosis within the aneurysm[8,9]. Since MFM devices placed in the aorta usually involve the aortic branches, it is crucial to maintain branch perfusion. It is easier to apply and does not require specific preparation from the patient[10].

This article gives an overview of the MFM based on the results of 12 patients treated with Stena-MFM® (S-MFM), a partially new product from Invamed (Ankara, Turkey). The published literature in this area has also been reviewed.

Methods

From July 2022 to December 2022, twelve patients (nine men and three females; mean age 60 years, range 34-79 years) from two different centers (in the cardiovascular departments of Meram and Mustafa Kemal hospitals, Turkey), underwent aneurysm repair with the S-MFM. Written informed consent was obtained from all participants, in accordance with the principles of the Declaration of Helsinki[11].

The number of patients treated in the centers, excluding the MFM procedure, is 215. Some of these patients were treated using open surgery and some using classical endovascular methods.

Ethics committee approval for this study was received from Hatay Mustafa Kemal University Local Ethics Committee (meeting date: March 17, 2022, decision no: 09).

Technical considerations for S-MFM

The S-MFM® is a knitted 5-layer tubular mesh stent made of a super-elastic biomedical metal alloy. Its self-expanding property makes the stent flexible and adaptable to the target area. It eliminates the need to individualize and subsequently make the S-MFM ready for use regardless of the vascular nature of the patient.

The multilayer braided design and low profile ensure extra durability. Its widened ends provide support compatibility with the aortic wall and optimal sealing at the proximal and distal descent sites, preventing the risk of type I and III leaks. There are also radiopaque tantalum markers at both ends to increase traceability.

The stent sizes are prepared in different models with a diameter of 25-45 mm and a length of 80-200 mm. The delivery system is compatible with 0.035” guide wire. The distribution system is compatible with 0.035” guide wire with a diameter of 18F-20F and a length of 100 cm. The Y sheath is attached to the pusher. The sheath locks into the holder when tightened to prevent premature activation of the multilayer system.

Characteristics of the patient and procedural aspects

All patients undergoing S-MFM were patients at high risk of mortality and/or morbidity for open surgical

repair and EVAR, including TEVAR or FEVAR. All patients underwent a pre-operative diagnostic study, including total aortic contrast computed tomography (CT) scans reconstructed from 1mm axial slices. In this way, the diameters and lengths of the aneurysms and landing zones and all aortic branches were evaluated in terms of the extent of any narrowing.

S-MFM interventions were performed under endotracheal general anesthesia with continuous invasive blood pressure monitoring. Depending on the patient, a combination of percutaneous femoral access with a closure device and surgical access was used. In all cases, S-MFMs were introduced under systemic heparinization through an 18F and 20F introducer inserted into the right femoral artery. To cross the artery, a 0.035-inch hydrophilic guidewire was used (Inwire, Invamed, Ankara, Turkey). Control angiograms were performed using a 5F graduated pigtail catheter through the left femoral artery. S-MFM sizing was meticulously selected, taking into account 15-25% oversizing compared to the native aortic diameter, regardless of the diameter of the aneurysm. Vascular closure device (AngioTEN, Invamed, Ankara, Turkey) was used to close the femoral artery puncture in all cases.

Technical success was defined as successful insertion and placement of the S-MFM without additional surgical intervention or mortality during the procedure or within the first 24 h after the procedure. The absence of significant kinks, twists, or obstruction was considered a marker of successful stent deployment.

For the present preliminary cases, post-operative CT angiography follow-up was planned at the 6th month. At the end of the 6th month, the maximum diameter of the sac was measured in the stretch images and the volumes of the aneurysms, including the thrombi, were calculated using a special vascular analysis software package according to the European Society of Cardiology guidelines[12]. All procedures were performed in accordance with established best practices and protocols.

Table 1 summarizes the characteristics of the aneurysm, the location of the S-MFM stents placed for each case, and the percentages of proximal and distal oversize.

Table 1. Outlined characteristics of aneurysms and stents

Case #	Size and localization in aorta	Stent site	Oversizing (%)
1	55 mm, Crawford type 1	Arcus aorta	Proximal: 20 Distal: 15
2	59 mm, Crawford type 4	Abdominal aorta	Proximal: 20 Distal: 20
3	56 mm, Crawford type 2	Thoracic abdominal aorta	Proximal: 20 Distal: 15
4	57 mm, Crawford type 1	Arcus aorta	Proximal: 22 Distal: 15
5	60 mm, Crawford type 2	Arcus aorta	Proximal: 20 Distal: 15
6	60 mm, Crawford type 4	Abdominal aorta	Proximal: 20 Distal: 15
7	55 mm, Crawford type 3	Thoracic abdominal aorta	Proximal: 20 Distal: 20
8	59 mm, Crawford type 4	Abdominal aorta	Proximal: 25 Distal: 15
9	78 mm, Crawford type 3	Thoracic abdominal aorta	Proximal: 20 Distal: 20
10	57 mm, Crawford type 4	Abdominal aorta	Proximal: 20 Distal: 15
11	65 mm, Crawford type 4	Abdominal aorta	Proximal: 25 Distal: 20
12	55 mm, Crawford type 2	Arcus aorta	Proximal: 20 Distal: 15

mm: millimeter.

Results

In all cases, the control angiograms confirmed normal patency of the aorta and S-MFM, and all overstented branch arteries remained patent without recorded ischemic events (Fig. 1).

Complete aneurysm thrombosis was detected in all patients on CT angiography at 6-month follow-up. The volume of the aneurysm sac was found to be slightly reduced in all cases, with an overall mean of 2.36% (Table 2 and Fig. 2).

Significant complications, such as ruptures, stent migrations, retractions, thrombosis, and fractures were not observed during this period. None of the cases required immediate intervention. The placement of S-MSM was technically successful in all patients. No endoleak (type I) associated with incomplete or ineffective placement of the stent at the proximal and distal ends was observed.

As summarized in table 3, the key metrics, such as the duration of the procedure and fluoroscopy, blood loss, and contrast volume were consistent with established standards[13].

The vascular surgeons mentioned in the study participated in the procedures and the most important

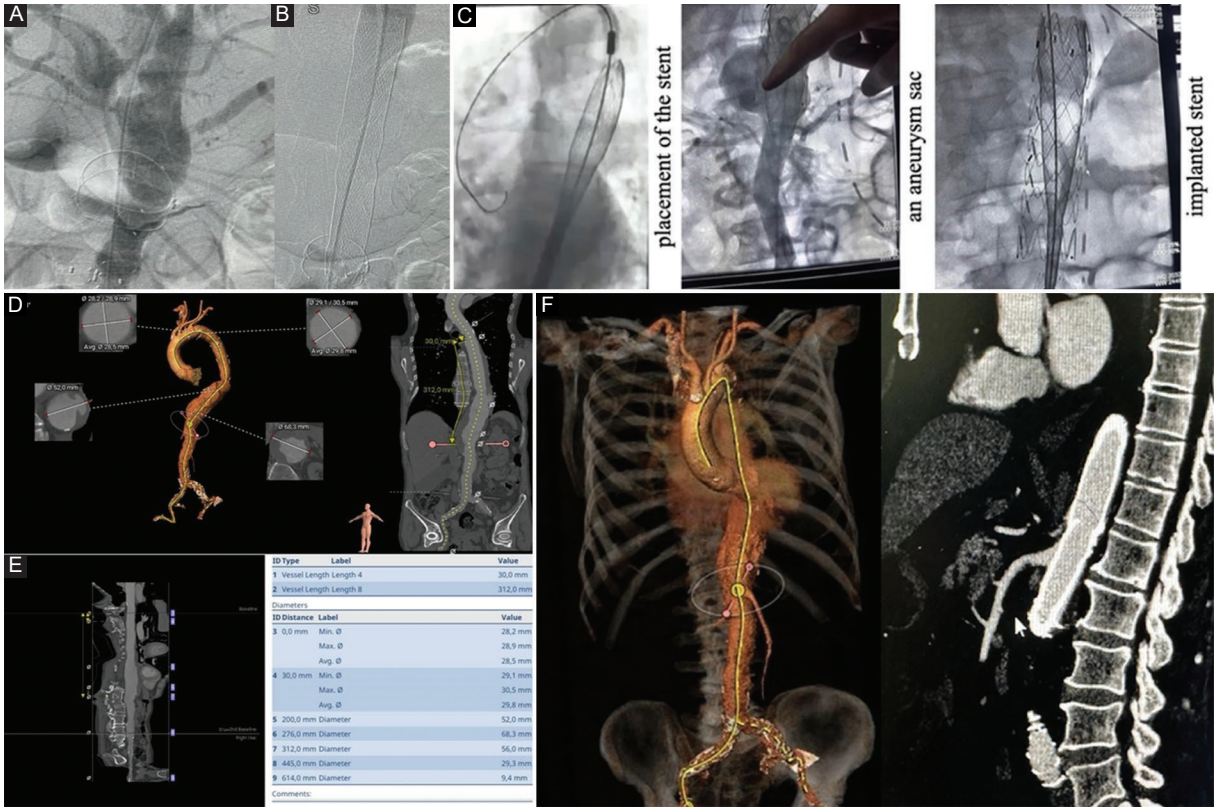

Figure 1. *Image of control angiograms regarding aortic aneurysm and Stena Multilayer Flow Modulator® (S-MFM) placement.* **A***: infrarenal aneurysm at the level of the celiac artery and superior mesenteric artery in a patient who had previously undergone aortobifemoral bypass surgery.* **B:** *simultaneous image of the Stena Multilayer Stent (Invamed, Turkey) with the procedure, applying 28 × 100 mm and 26 × 100 mm just below it.* **C:** *successful placement of the S-MFM.* **D:** *pre-procedural vascular metrics. The level of the celiac trunk and superior mesenteric artery are shown with a circle.* **E:** *post-procedural vascular metrics. The level of the celiac trunk and superior mesenteric artery are shown with a circle.* **F:** *even after S-MFM placement, patency and blood flow of the superior mesenteric artery continues (shown with circle and arrow in the left and right figure, respectively).*

Table 2. Impact of the S-MFM on aneurysm sac volume.

Case#	Baseline (mL)	At 6 months (mL)	Change (%)
1	193.2	193.1	0.05
2	250.5	243.5	−2.79
3	98.7	96.8	−1.92
4	105.6	102.3	−3.12
5	365.8	357.7	−2.21
6	241.4	238.0	−1.40
7	123.5	119.7	−3.07
8	95.3	91.2	−4.30
9	138.6	138.5	0.07
10	120.9	117.6	−2.72
11	216.0	208.5	−3.47
12	122.1	118.2	−3.19
Mean	172.63	168.75	−2.36

mL: milliliter.

problem encountered was the risk of early rupture. This is because the sac is still filling despite the pressure reflected on the aneurysm wall in the early period. In addition, bleeding problems in the femoral artery region may be observed due to the femoral incision made during the early period. No post-operative HCT decrease of <10%, tachycardia or hypotension developed in any patient and no bleeding or rupture was observed.

Discussion

AA is usually seen in men 65 years of age. Most of the time, the diagnosis is made as a result of screening performed for another reason. Screening programs show that the prevalence of AA is decreasing in this age group in high-income countries[13]. This is probably related to the improvement in treatment options and the availability of this facility in developed countries. However, the global death rate from AA increased by 12%

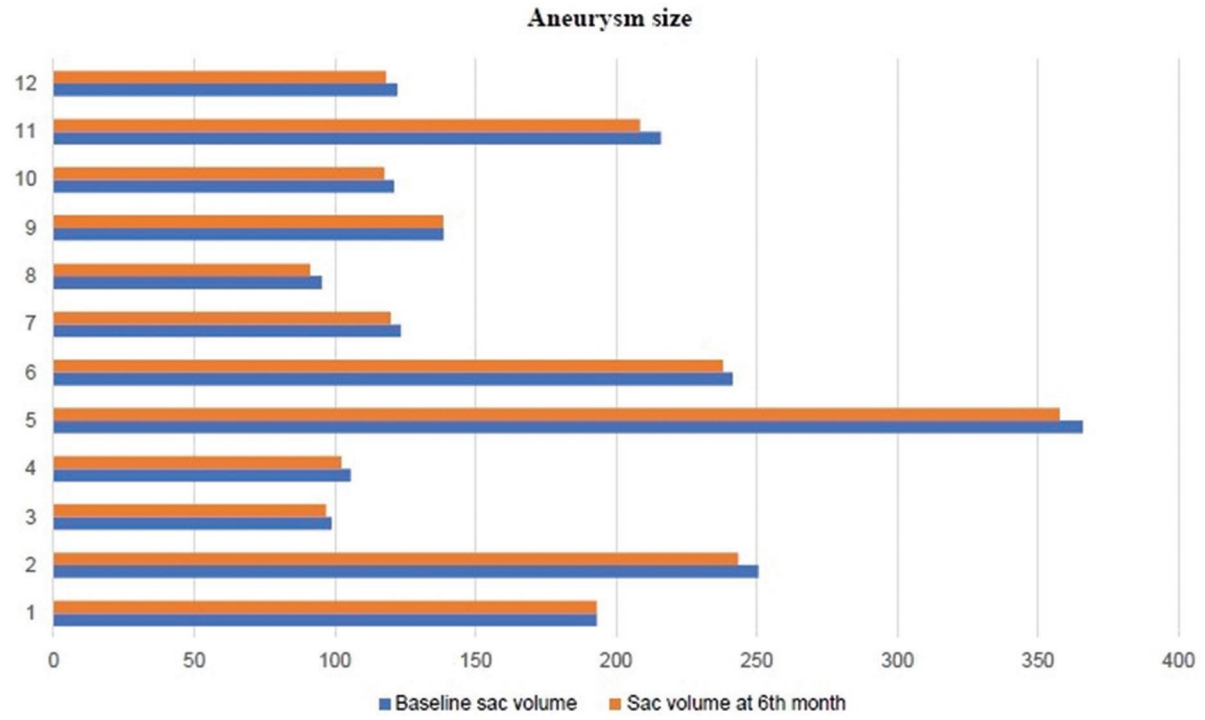

Figure 2. *Schematic demonstration of the impact of Stena-multilayer flow modulator on aneurysm sac volume.*

Table 3. Key operational metric details

Case #	Procedure time (min)	Fluoroscopy time (min)	Blood loss (mL)	Contrast volume (mL)
1	65	22	< 100	55
2	55	21	< 100	70
3	50	31	< 100	45
4	45	24	< 100	55
5	70	21	120	70
6	55	23	< 100	50
7	50	27	< 100	55
8	55	32	< 100	70
9	55	24	< 100	60
10	45	28	< 100	55
11	50	30	< 100	65
12	55	29	< 100	50
Mean	54.17	26	-	58.33

during this period[13]. This is probably because AA is recognized as a cause of death in low- and middle-income countries.

At present, there are no specific guidelines for the treatment of AA[13]. Although open surgical repair is the gold standard and even present case series on the treatment of AA, it still has high mortality and morbidity rates, such as paraplegia and renal failure that require dialysis[10,14]. In recent years, endovascular methods have become the first treatment option not only due to their minimal invasiveness, but also with the hope that they can prevent adverse events related to open surgery based on initial data[14]. However, there are several limitations to this technology, such as the problem of implantation due to the complex peripheral anatomy caused by the large branches in the immediate vicinity of the aneurysm[8,14]. The clinical results are also unsatisfactory[15].

In this respect, flow-diverting stents (FDSs) that have recently been developed offer an encouraging option. Conceptually, FDSs alter blood flow from aneurysm turbulence to laminar in the main artery. The special design of the FDSs allows one to reduce the flow velocity vortex within the aneurysm and to support laminar flow in the main artery and lateral branches. By inducing positive shear stresses, it also promotes endothelialization of the graft and thrombosis in the aneurysmal sac[8].

One of the most important problems encountered is the filling of the aneurysm sac after stent application and the

risk of early rupture. As stated in the sources, the procedure was performed with the expectation that the tension reflected on the sac wall would decrease over time.

In addition, as observed in cranial aneurysm treatments, multilayer stents do not prevent the branches from feeding, as well as reducing the tension of the aneurysm sac.

Apart from the S-MFM®, several MFM stents, such as the Streamliner Aortic MFM (Cardiatis, Isnes, Belgium) with flow guidance concept, have shown satisfactory results in terms of technical success, aneurysm thrombosis and shrinkage, and branch vessel patency[13]. These stents are easier to apply and do not require pre-preparation, such as a patient-specific design[10]. The first patient-level meta-analysis study revealed a 30-day mortality rate of 2.9% with SMFM when used in patients with complex thoracic aortic pathology. Furthermore, there were no incidences of paraplegia, stroke, or renal failure[16].

In our preliminary study of 12 cases, control angiograms confirmed continued blood flow in the main aorta and lateral branch arteries without significant adverse events or death. The technical success rate was 100% and all patients had complete aneurysm thrombosis.

The MFM technology has advantages over a single-layer bare metal stent. This is because unique multiple layers allow for flow modulation and pressure distribution across the layers. When blood flows through the first layer of the MFM, the pressure is reduced across the layers. This eventual reduction in pressure at the aneurysm sac corresponds to an increase in velocity across the stent. The immediate reduction in wall stress can be up to 55%[14]. As with the S-MSM, the self-expanding design further supports hemodynamic modulation by increasing laminar flow in the lumen of the main aorta and vital branches while reducing the flow velocity vortex in the aneurysm sac.

Although the mean total volume of the MFM-treated aortic sac increases by 6-7% in the first 3 months, the mean total volume of the sac begins to decrease after 6 months[14]. This is likely a result of the body's inflammatory and other physiological responses. The mean decreasing in aneurysm sac volume of 2.36% at the end of the 6th month was consistent with these observations.

Study limitations

This study has some limitations. The sample size was relatively small and users of the S-MFM® had no experience with this product, although they had experience in the treatment of AAs. The usability, safety, efficacy, and placement of S-MSM were evaluated based on the results of the perioperative period and the 6th month. There was no short-, medium-, or long-term evaluation. The study also did not have a control arm. Detailed results are not also available for other equivalent products to make a definitive assessment with all dimensions.

Conclusions

MFM technology could be an attractive alternative to surgery or other endovascular techniques for AAs, for reasons such as shrinking the aneurysm sac and preserving the side branch blood flow. It reduces the risks of mortality and morbidity, including kidney failure and paraplegia. MFM stents can be successfully placed even in a patient with complex aortic anatomy. Its ready-to-use structure, which does not require adaptation to the individual, allows it to be easily applied to complex AAs and prevents time loss. Although the present research results and the unique design of the technology encourage it for use, further research and longer follow-up are required to fully understand the clinical implications.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. This is a retrospective study, so it was exempted from ethics committee approval. The study results were endorsed by the Ethics Committee of Hatay Mustafa kemal University.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Rosmarinic acid alleviate hepatotoxicity induced by cyclophosphamide in rats

El ácido rosmarínico alivia la hepatotoxicidad inducida por ciclofosfamida en ratas

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Abstract

Objective: *This study aimed to investigate the hepatoprotective effects of Rosmarinic acid (RA) against cyclophosphamide (CP)-induced liver injury in rats.* **Methods:** *Twenty-one male Wistar Albino rats were divided into three groups: Control, CP, and CP + RA. Hepatotoxicity was induced by administering CP (20 mg/kg/day) intraperitoneally for 14 days. RA (20 mg/kg/day) was administered for 14 days after CP induction. Serum biochemical parameters including malondialdehyde (MDA), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were measured. Liver tissues underwent histological and immunohistochemical analysis for B-cell lymphoma 2 (Bcl-2), apoptotic protease activating factor 1 (Apaf-1), nuclear factor erythroid 2-related factor 2 (Nrf-2), and tumor necrosis factor (TNF)-α. In addition, in silico analysis was performed to explore potential molecular targets of RA and their biological pathways.* **Results:** *CP significantly increased liver weight, MDA content, ALT and AST enzyme activities, indicating hepatic oxidative stress and injury. Histologically, CP caused severe hepatocellular damage characterized by hepatocyte degeneration, hemorrhage, and disrupted hepatic architecture. Immunohistochemically, CP exposure upregulated pro-apoptotic (Apaf-1), oxidative stress (Nrf-2), and inflammatory (TNF-α) markers, while downregulating anti-apoptotic (Bcl-2) proteins. RA administration significantly reversed these biochemical and histopathological changes. In silico analysis revealed RA interacts with multiple inflammatory and oxidative stress pathways, reinforcing its hepatoprotective role.* **Conclusion:** *RA demonstrates significant hepatoprotective activity against CP-induced liver toxicity by attenuating oxidative stress, inflammation, and apoptosis pathways. RA represents a promising therapeutic agent to manage drug-induced hepatotoxicity.*

Keywords: *Apoptosis. Cyclophosphamide. Hepatotoxicity. Inflammation. Oxidative stress.*

Resumen

Objetivo: *Investigar los efectos hepatoprotectores del ácido rosmarínico (AR) frente a la lesión hepática inducida por ciclofosfamida (CP) en ratas.* **Métodos:** *Se dividieron 21 ratas macho Wistar Albino en tres grupos: control, CP y CP + AR. La hepatotoxicidad fue inducida administrando CP (20 mg/kg/día) por vía intraperitoneal durante 14 días. Posteriormente se administró AR (20 mg/kg/día) durante 14 días. Se midieron parámetros bioquímicos séricos incluyendo malondialdehído (MDA), alanina aminotransferasa (ALT) y aspartato aminotransferasa (AST). Se realizaron análisis histológicos e inmunohistoquímicos en tejidos hepáticos para Bcl-2, Apaf-1, Nrf-2 y TNF-α. Además, se realizó un análisis in silico para explorar posibles dianas moleculares del AR y sus vías biológicas relacionadas.* **Resultados:** *El CP incrementó significativamente el peso hepático, el contenido de MDA y las actividades de ALT y AST, indicando estrés oxidativo y lesión hepática. Histológicamente, el CP causó daño hepatocelular grave caracterizado por degeneración hepatocitaria, hemorragia y arquitectura hepática alterada. Inmuno-*

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histoquímicamente, la exposición al CP aumentó los marcadores proapoptóticos (Apaf-1), de estrés oxidativo (Nrf-2) e inflamatorios (TNF-α), y disminuyó las proteínas antiapoptóticas (Bcl-2). La administración de AR revirtió de manera significativa estos cambios bioquímicos e histopatológicos. El análisis in silico reveló que el AR interactúa con múltiples vías inflamatorias y de estrés oxidativo, fortaleciendo su rol hepatoprotector. Conclusione: El AR mostró actividad hepatoprotectora significativa contra la toxicidad hepática inducida por CP, atenuando las vías de estrés oxidativo, inflamación y apoptosis. El AR representa un agente terapéutico prometedor para manejar la hepatotoxicidad inducida por fármacos.

Palabras clave: *Apoptosis. Ciclofosfamida. Hepatotoxicidad. Inflamación. Estrés oxidativo.*

Introduction

Cyclophosphamide (CP) is a medication and has been mainly used in the treatment of malignant and non-malignant disease for many years. CP exerts its effects by alkylating deoxyribonucleic acid (DNA), disrupting DNA replication and introducing DNA breaks[1]. Cytotoxic and mutagenic effects of CP are mostly observed in proliferating cells. Studies showed that CP is associated with significant toxicity across multiple organs such as the heart, testes, urinary bladder, gonads, and limits the use of this drug in cancer treatment[2]. Since CP is primarily metabolized by hepatic enzymes through hepatic oxidation system, hepatotoxicity is a major side effect of CP. Metabolization of CP generates active metabolites which cause immunosuppression and cytotoxicity[3]. These metabolites induce apoptosis and inflammatory response, leading to tissue damage[4,5].

Rosmarinic acid (RA) is a constituent of *Rosmarinus officinalis* and various other plants[6]. RA exhibits a wide range of beneficial properties including antioxidant[7], anti-inflammatory[8], antiapoptotic[9], antimicrobial, antimutagenic, anti-cancer, antidepressant, antiangiogenic, antiallergenic activities and additionally hepatoprotective, cardioprotective nephroprotective effects[10-12]. Many studies have investigated the role of RA in liver diseases and showed possible action of mechanisms of RA on the liver. Osakabe et al.[13] found that RA protected the liver injury against lipopolysaccharide by conferring anti-tumor necrosis factor (TNF)-α and superoxide dismutase (SOD) activity. Another study demonstrated that RA can mitigate acute oxidative liver injury by reducing serum markers of hepatotoxicity, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and lipid peroxidation, following exposure to a pro-oxidant agent[14]. Touiss et al. found that RA alleviated hepatotoxicity caused by administration of carbon tetrachloride (CCL4) by lowering serum ALT, AST, LDH levels. The authors also found that animals restored weight loss after RA treatment[15].

An experimental study showed that RA treatment significantly reduced TNF-α expression release ameliorating collagen-induced arthritis under *in vivo* conditions, suggesting a potential novel therapy for bone disorders such as rheumatoid arthritis and osteoporosis[16]. Liang et al.[17] revealed that RA treatment against asthma mouse model prevented inflammation, favored the antioxidant enzymes in lung tissues. A study investigated the *in vivo* and *in vitro* effects of RA on samples from humans and revealed that RA increased serum SOD and decreased the serum malondialdehyde (MDA)[18]. Taking all these into consideration, RA has been found to exert different biological activities in *in vitro* and *in vivo* studies.

Given that CP has cytotoxic effects on many organs including liver, we conducted biochemical, histochemical, and bioinformatic analysis to show differential roles (anti-inflammatory, anti-oxidant, anti-apoptotic) of RA on CP-induced hepatic injury.

Methods

Study design

All animal experimentations were approved by the Animal Experiments Local Ethics Committee of Dicle University (date: April 24, 2024 and approval number: 694769). This study was conducted in accordance with the ARRIVE guidelines (Animal Research: Reporting of *in vivo* Experiments) to ensure transparent and reproducible reporting of animal research[19]. Twenty-one male Wistar Albino rats (15-16 weeks old, weighing 200-250 g) were assigned to 3 groups (7 rats/group). The animals were housed in their cages at 12/12-h day/night period at 23 ± 1°C. The animals were fed with water and animal pellets *ad libitum*. CP (Endoxan®, Baxter Oncology GmbH, Halle, Germany) and RA (catalog no: sc-202796, Santa Cruz Biotechnology Inc, Heidelberg, Germany) were commercially purchased. RA was dissolved in 1% ethanol. The mixture was daily prepared and freshly injected intraperitoneally (i.p.) to rats at the

same time of day each day. The sample size per group (n = 7) was determined based on previous studies with similar designs that evaluated hepatotoxicity and protective agents using CP in rodents. The selected number ensured adequate statistical comparison while minimizing animal usage (Gpower v3.1 software, analysis, power: 80%, effect size: 0.6, α = 0.05). The dose of RA (20 mg/kg/day) was chosen in accordance with previous studies which demonstrated that this dose significantly ameliorated liver and kidney injury induced by toxic substances in animal models[20,21].

- Control group (n = 7): Animals were given 1 mL of physiological saline solution daily for 14 days. No further treatment was done.
- CP group (n = 7): Animals were administered 20 mg/kg CP daily for 14 days. No further treatment was done.
- CP + RA group (n = 7): Animals were administered 20 mg/kg CP and then 20 mg/kg RA daily for 14 days. No further treatment was done.

At the end of the 14th day, animals were euthanized with an intramuscular injection of 90 mg/kg ketamine (Ketasol; Richter Pharma AG, Feldgasse 19, Wels, Austria) and 8 mg/kg xylazine (Rompun; Bayer, Leverkusen, Germany). Blood samples of animals were collected for biochemical analysis. Liver organs were excised and weighted for each animal per group, and tissue samples were dissected for routine paraffin wax tissue embedding protocol. Final weight of liver organs was measured and an average value was calculated per group (n = 7). Average weight of livers per group was statistically compared with other groups.

Determination of MDA levels and hepatic enzyme activity

Intracardiac blood samples were collected for colorimetric analysis of blood parameters. MDA (#MAK085, Merck, Germany), alanine transaminase (ALT, #MAK052, Merck, Germany), and AST (AST, #MAK055, Merck, Germany) kits were commercially purchased. Blood samples from each rat were centrifuged at 2000 rpm for 10 min, and the supernatant was collected. Serum plasma analyzed for MDA content (oxidative stress marker), ALT (specific hepatic injury marker), and AST (non-specific hepatic injury marker) enzymatic activities according to the manufacturer's instructions. MDA content was measured in nmol/L. Enzymatic activities of ALT and AST were measured in U/L.

Immunohistochemical protocol

Hepatic tissue samples were fixed in 10% formaldehyde solution and passed through ascending ethanol series. Samples were treated with xylene solution and incubated in paraffin wax. Paraffin blocks of tissue samples were cut in 5 μm thick. Sections were deparaffinized, passed through a descending ethanol series, and treated with antigen retrieval solution. Samples were washed in phosphate-buffered saline (PBS) and incubated with 3% hydrogen peroxide for 20 min before blocking solution for 8 min. Samples were incubated with primary antibody B-cell lymphoma-2 (Bcl-2), apoptotic protease activating factor 1 (Apaf-1) and TNF-α, (catalog no: sc-65891, sc-7382, sc-52746, Santa Cruz Biotechnology Inc, Heidelberg, Germany, dilution ratio:1/100) and Nuclear factor erythroid 2-related factor 2 (Nrf-2) (catalog no: AF0639, Affinity Biosciences, US, dilution ratio:1/100). Samples were washed in PBS, biotinylated with a secondary antibody and treated with streptavidin peroxidase for a complex of avidin-biotin peroxidase for 15 min. Diaminobenzidine chromogen was used to visualize expression. Counterstaining was performed with Harris hematoxylin, and the preparations were mounted. Sections were imaged with Zeiss light microscope[22].

Semi-quantitative histological score

The staining intensity (expression) of primary antibodies was measured by Image J software (version 1.53, http://imagej. nih.gov/ij). Signal intensity was measured by the method of Crowe et al.[23]. Quantification was recorded by analyzing 5 fields from each specimen per group according to the method described by Aşır et al.[24]. In specimens, the brown color represented a positive expression of the antibody of interest, while the blue color represented a negative expression of the antibody of interest. Signal intensity from the analyzed field was calculated by dividing the intensity of the antibody of interest by the whole area of the specimen. A value for staining area/whole area was calculated for each specimen from five fields. An average value was measured for each group and recorded as semi-quantitative immunohistochemistry scoring. All images were processed and quantified using ImageJ software.

In silico analysis

To elucidate the pathways potentially implicated in regulating the mitigating effects of RA on CP toxicity,

Table 1. Hepatic weight, serum MDA, ALT, and AST levels in experimental groups after 14 days of treatment

Parameters	Control (n = 7)	CP (n = 7)	CP + RA (n = 7)	Group comparisons
Hepatic weight, g	2.4 (1.7-2.6)	3.8 (3.3-4.2)	2.5 (1.8-2.7)	Control versus CP < 0.01 CP versus CP + RA < 0.01
MDA (nmol/L)	9.2 (7.9-9.7)	32 (25-39)	13 (12-17)	Control versus CP < 0.0001 CP versus CP + RA < 0.05
ALT (U/L)	50 (46-53)	149 (143-153)	118 (110-123)	Control versus CP < 0.0001 CP versus CP + RA < 0.05
AST (U/L)	54 (52-57)	179 (168-185)	203 (98-106)	Control versus CP < 0.0001 CP versus CP + RA < 0.05

*Data was presented as median (Q1-Q3). Test: Kruskal Wallis (*post hoc* Dunn's test); CP: cyclophosphamide; RA: Rosmarinic acid; AST: aspartate; MDA: malondialdehyde; ALT: alanine transaminase; AST: aspartate aminotransferase.

an analysis was conducted on the RA targets associated with Apaf-1, Bcl-2, Nrf-2, and TNF-α, along with their functional annotations. Potential protein targets of RA were identified by exploring various databases, including SwissTargetPrediction (https://www.swisstargetprediction.ch, accessed on: 20 February 2024), STITCH (http://stitch.embl.de/accessed on: February 20, 2024) and the ChEMBL database (https://www.ebi.ac.uk/chembl/accessed on: February 20, 2024). For the STITCH database and interactors of the 4 genes, STITCH: protein (maximum interactors: 50) and Search Tool for the Retrieval of Interacting Genes/Proteins (STRING, https://string-db.org): protein modules (maximum interactors: 100) of Cytoscape v3.10.1 (San Diego, CA, USA) were utilized, respectively. The confidence cut-off values were maintained at the default level of 0.40, representing a moderate level of confidence[25]. Parameters for SwissTargetPrediction and ChEMBL were also set to default, except for specifying the species as Homo sapiens. To detect the shared targets of RA and 4 proteins of interest, Venn diagrams were constructed using the jvenn tool[26]. Afterward, kyoto encyclopedia of genes and genomes (KEGG) pathway enrichment analysis, which refers to a computational approach that identifies biological pathways significantly associated with a list of genes or proteins of interest, was conducted using these shared proteins through ShinyGO 0.80 (http://bioinformatics.sdstate.edu/go/, accessed on: February 25, 2024)[27]. Pathway enrichment analysis refers to a computational approach that identifies biological pathways significantly associated with a list of genes or proteins of interest. Bar plots were generated for the top 10 ranked pathways with a false discovery rate below 0.05, encompassing KEGG and gene ontology biological process.

Statistical analysis

All statistical analyses were performed by GraphPad Prism Software (Version 9.2.0; Graph Pad Software, Inc., San Diego, CA). Data distribution was analyzed by the Shapiro-Wilk test. The non-normal distributed data was recorded as median (interquartile range, Q1-Q3). Multiple comparisons were performed by Kruskal-Wallis and followed by *post hoc* Dunn's test. Significance level was shown as *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$, ****$p \leq 0.0001$.

Results

RA reduced hepatic weight, MDA content, and ALT-AST activities after CP induction

Table 1 demonstrates the protective effects of RA against CP-induced hepatic toxicity in rats. CP administration significantly increased hepatic weight, serum MDA levels, and liver enzyme activities (ALT and AST) compared to the control group, indicating oxidative stress, liver inflammation, and hepatocellular damage. Specifically, hepatic weight rose from a median of 2.4 g in the control group to 3.8 g in the CP group ($p < 0.01$), while MDA levels markedly increased from 9.2 nmol/L to 32 nmol/L ($p < 0.0001$), reflecting heightened lipid peroxidation. Serum ALT and AST levels were also significantly elevated in the CP group ($p < 0.0001$), confirming hepatocellular injury. Treatment with RA significantly reduced all these parameters, including hepatic weight and MDA levels ($p < 0.01$, $p < 0.05$, respectively), as well as ALT and AST activities ($p < 0.05$), suggesting that RA alleviates CP-induced

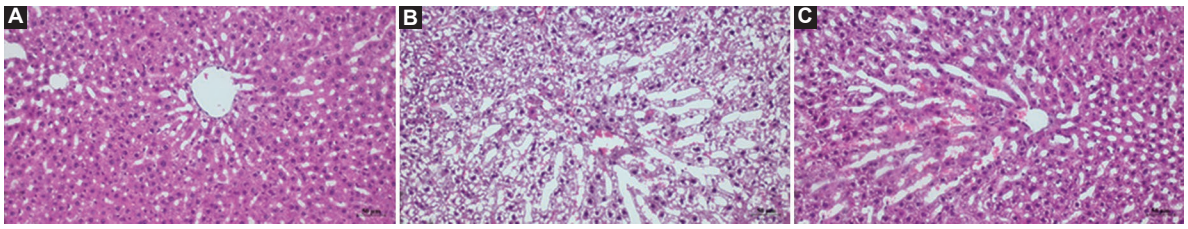

Figure 1. *Microscopic sections of hepatic tissue from control* **(A)**, *cyclophosphamide (CP)* **(B)** *and CP + rosmarinic acid* **(C)** *groups. Hematoxylin eosin staining, scale bar: 50 μm, magnification: ×20.*

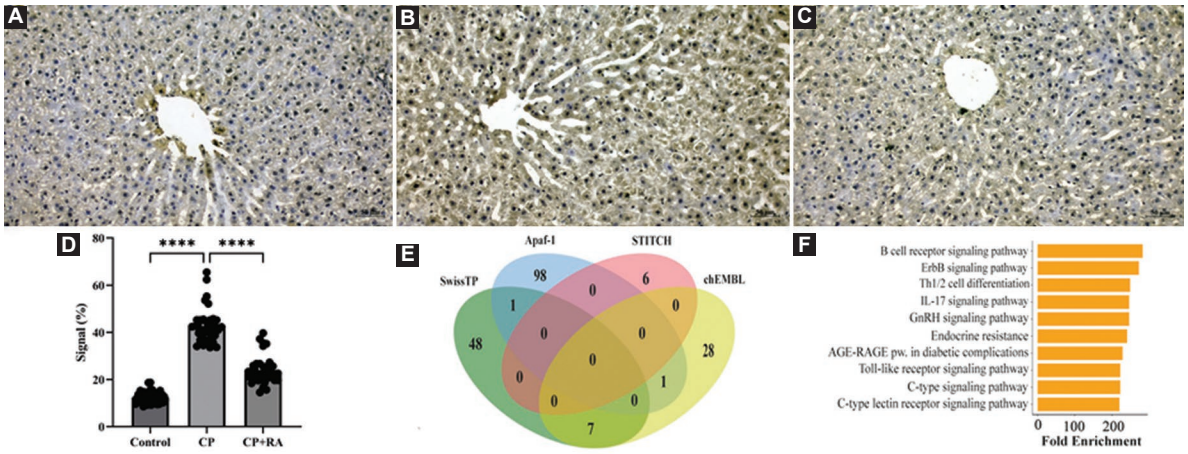

Figure 2. *Immunoexpression of pro-apoptotic marker of apoptotic protease activating factor 1 (Apaf-1) in hepatic tissues of control* **(A)**, *cyclophosphamide (CP)* **(B)** *and CP + rosmarinic acid (RA)* **(C)** *groups, scale bar: 50 μm, magnification: ×20;* **(D)** *Immunostaining scores in groups;* **(E)** *Intersection of RA protein targets with Apaf-1.* **(F)** *Kyoto encyclopedia of genes and genomes analysis of Apaf-1-associated RA targets. Significance level was shown as *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, ****p ≤ 0.0001.*

hepatotoxicity through antioxidant and hepatoprotective mechanisms.

RA alleviated the histopathological alterations in hepatic tissue

Normal histology was observed in hepatic tissue with radial organization of hepatocytes, regular central vein, and hepatic sinusoids (Fig. 1A). CP toxicity caused pathology in hepatic tissue (Fig. 1B). Hepatocyte degeneration with pyknotic nuclei, dilated sinusoids with hemorrhage, glycogen depletion and disruption in radial organizations were observed in CP group. RA treatment improved the histology of liver tissue in CP + RA group, suggesting hepatoprotective effects of RA on liver tissue (Fig. 1C). Hepatic cords with hepatocytes, radial organization, and sinusoids were restored to normal histology, however, hemorrhage was continued. These findings suggest that RA has hepatoprotective effects against adverse histological changes of CP in hepatic tissue.

Impacts of RA on apoptotic pathways were analyzed by Apaf-1 expression (Fig. 2). Apaf1 expression in hepatocytes was mainly negative in control group (Fig. 2A). In CP group, overexpression of Apaf1 was observed in hepatocytes due to toxic effects of CP in liver cells (Fig. 2B). RA treatment downregulated Apaf-1 expression in CP + RA group, indicating anti-apoptotic properties of RA in hepatic tissue (Fig. 2C). Semi-quantitative analysis also showed that Apaf-1 expression was significantly reduced in CP + RA group, compared to CP group (Fig. 2D). The intersection between the targets of RA and the Apaf-1 protein network revealed 2 common target proteins (Fig. 2E). The KEGG analysis of these shared targets highlighted pathways such as the B cell receptor signaling pathway, Erythroblastic oncogene B signaling pathway, Th1 and Th2 cell differentiation (Fig. 2F). In the enrichment bar graphs, the term “fold enrichment” indicates the ratio between the observed and expected number of genes involved in a specific pathway, highlighting how prominently a particular pathway is

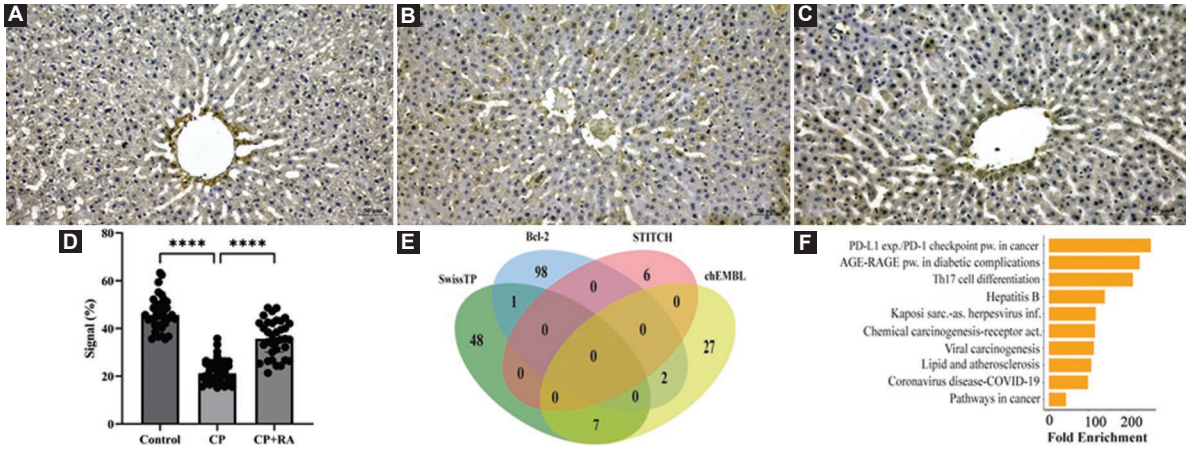

Figure 3. *Immunoexpression of anti-apoptotic marker of B-cell lymphoma 2 (Bcl-2) in hepatic tissues of control* **(A)**, *cyclophosphamide (CP)* **(B)** *and CP + rosmarinic acid (RA)* **(C)** *groups, Scale bar: 50 μm, magnification: x20;* **(D)** *Immunostaining scores in groups.* **(E)** *Intersection of RA protein targets with Bcl-2.* **(F)** *Kyoto encyclopedia of genes and genomes analysis of Bcl-2-associated RA targets. Significance level was shown as *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, ****p ≤ 0.0001.*

represented among the shared targets. Here, "targets" refer to the individual proteins identified as common interactors between RA and the CP-related key molecules (Apaf-1, Bcl-2, Nrf-2, and TNF-α), whereas "pathways" represent the broader biological processes in which these targets are significantly involved. These findings showed that RA exerts its anti-apoptotic effect on Apaf-1 associated pathways to influence immune response and cellular signaling cascades.

Anti-apoptotic effect of RA was shown by evaluating immune stained sections of hepatic tissue with Bcl-2 (Fig. 3). Bcl-2 expression was moderate in hepatocytes in control group (Fig. 3A). CP toxicity induced apoptotic pathway, leading to downregulation of Bcl-2 expression in hepatic sections of CP group compared to control group (Fig. 3B). Upregulation of Bcl-2 was observed in hepatocytes after RA treatment in CP+RA group (Fig. 3C). Immune score for Bcl-2 was also increased after RA treatment in CP + RA group compared to CP group (Fig. 3D). The intersection of the RA targets with the Bcl-2 protein network identified 3 common target proteins (Fig. 3E). The enriched pathways of these shared targets encompassed the programmed death-ligand 1 (PD-L1)/programmed death-1 (PD-1) pathways in cancer, advanced glycation end products (AGE)- receptors of advanced glycation end products (RAGE) signaling pathway in diabetic complications, Th17 cell differentiation (Fig. 3F). Our results indicated that RA interacts with Bcl-2 with many pathways such as immune modulation and inflammation, in addition to apoptotic pathways.

RA showed antioxidant activity in CP induced hepatotoxicity

To show antioxidant effects of RA, hepatic sections were immunostained with Nrf-2 (Fig. 4). Nrf-2 expression was moderate in control sections (Fig. 4A). Compared to control group, CP toxicity increased reactive oxygen species in hepatocytes, causing oxidative stress and elevation of Nrf-2 expression in CP group (Fig. 4B). With antioxidant effects of RA on hepatocytes, Nrf-2 expression was downregulated in hepatocytes after RA treatment in CP+RA group (Fig. 4C). Semi-quantitative analysis showed Nrf-2 expression was significantly decreased after RA treatment in CP + RA group compared to CP group (Fig. 4D). The intersection of RA targets with the Nrf-2 protein network identified 5 common target proteins ((Fig. 4E). The enriched pathways for the shared targets comprised leishmaniasis, PD-L1/PD-1 pathways in cancer, and interleukin (IL)-17 signaling pathway (Fig. 4F). Our results highlighted that RA interacted with oxidative stress and additionally with immune responses and inflammatory processes through Nrf-2 mediated mechanisms.

RA showed anti-inflammatory activity in CP-induced hepatotoxicity

Role of RA in the inflammatory pathway was shown though expression of TNF-α (Fig. 5). TNF-α expression was mainly negative in control group (Fig. 5A). CP

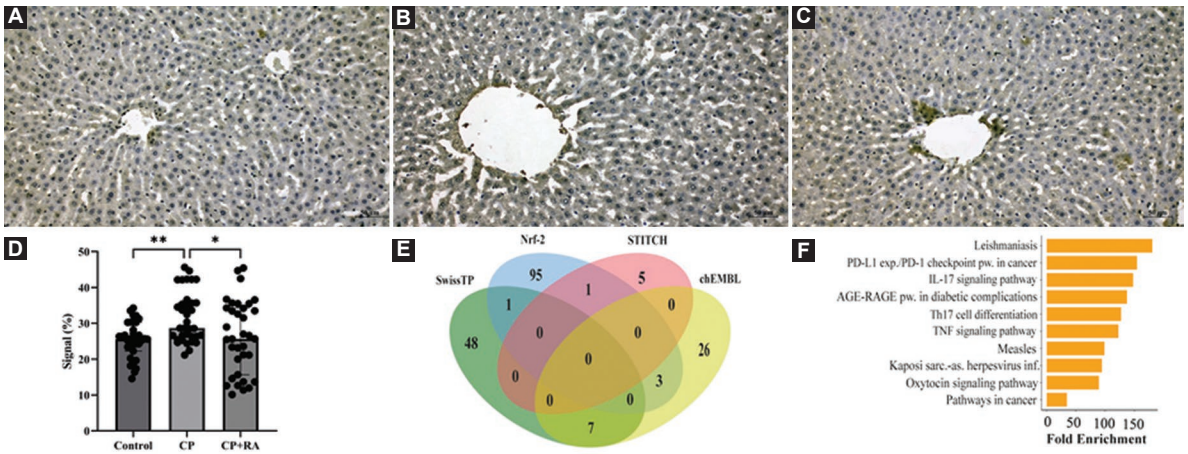

Figure 4. *Immunoexpression of oxidative stress marker of Nuclear factor erythroid 2-related factor 2 (Nrf-2) in hepatic tissues of control* **(A)**, *cyclophosphamide (CP)* **(B)** *and CP + rosmarinic acid (RA)* **(C)** *groups, scale bar: 50 μm, magnification: x20;* **(D)** *Immunostaining scores in groups;* **(E)** *Intersection of RA protein targets with Nrf-2.* **(F)** *kyoto encyclopedia of genes and genomes analysis of Nrf-2-associated RA targets. Significance level was shown as *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, ****p ≤ 0.0001.*

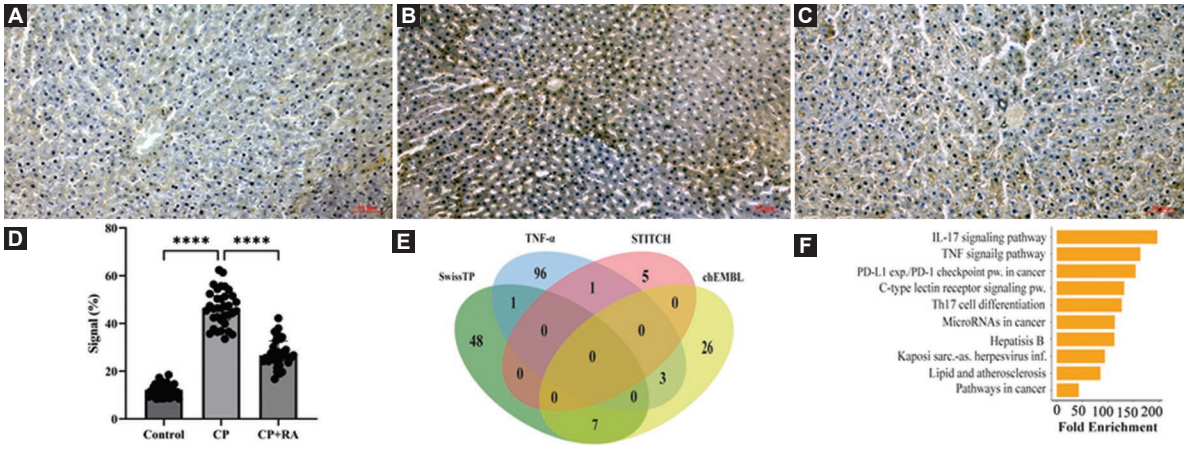

Figure 5. *Immunoexpression of inflammation marker of tumor necrosis factor (TNF)-α in hepatic tissues of control* **(A)**, *cyclophosphamide (CP)* **(B)** *and CP + rosmarinic acid (RA)* **(C)** *Groups, scale bar: 50 μm, magnification: x20;* **(D)** *Immunostaining scores in groups;* **(E)** *Intersection of RA protein targets with TNF-α.* **(F)** *Kyoto encyclopedia of genes and genomes analysis of TNF-α-associated RA targets. Significance level was shown as *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, ****p ≤ 0.0001.*

injection caused hepatotoxicity and promoted inflammatory response in hepatic tissue, leading to upregulation of TNF-α expression in hepatocytes compared to control group (Fig. 5B). RA administration showed anti-inflammatory effects in hepatocytes, downregulating the TNF-α expression in hepatic tissues in CP + RA group (Fig. 5C). Immune scores also reflected similar results of histological staining, indicating TNF-α expression was significantly decreased after RA treatment in CP + RA group compared to CP group (Fig. 5D). 5 common target proteins were identified in intersection of the RA targets with TNF-α interactors (Fig. 5E). The enriched pathways of these common targets included the IL-17 signaling pathway, TNF signaling pathway, PD-L1 expression and PD-1 checkpoint pathway in cancer (Fig. 5F). These data signify that RA's role in inflammatory process and cellular differentiation through TNF-α mediated mechanisms.

Summary of our study is shown in table 2. The table presented the key protein targets affected by CP toxicity, the reversing effects of RA treatment, and their associated cellular signaling pathways identified through *in silico* analysis.

Discussion

The present study suggests pharmacological perspective targeting an oxidative stress, apoptosis, and inflammation disease module as a potential target of CP induced hepatotoxicity. *In silico* analysis can also

Table 2. Summary of immunohistological and *in silico* findings

Target protein	Role in CP toxicity	Effect of RA treatment	Pathways involved
Apaf-1	Apoptosis ↑	Suppresses apoptosis	BCR signaling, ErbB signaling
Bcl-2	Anti-apoptotic defense ↓	Enhances anti-apoptosis	PD-L1 pathway, AGE-RAGE pathway
Nrf-2	Oxidative stress response ↑	Reduces oxidative damage	Nrf2 pathway, immune regulation
TNF-α	Inflammation ↑	Inhibits inflammatory response	IL-17 signaling, TNF signaling

↑: upregulation of molecular expression or activity.

↓: downregulation of molecular expression or activity.

CP: cyclophosphamide; RA: rosmarinic acid; Bcl-2: B-cell lymphoma 2; Apaf-1: apoptotic protease activating factor 1; Nrf-2: nuclear factor erythroid 2-related factor 2; TNF-α: tumor necrosis factor; PD-L1: programmed death-ligand 1; AGE-RAGE: advanced glycation end products-receptors of advanced glycation end products; IL: interleukin; TNF: tumor necrosis factor.

reveal the association of these mechanisms and pathways related to RA. Administration of RA after CP injection ameliorated MDA content, ALT-AST activities and toxicity in hepatic tissue of rats.

In certain instances, the administration of chemotherapeutic agents may lead to the occurrence of adverse effects, thereby posing potential challenges to patient health and treatment outcomes[28]. CP, a commonly used chemotherapeutic agent, has been associated with hepatotoxicity, indicating its potential to induce liver damage. This hepatotoxic effect has been documented in various studies, suggesting a need for close monitoring of liver function in patients undergoing CP treatment[29,30].

Jia et al.[31] found that RA showed hepatoprotective effects on ovalbumin-induced hepatic injury by lowering serum ALT, AST activities and preventing expression of proinflammatory cytokines (TNF-α, IL-4 and IL-6) in liver. Another study on cholestatic liver showed that RA treatment improved hepatic histopathology, serum biochemical parameters, oxidative stress and fibrosis. The inflammatory response was also suppressed by RA treatment through modulation of NF-κB activity[32]. In our study, RA treatment effectively mitigated CP-induced hepatotoxicity, as evidenced by reduced hepatic weights, improved liver histology, and decreased levels of MDA, ALT, and AST, demonstrating its antioxidant and hepatoprotective properties.

Studies showed that RA can inhibit pro-apoptotic pathway Apaf-1 expression or promote anti-apoptotic pathway through Bcl-2 expression. Yıldızhan et al.[33] found that RA treatment protected kidney tissue against deltamethrin toxicity, by suppressing apoptosis through inhibition of Apaf-1 expression. In an *in vitro* study of pancreatic β cell culture, RA was found to protect β-cells against streptozotocin toxicity by upregulating increased expression of Bcl-2 and maintaining normal morphology of β-cells[34]. RA administration suppressed CP-induced apoptosis by increasing Bcl-2 and reducing Apaf-1 expression in hepatic tissue. Supporting this, *in silico* analysis identified key enriched pathways associated with these targets, including the B cell receptor and ErbB signaling pathways for Apaf-1, and PD-L1/PD-1 and AGE-RAGE signaling pathways for Bcl-2. These pathways are closely linked to inflammatory regulation[35], oxidative stress and apoptotic control[36], suggesting that RA exerts its protective effects through modulation of multiple signaling networks involved in CP-induced liver injury. *In silico* pathway analysis is a valuable tool for predicting potential biological pathways and interactions based on gene expression data. In the context of our study with RA's hepatoprotective effects, bioinformatic analysis can suggest involvement in pathways related to apoptosis and immune signaling[37,38]. However, such predictions are based on existing databases and known interactions, which may not account for novel or context-specific mechanisms. Therefore, while our bioinformatical analysis provides hypotheses, it does not offer definitive proof of pathway involvement.

Oxidative stress is an indicator of cell death and Nrf-2 is a key transcription factor that regulates genes involved in antioxidant mechanisms[39]. Yu et al.[40] studied the role of RA in neuroinflammation and found that RA administration significantly modulated Nrf-2 expression in histologically damaged brains. In a CCl_4-induced hepatotoxicity, RA was found to show hepatoprotective effects by improving antioxidant mechanism, inhibiting inflammation, and hepatocyte apoptosis through Nrf-2 signaling pathway[41]. Recent studies have further elucidated the molecular pathways underlying the hepatoprotective effects of RA. Lu et al.[38] reported that RA attenuated CCL4-induced liver injury by activating the Nrf2 signaling pathway, thereby enhancing antioxidant defense mechanisms and reducing oxidative stress and inflammation. Luo et al.[42] demonstrated that RA mitigates toosendanin-induced

hepatic damage by restoring autophagic flux and lysosomal functions through activation of the JAK2/STAT3/CTSC signaling axis. Moreover, Karaca et al.[43] found that RA protects against tramadol-induced hepatorenal toxicity by modulating multiple pathways, including oxidative stress, inflammation, endoplasmic reticulum stress, and apoptosis. Collectively, these findings are consistent with our results, emphasizing RA's multifaceted role in reducing drug-induced hepatic injury thorugh diverse molecular mechanisms.

RA can influence the activity and response of the immune system, potentially aiding in immune function regulation and defense against pathogens or harmful substances[44]. RA has been shown to prevent inflammatory diseases via preventing activity of TNF-α through its anti-inflammatory activity. In an experimental osteoarthritis rat model, Hu et al.[45] showed that RA inhibited extracellular matrix formation and production of IL-6 and prevented activation of IL-1β induced genes. Immunostaining revealed that CP-induced liver injury was associated with elevated Nrf-2 and TNF-α expression, reflecting increased oxidative stress and inflammation. RA treatment significantly reduced the expression of both markers, supporting its antioxidant and anti-inflammatory effects. KEGG pathway analysis identified shared targets between RA and Nrf-2 or TNF-α, highlighting enrichment in immune and stress-related pathways, including PD-1/PD-L1, IL-17, and AGE-RAGE signaling. Notably, the association of RA-Nrf-2 targets with pathways involved in leishmaniasis[46] suggests broader immunomodulatory roles for RA. The strong link between TNF-α and IL-17 signaling further implies that RA may exert protective effects by modulating cytokine networks implicated in hepatic and renal toxicity[47]. Together, these findings support the role of RA in mitigating CP-induced liver damage through coordinated regulation of oxidative and inflammatory pathways.

Conclusion

This experimental study sheds light on the potential protective effects of RA against CP induced hepatotoxicity. Our findings demonstrate that RA ameliorated CP-induced liver damage as evidenced by reduced hepatic weight, serum liver enzymes, decreased histopathological alterations, and enhanced antioxidant defenses. The mechanistic insights revealed RA's ability to attenuate oxidative stress, inflammation, and apoptosis pathways, which are pivotal in CP-induced liver injury. For the future, RA may be a potential therapeutic candidate for clinical use. In addition, interaction between RA and CP metabolism may promise as an adjuvant therapy for CP -based chemotherapy regimens.

Limitations and future perspectives

The limitations of this study include a small sample size and potential biases due to animal model use, which may affect the generalizability of the findings. Methodological constraints and resource limitations may have also influenced the study outcomes and their applicability to broader contexts. In future studies, mechanisms through which RA may be effective in reducing CP toxicity could be elucidated at the experimental level.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the Institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Emergence agitation in open rhinoplasty operations neutrophil/lymphocyte and platelet/lymphocyte ratio as a predictive marker

Agitación de emergencia en operaciones de rinoplastia abierta: cocientes neutrófilos/linfocitos y plaquetas/linfocitos como marcadores predictivos

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Abstract

Objective: *We aimed to evaluate the relationship between emergence agitation and pre-operative neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) after rhinoplasty.* **Methods:** *Our study included 104 patients. All patients underwent surgery under standard general anesthesia. In the pre-operative period, receiver operating curve analysis was performed to determine the cutoff values of NLR and PLR for the risk of emergence agitation and pre-operative anxiety. A correlation analysis was performed between NLR and PLR, the State-Trait Anxiety Inventory scale, and the body image disturbance scale.* **Results:** *While the area under the curve (AUC) value of NLR for emergence agitation was not significant (p = 0.76), the cutoff value for PLR was 113.37 (AUC = 0.624, sensitivity = 80.65%, specificity = 45.21%, p = 0.046). Median PLR values were higher in patients with emergence agitation (p = 0.046). The AUC value for pre-operative anxiety was not significant. There was no correlation between NLR and PLR and the scales assessed.* **Conclusions:** *We suggest that PLR may be a predictive biomarker in evaluating the risk of pre-operative emergence agitation in patients scheduled for rhinoplasty.*

Keywords: *Emergence agitation. Neutrophil-lymphocyte ratio. Platelet-lymphocyte ratio. Anxiety. Body dysmorphic disorder.*

Resumen

Objetivo: *Evaluar la relación entre la agitación de emergencia y los cocientes preoperatorios neutrófilos/linfocitos (NLR) y plaquetas/linfocitos (PLR) tras una rinoplastia.* **Métodos:** *En el estudio participaron 104 pacientes, todos ellos sometidos a cirugía bajo anestesia general estándar. En el periodo preoperatorio se realizó un análisis de curva operativa del receptor para determinar los valores de corte de NLR y PLR para el riesgo de agitación de emergencia y de ansiedad preoperatoria. Se realizó un análisis de correlación entre NLR y PLR, la Escala de Ansiedad Estado-Rasgo y la Escala de Alteración de la Imagen Corporal.* **Resultados:** *Mientras que el valor del área bajo la curva (AUC) de NLR para la agitación de emergencia no fue significativo (p = 0.76), el valor de corte para PLR fue de 113.37 (AUC = 0.624, sensibilidad del 80.65% y especificidad del 45.21%; p = 0.046). Los valores medios de PLR fueron mayores en los pacientes con agitación de emergencia (p = 0.046). El valor del AUC para la ansiedad preoperatoria no fue significativo. No hubo correlación entre NLR y PLR y las escalas evaluadas.* **Conclusiones:** *Sugerimos que el PLR puede ser un biomarcador predictivo en la evaluación del riesgo de agitación de emergencia preoperatoria en pacientes programados para rinoplastia.*

Palabras clave: *Agitación de emergencia. Cociente neutrófilos/linfocitos. Cociente plaquetas-linfocitos. Ansiedad. Trastorno dismórfico corporal.*

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Introduction

Emergence agitation is defined as a state of psychomotor excitement that occurs before full emergence of consciousness after general anesthesia and is self-limiting within 5-15 min[1]. Its incidence has been reported to reach approximately 50% after facial surgeries such as ear-nose-throat and orthognathic procedures[2,3].

Pathophysiologically, it has been reported that it may occur as a result of sympathetic activation secondary to inadequate analgesia or mental disorders that trigger neuroinflammation[2,4]. Etiologic factors include post-operative pain, pre-operative anxiety, young age, type of surgery, anesthetic agent used, and psychic problems[5,6].

Especially recently, rhinoplasty has become the main esthetic operation performed by half a million people a year to improve the appearance of the nose[7]. In a literature review, a history of plastic surgery was found to be associated with a high level and incidence of anxiety[8]. In rhinoplasty surgery, which is not only a technical procedure, body dysmorphic disorder (BDD) is one of the factors that are important in determining the person's mood and affect post-operative satisfaction[9]. Even if the existing defect is small, obsession and anxiety about it are excessive[10].

Neuroinflammation is emphasized as the main factor in the pathophysiology of emergence agitation, anxiety disorders, and obsessive-compulsive-related disorders. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which are neurobiological markers, are accepted as easily measurable and low-cost parameters reflecting the inflammatory state[11].

NLR and PLR are affected by the presence of systemic pathologies, including malignancies and various diseases such as mood disorders[12]. An association between NLR and PLR and diseases in which neuroinflammation plays a role in pathophysiology, such as mood disorders, anxiety disorders, and schizophrenia, has been demonstrated[13-16]. Although there are studies in the literature on the relationship between NLR and PLR with neuropsychiatric disorders such as major depressive disorder, schizophrenia, and obsessive-compulsive disorder (OCD), no study was found to be related to emergence agitation, pre-operative anxiety, State-Trait Anxiety Inventory (STAI) scale, and BDD scale.

The primary aim of our study was to investigate the relationship between NLR and PLR levels, which are neurobiological markers, and emergence agitation in adult patients with post-operative emergence agitation. The secondary aim was to evaluate the relationship between neurobiological markers (NLR and PLR) and pre-operative anxiety, STAI scale, and BDD scale scores.

Methods

Our study was prospectively conducted on a total of 104 patients with American Society of Anesthesiologists (ASA) risk classification I and II, 18-45 years of age, who underwent open rhinoplasty surgery by Plastic Reconstructive and Esthetic Surgery after approval of the local ethics committee of Karadeniz Technical University Faculty of Medicine (protocol number: 2021/374), and whose written and verbal informed consent was obtained after verbal information about the study.

Body mass index > 30 kg/m^2, allergy to induction agent(s) and opioid, chronic pain medication, active infection, autoimmune, cardiovascular, gastrointestinal and neurological diseases, renal or hepatic insufficiency, chronic respiratory pathology, malignancy diagnosis (colorectal, gastric, pancreatic, esophageal, lung, gynecologic, etc.), history of chronic systemic diseases (hypertension and diabetes mellitus), hematologic (leukocyte and platelet) diseases, non-cooperative patients and patients with physical and verbal comparison.), patients with a history of chronic systemic diseases (hypertension and diabetes mellitus), patients with hematologic (leukocyte and platelet) diseases, patients who were unable to cooperate, and patients who were physically and verbally incapable of comparison were excluded.

In our study, demographic data (age, gender, ASA score, presence of surgical history, duration of surgery, and duration of anesthesia), pre-operative measurements (STAI-I and II scale) scores, body image disturbance questionnaire (BIDQ) score, presence of pre-operative anxiety, laboratory variables (NLR and PLR), and post-operative emergence agitation were recorded.

NLRs and PLRs were manually calculated using absolute values from the patient's complete blood count (absolute and relative values of leukocytes, neutrophils, lymphocytes, and platelets) requested by the relevant branch before the operation.

After an adequate pre-operative fasting period, patients who came to the operating room were

monitored non-invasively for arterial pressure, heart rate (HR), electrocardiogram, peripheral oxygen saturation, end-tidal carbon dioxide, and bispectral index values (BIS) during anesthesia monitoring. Anesthesia induction was performed with intravenous (IV) 1μg/kg fentanyl, 3 mg/kg propofol, and 0.6 mg/kg rocuronium for muscle relaxation in all patients included in our study. Anesthesia maintenance was achieved by inhalation anesthesia with sevoflurane (minimum alveolar concentration 1-1.5) and 1:1 O_2/Air with a BIS value of 40-60 and remifentanil infusion (0.01-0.2 μg/kg/min). Near the end of the operation, all patients received IV 1 g paracetamol and 50 mg tramadol for post-operative analgesia as standard.

Open rhinoplasty surgeries performed on all patients participating in the study were performed by the same Plastic Reconstructive and Esthetic Surgery specialist, and the same internal nasal splints (Eon Meditech internal nasal airway splint standard, silicone, double hole) were used.

Emergence agitation after extubation and in the post-anesthesia care unit was evaluated with the Richmond agitation sedation scale (RASS) (+ 1 to + 4: anxiety or agitation, 0: calm and awake, −1 to −5: sedated, −5: not arousable). Patients with a RASS score ≥ 2 were considered to have developed emergence agitation[17].

Pre-operative anxiety was considered to be present in patients with an STAI-I score of 30 and above, which was used to evaluate the level of state anxiety in the pre-operative period[18].

Patients' concerns about their general body image and bodily concerns in social life were evaluated with the body image disorder scale questionnaire (1: none, 2: mild, 3: moderate, 4: severe, and 5: extreme)[19]. High values indicated a negative body perception and a severe negative effect of this perception on psychosocial functions, whereas low values were interpreted as no disturbing problem in body image.

Statistical analysis

The data were analyzed using IBM Statistical Package for the Social Sciences Statistics v23. Compliance with normal distribution was examined by the Shapiro–Wilk and Kolmogorov–Smirnov tests. Categorical data by groups were compared using the χ^2, Yates' correction, and Fisher's exact tests. An Independent two-sample t-test was used to compare normally distributed data, and the Mann–Whitney U-test was used to compare non-normally distributed data. The relationship between non-normally distributed quantitative data was analyzed by Spearman's ρ correlation. The point biserial correlation coefficient was used to examine the relationship between quantitative data and two-group categorical data. Receiver operating characteristic (ROC) analysis was performed to determine the cutoff value of the parameters for agitation and pre-operative anxiety. The analysis results were presented as mean ± SD and median (minimum-maximum) for quantitative data and frequency (percentage) for categorical data. The significance level was taken as $p < 0.05$.

Results

One hundred four patients who underwent open rhinoplasty surgery and met the inclusion criteria were included in the study. The patients' demographic data and clinical characteristics are shown in table 1.

Pre-operative anxiety (STAI-I ≥ 30) was detected in 85.58% (n: 85) of the participants, whereas emergence agitation (RASS ≥ + 2) was observed in 29.81% (n: 31) in the post-operative period.

ROC analysis was performed to determine the usefulness of NLR and PLR as predictive markers in determining emergence agitation and pre-operative anxiety (Table 2).

While the AUC value of NLR cutoff value for emergence agitation was not statistically significant ($p = 0.76$), the cutoff value for PLR was 113.37 (AUC = 0.624, sensitivity = 80.65%, specificity = 45.21%, positive predictive value (PPV): 38.46%, negative predictive value (NPV): 84.62%, $p = 0.046$) (Fig. 1). The change in PLR values according to the presence of emergence agitation is shown in Fig. 2. The median PLR values were statistically significantly higher in patients with emergence agitation than those without (135.9 vs. 120.97, $p = 0.046$), respectively.

The AUC value of NLR and PLR cutoff value for pre-operative anxiety was not statistically significant ($p = 0.08$; 0.33) (Fig. 3).

The relationship between NLR and PLR, and STAI I-II and BIDQ is shown in table 3, and no statistically significant difference was found ($p > 0.050$).

Discussion

As a result of our study, PLR in the pre-operative period is a predictive biomarker in assessing the risk of emergence agitation. In addition, NLR and PLR

Table 1. Demographic data and laboratory parameters

Variables	Total (n = 104)
Gender	
Female	65 (62.5)
Male	39 (37.5)
Age	28.18 ± 9.14
ASA score	
ASA 1	58 (55.8)
ASA 2	46 (44.2)
Education level	
Primary school	10 (9.6)
High school	39 (37.5)
University	55 (52.9)
Duration of anesthesia (min)	66.39 ± 15.00
Duration of surgery (min)	53.47 ± 14.34
Neutrophil count (× 10^3/μL)	4.25 ± 1.50
Lymphocyte count (× 10^3/μL)	2.25 ± 0.63
Platelet count (× 10^3/μL)	272.89 ± 59.65
NLR	1.99 ± 0.82
PLR	129.60 ± 47.00
STAI-I score	37.21 ± 8.32
STAI-II score	39.03 ± 7.88

Frequency (percentage), mean ± SD.
ASA: American Society of Anesthesiologists; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; STAI-I: state anxiety scale; STAI-II: trait anxiety scale; Min: minute.

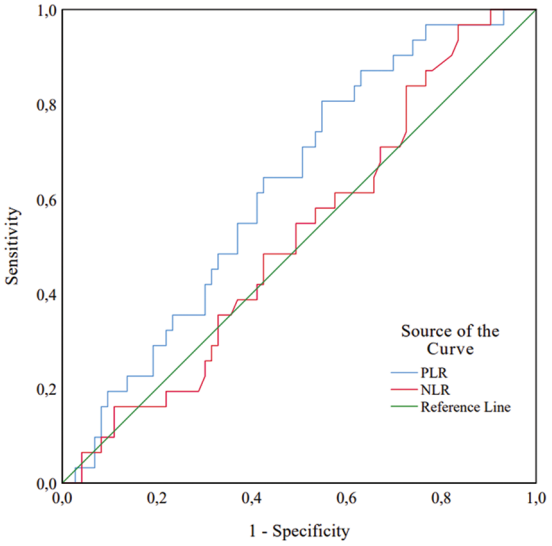

Figure 1. *ROC curve of PLR and NLR values for emergence agitation state*

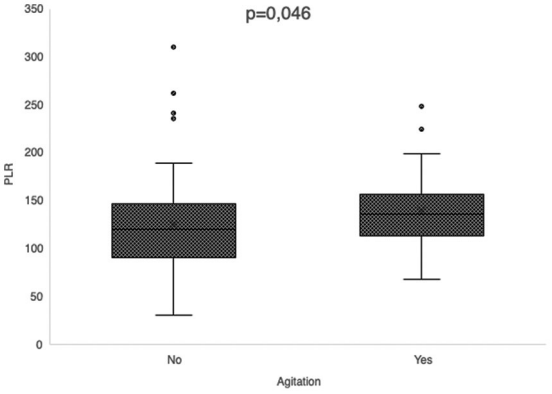

Figure 2. *Change in PLR values according to the presence of emergence agitation*

were not associated with pre-operative anxiety, STAI scale score, and BDD scale score.

Emergence agitation is a state of hyperactivity that occurs during recovery of consciousness during awakening from general anesthesia. Two mechanisms are generally emphasized in its pathophysiology. The first is sympathetic activation secondary to stimuli due to inadequately treated nociception, and the second is neuroinflammatory mechanisms because it is more common postoperatively in patients with higher inflammatory mediators (interleukin-6, tumor necrosis factor-α, and T and B lymphocytes) and endogenous catecholamine levels[1,20,21].

Stress and severe diseases may increase cortisol levels, activating neutrophil count and increasing lymphocyte apoptosis due to hypothalamic-pituitary-adrenal (HPA) axis activation[22]. While neutrophil production from the bone marrow increases, lymphopenia occurs[23]. This leads to an increase in NLR. Similarly, both stress and inflammatory factors increase platelet count, leading to high PLR levels in a lymphopenic environment[24].

NLR and PLR are frequently used to determine the severity of inflammation because of their low cost and easy applicability. Various cutoff values of NLR and PLR have been determined as prognostic or predictive biomarkers[25-27].

A study conducted in open rhinoplasties found that NLR > 2.1 was associated with severe post-operative edema, and NLR > 1.5 was associated with severe post-operative ecchymosis[28]. In this study, only a cut-off value for NLR was obtained, and PLR was not used as a prognostic or predictive biomarker, which can be considered a study limitation.

Table 2. ROC analysis result of NLR and PLR values for emergence agitation and pre-operative anxiety

Variables	Cutoff value	AUC (95% CI)	p	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Emergence agitation							
NLR		0.519 (0.402-0.636)	0.763				
PLR	≥ 113.37	0.624 (0.513-0.735)	**0.046***	80.65	45.21	38.46	84.62
Pre-operative anxiety							
NLR		0.641 (0,494-0.787)	0.082				
PLR		0.578 (0.428-0.727)	0.338				

*p < 0.05. AUC: area under curve; CI: confidence interval; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PPV: positive predictive value; NPV: negative predictive value.

Table 3. Relationship between NLR and PLR, and STAI I-II and BIDQ

Variables	NLR		PLR	
	r	p	r	p
STAI-I score	0.130	0.189	0.104	0.291
STAI-II score	–0.034	0.733	0.086	0.384
BIDQ score	0.129	0.192	0.004	0.972

r: spearman's ρ correlation coefficient; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; STAI-I: state anxiety scale; STAI-II: trait anxiety scale; BIDQ: body image disorder questionnaire.

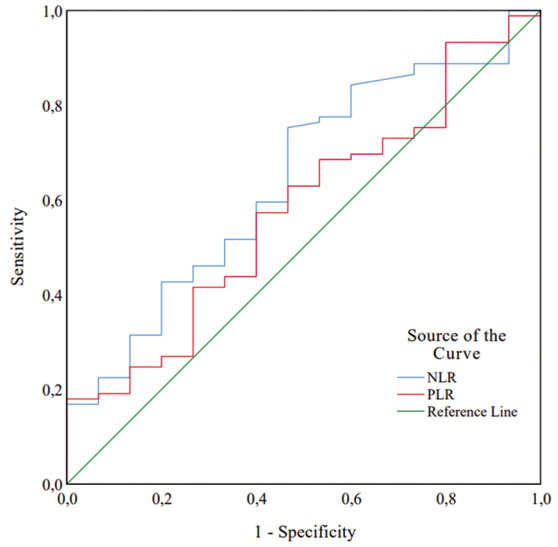

Figure 3. *ROC curve of NLR and PLR values for preoperative anxiety status.*

The role of autoimmunity and inflammation in neurocognitive pathophysiology has been the subject of many studies[29,30]. Dysregulated cognitive activation contributes to systemic inflammation in relation to HPA axis dysregulation[31]. In a review, anxiety disorders were found to be associated with chronic systemic inflammation[32].

In the central nervous system, serotonin is involved in the pathophysiology of anxiety disorders and the regulation of platelet function[33]. It is also known that peripheral platelets reflect serotonergic function when the central nervous system is inaccessible[34]. In addition, platelet activation stimulated by serotonin plays an active role in neurocognitive pathophysiology, leading to anxiety[35,36].

Experimental studies have shown that triggered stress causes inflammation and that inflammation may occur, especially in anxiety disorders secondary to acute stress[37,38]. At the same time, different studies on animals have shown that inflammation activates the limbic regions of the brain and leads to anxiety and avoidance behaviors[39,40].

In a study conducted on adolescents, it was reported that PLR (> 127.5) may indicate an increased risk of suicidality[41]. It has been reported that PLR may be more significant than NLR in patients with major depressive disorder and suicide attempts[42]. In addition, PLR was associated with the severity of major depressive disorder, especially with the psychotic process[43]. In another study, PLR was found to be an independent predictor of manic episodes[44].

In a study evaluating the risk of post-operative delirium in patients scheduled for vascular surgery, cut-off values of NLR > 3.57 and PLR > 139.2 were associated with an increased incidence of post-operative delirium[45]. High PLR values (>100) in patients admitted to the intensive care unit were reported as an independent risk factor for delirium and found to be associated with a high incidence of delirium[46].

In the literature, we did not find any study investigating the relationship between NLR and PLR and emergence agitation, pre-operative anxiety, STAI scale scores, and BDD scale scores.

Our study investigated whether pre-operative NLR and PLR are predictive markers secondary to neuroinflammation in determining the risk of post-operative

emergence agitation. As a result of our data analysis, the PLR cutoff value (113.37) was found for emergence agitation but not for NLR. Our results were consistent with the studies in the literature investigating the relationship between different psychiatric disorders and neurobiological markers. It was concluded that the significant elevation of PLR in our study was due to neuroinflammatory mechanisms in the development of emergence agitation and stress-induced HPA axis dysregulation.

BDD was included in the obsessive-compulsive and related disorders section of the Diagnostic and Statistical Manual of Mental Disorders-5 due to similarities with OCD, including repetitive behaviors[47]. In the literature, it was observed that patients with BDD who wanted to undergo cosmetic surgery were more depressed and anxious and showed frequent compulsive behaviors, resulting in excessive mental activity[48].

In a study, it was observed that chronic inflammation caused neuronal activity changes in the anterior cingulate cortex and prefrontal cortex associated with OCD[49]. In another study, it was observed that NLR and PLR values were significantly higher in adolescents with OCD and anxiety disorders compared to those with OCD alone, and it was stated that this may be the result of increased inflammatory response secondary to more irregular cognitive actions[50].

In our study, no correlation was detected between BDD scale scores and NLR, PLR, and trait anxiety scores. We attribute this to the fact that the participants were less obsessed with the nasal structures due to the region-specific nasal anatomy and, as a result, did not trigger sufficient inflammatory processes. In addition, the results of the diagnostic tests applied in the pre-operative period and used to determine both STAI level and BDD may vary according to the intellectual characteristics of the participants. As a result, the relationship between scoring systems and neurologic biomarkers cannot be determined effectively. For this reason, it may be more appropriate to use a biomarker such as PLR, which is frequently used in the literature and has high reliability in evaluating emergence agitation.

Limitations

The current study has some limitations. Regarding the current study, emergence agitation risk factors were not primarily evaluated. Concomitant proinflammatory mediators were not examined. The current study used self-report scales and was completed over a long period of time. Participants were not subjected to additional psychiatric evaluation. In addition, it can be considered a limitation that participants with a history of smoking and antidepressant use, which affect biomarker rates, should not be excluded from the study as a limitation.

Conclusions

Our study shows that PLR > 113.37 is associated with emergence agitation in patients undergoing open rhinoplasty. Clinicians can use pre-operative PLR as a predictive neurobiological marker to evaluate emergence agitation risk in patients scheduled for open rhinoplasty surgery. This way, the risk of emergence agitation can be reduced by taking necessary precautions. Additional prospective studies should be conducted to confirm our findings.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ARTÍCULO ORIGINAL

Estudio de tiempos y movimientos en el preoperatorio de cirugía de catarata

Time motion study in the preoperative phase of cataract surgery

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Resumen

Objetivo: *Identificar, mediante un estudio de tiempos y movimientos, oportunidades para acortar el diferimiento quirúrgico en cirugía de catarata.* **Métodos:** *Se desarrolló un estudio de tiempos y movimientos, no clínico, prospectivo, transversal y analítico, en el cual un grupo de expertos estimó los tiempos mínimos, habituales y máximos para 12 actividades en el preoperatorio de cirugía de catarata. Con una distribución beta se estimaron la dispersión de la duración de cada actividad y el tiempo medio por actividad y de toda la secuencia preoperatoria, desde la valoración oftalmológica inicial hasta la cirugía.* **Resultados:** *El tiempo medio del preoperatorio de la cirugía de catarata fue 269 días; la actividad con mayor dispersión fue el lapso entre la recepción de insumos y la cirugía; los estudios y las valoraciones de riesgo preoperatorio representaron el 40.9% del tiempo, y los estudios preoperatorios oftalmológicos el 17.4%.* **Conclusiones:** *Acortar la duración de las evaluaciones preoperatorias, facilitando el acceso a estudios de diagnóstico, podría reducir un 60% la duración del proceso de programación quirúrgica de catarata.*

Palabras clave: *Cirugía de catarata. Diferimiento quirúrgico. Preoperatorio. Tiempos y Movimientos.*

Abstract

Objective: *To identify opportunities of shortening surgical deferral with a time-motion study, in the preoperative phase of cataract surgery.* **Methods:** *Non-clinical, prospective, cross-sectional and analytical time-motion study; a group of experts estimated minimal, usual and maximal durations for twelve activities in the preoperative phase of cataract surgery. We used a beta distribution to estimate the dispersion of each activity's duration, as well as the mean time by activity and for the entire preoperative sequence, from initial ophthalmic evaluation to surgery.* **Results:** *Mean preoperative time in cataract surgery was 269 days; the activity with larger dispersions were the time between receiving surgical inputs and surgery; preoperative risk evaluations and studies accounted for 40.9% of the time, and ophthalmic preoperative studies consumed 17.4%.* **Conclusions:** *Shortening the length of preoperative evaluations by having an easier access to diagnostic studies, might reduce by 60% the duration of the preoperative phase of cataract surgery.*

Keywords: *Cataract surgery. Surgical deferral. Preoperative. Time-motion.*

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Introducción

El estudio de tiempos y movimientos se emplea en Administración para identificar el tiempo que consumen las actividades en un proceso y los momentos en que puede optimizarse su duración[1]. La metodología de los estudios de tiempos y movimientos puede ser directa, en la cual se asignan observadores externos al proceso para medir la duración de las actividades, o indirecta, en la cual se emplean mediciones ya realizadas o la opinión de grupos focales. En el ámbito médico, los estudios de tiempos y movimientos se aplican a procedimientos (por ejemplo, cirugía) o procesos, como las secuencias de actividades para otorgar una atención[2].

La cirugía de catarata es uno de los procedimientos realizados con mayor frecuencia[3], pero aun así existe un rezago en la cobertura global. Entre las barreras para la atención se encuentran el desconocimiento de la población sobre el padecimiento, el que las cirugías se realicen predominantemente en áreas urbanas y el costo del procedimiento.

Para los pacientes con acceso a cirugía de catarata, una limitante es el diferimiento que se presenta en las instituciones; aunque en el medio privado la resolución del padecimiento consume poco tiempo, el periodo preoperatorio institucional puede ser largo, y se carece de mediciones que permitan identificar elementos que permitan abreviarlo. Existen estudios de tiempos y movimientos en cirugía de catarata que se han enfocado principalmente al procedimiento quirúrgico[4-6]; en general, existe poca información acerca del tiempo que se requiere entre la primera evaluación oftalmológica y la cirugía de catarata.

Se desarrolló un estudio de tiempos y movimientos para identificar las actividades que consumen más tiempo en el preoperatorio de cirugía de catarata e identificar aquellas cuya duración pudiera acortarse en el ámbito institucional, con la finalidad de reducir el diferimiento quirúrgico.

Métodos

Se llevó a cabo un estudio observacional, prospectivo, transversal, analítico, no clínico, de tiempos y movimientos, para estimar el tiempo medio que se requirió para realizar una cirugía de catarata desde el momento en que un paciente ingresó a una unidad de atención médica hasta el día de la cirugía. Se trabajó con estimaciones de tiempo emitidas por un grupo de expertos, oftalmólogos especialistas en cirugía de catarata; no se incluyó información de pacientes.

Se trabajó con la información generada por cinco unidades públicas de atención médica donde habitualmente se realiza cirugía de facoemulsificación. El grupo diseñó primero una secuencia de actividades, con la cual se consideró que podría acortarse el tiempo para realizar la cirugía de catarata, las cuales fueron:

1. Valoración oftalmológica inicial.
2. Microscopía especular.
3. Cálculo del poder del lente intraocular.
4. Obtención de electrocardiograma.
5. Toma de muestras de laboratorio.
6. Toma de radiografía de tórax.
7. Valoración de riesgo quirúrgico cardiovascular.
8. Valoración preanestésica.
9. Consulta de programación quirúrgica.
10. Solicitud de insumos quirúrgicos.
11. Recepción de insumos quirúrgicos.
12. Cirugía de facoemulsificación.

Para cada actividad se estimaron el tiempo mínimo, el tiempo habitual y el tiempo máximo que requerirían en días, en forma secuencial, en cada unidad de atención médica. Los tiempos mínimo, habitual y máximo se promediaron entre las unidades. Para una distribución beta, se calculó la desviación estándar de cada actividad al dividir la diferencia entre el tiempo máximo y el tiempo mínimo (recorrido) entre seis[1].

Se identificó la duración de las actividades que requerían mayor tiempo en promedio, en forma descendente. Se utilizó una distribución beta para estimar el tiempo medio de cada actividad, con la siguiente fórmula: tiempo medio = (tiempo mínimo + [tiempo habitual × 4] + tiempo máximo)/6. El tiempo medio se redondeó al dígito superior. Se sumó el tiempo medio de cada actividad para obtener el tiempo medio de la secuencia de actividades[1]; como la actividad 8 tiene dos antecedentes, solo se consideró en la suma el de mayor duración.

Resultados

Los valores mínimos y máximos en promedio identificados para cada movimiento se presentan en la tabla 1, así como su recorrido y desviación estándar. Las actividades cuyo tiempo tuvo mayor dispersión fueron el lapso entre la recepción de los insumos y la

Tabla 1. Tiempos mínimos y máximos, recorrido y desviación estándar de los movimientos

Actividad	Descripción	Tiempo mínimo (días)	Tiempo máximo (días)	Recorrido	Desviación estándar
12	Cirugía	23	96	73	12.2
4	Obtención de electrocardiograma	7	66	59	9.8
7	Valoración cardiológica	30	62	32	5.3
3	Cálculo del poder del lente intraocular	4	54	50	8.3
9	Cita a programación quirúrgica	11	49	38	6.3
2	Microscopía especular	4	48	44	7.3
1	Valoración inicial	7	40	37	6.1
6	Toma de radiografía de tórax	11	36	25	4.2
5	Toma de muestras para laboratorio	11	30	19	3.2
8	Valoración preanestésica	7	27	20	3.3
10	Solicitud de insumos	2	17	15	2.5
11	Recepción de insumos	2	17	15	2.5

cirugía, la obtención del electrocardiograma y el cálculo del poder del lente intraocular.

Los promedios de los tiempos mínimo, habitual y máximo para cada actividad, así como el tiempo medio, se presentan en la tabla 2. Las actividades con un tiempo medio mayor fueron el periodo entre la recepción de los insumos y la cirugía, la valoración del riesgo quirúrgico cardiovascular y la obtención del electrocardiograma; las que tuvieron un tiempo medio menor fueron la solicitud y la recepción de los insumos, la valoración preanestésica y la toma de muestras para laboratorio.

El tiempo medio de la secuencia de actividades fue 269 días. La duración de la secuencia con los tiempos considerados habituales fue de 244 días, mientras que la que correspondería a los tiempos mínimos fue de 108 días.

La proporción del tiempo medio que correspondió a los estudios y las evaluaciones para el riesgo preoperatorio fue un 40.9% (110/269 días), la de los estudios oftalmológicos fue un 17.4% (47/269 días) y la del tiempo entre la recepción de los insumos y la cirugía fue un 19.3% (52/269 días).

Discusión

Se encontró un tiempo medio prolongado para llegar a realizar una cirugía electiva de catarata. Las actividades que requieren más tiempo son las correspondientes a la evaluación del riesgo preoperatorio, la realización de la cirugía una vez que se cuenta con los insumos y los estudios oftalmológicos preoperatorios.

Como referencia, el estándar de tiempo de espera para cirugía de catarata en Canadá es de 112 días[7], aunque otro estudio de ese país reportó un promedio de 95.7 ± 77 días[8]. Un estudio español reportó un tiempo de espera de 123 días[9] y un estudio australiano identificó que reducir el tiempo de espera para cirugía de catarata de 12 a 3 meses representaba un ahorro de costos al sistema de salud por la reducción en la atención de caídas y accidentes de tránsito[10].

La estimación de este estudio corresponde a unidades de atención médica que no solo atienden pacientes con catarata, que pueden requerir la valoración preoperatoria para múltiples especialidades. Además, los espacios quirúrgicos en estas unidades se comparten no solo con otras especialidades, sino también con procedimientos oftalmológicos distintos. Otra característica por considerar es que algunas unidades cuentan con los equipos para los estudios oftalmológicos, mientras que otras requieren apoyo de otra institución para realizarlos.

Cada institución participante en este estudio cuenta con un proceso propio de atención prequirúrgica, y en algunos casos los tiempos para los movimientos evaluados son menores. Al diseñar el proceso por evaluar, se consideraron actividades que podrían

Tabla 2. Promedio de tiempos en los movimientos

Actividad	Descripción	Tiempo mínimo (días)	Tiempo habitual (días)	Tiempo máximo (días)	Tiempo medio (días)
1	Valoración inicial	7	20	40	22
2	Microscopía especular	4	18	48	21
3	Cálculo del poder del lente intraocular	4	24	54	26
4	Obtención de electrocardiograma	7	35	66	36
5	Toma de muestras para laboratorio	11	13	30	16
6	Toma de radiografía de tórax	11	13	36	17
7	Valoración cardiológica	30	43	62	44
8	Valoración preanestésica	7	11	27	13
9	Cita a programación quirúrgica	11	24	49	26
10	Solicitud de insumos	2	4	17	6
11	Recepción de insumos	2	4	17	6
12	Cirugía	23	48	96	52

identificar secuencialmente a pacientes con características de riesgo para una cirugía de facoemulsificación, y que permitirían facilitar que un paciente con bajo riesgo quirúrgico tuviera un acceso más rápido a su cirugía. La secuencia de actividades varía de acuerdo con cada unidad de atención médica, que trabaja según sus procedimientos vigentes.

Una limitante del estudio es que la medición fue indirecta, dependiente de la opinión del grupo, pero la estimación de los cirujanos permite identificar los elementos del proceso que consumen más tiempo, para poder enfocar hacia ellos las acciones que puedan abreviarlos; para evaluar las modificaciones al proceso idealmente deberían observarse de manera directa las actividades y hacer una medición estandarizada, para estimar el impacto de la intervención.

Otra limitante es que las actividades varían entre las unidades de atención médica: algunas cuentan con un inventario de insumos, y contar con ellos antes de la cirugía solo requiere verificar su existencia; otras deben solicitarlos a un proveedor, por lo que asegurar su disponibilidad antes de la cirugía implica un proceso externo a la institución. Una limitante más es que el estudio no consideró los costos, lo cual limita estimar si una intervención para abreviar una actividad es viable con los recursos disponibles y si su implementación permite a futuro alcanzar una mayor eficiencia, aunque requiera una inversión adicional inicial.

Una fortaleza del estudio es que permitió comparar procesos entre instituciones, de forma indirecta. Al promediar los tiempos reportados por cada unidad puede estimarse la magnitud en la cual la duración de las actividades tendría oportunidad de cambiar, lo que puede dificultarse si solo se tiene como referencia el desempeño histórico propio.

Medir es necesario para modificar. Aun cuando las mediciones estimadas en este estudio pueden mejorar, permitieron identificar cuellos de botella sobre los cuales sería más eficaz intervenir; ampliar la cobertura de cirugía de catarata requiere aumentar los espacios quirúrgicos y optimizar el proceso preoperatorio para poder aprovecharlos.

Un factor que influye actualmente en la demora de la atención quirúrgica del paciente con diagnóstico de catarata es el tiempo transcurrido entre la solicitud de atención del paciente en la institución de salud y la valoración oftalmológica inicial; este periodo es largo y condiciona que un paciente con bajo riesgo quirúrgico pueda progresar a mediano o alto riego por variables sistémicas y oftalmológicas no controladas.

Más allá de retrasar la recuperación visual, el diferimiento en la cirugía de catarata representa para el paciente una limitación funcional que puede interferir con su movilidad para desplazarse[11,12] (con el riesgo

de presentar caídas y fracturas)[13,14] y con sus funciones cognitivas (lo que puede llevar al aislamiento y la depresión)[15,16]. Desde una perspectiva de salud pública, prevenir estas complicaciones y el beneficio de la cirugía de catarata sobre la salud en general[17,18] agrega valor a las intervenciones que permitan acortar el proceso quirúrgico, como contar con acceso rápido a recursos para la valoración preoperatoria cardiovascular y a los estudios de diagnóstico oftalmológico.

En un comentario sobre la definición de precios de la cirugía de catarata en Canadá, Falk menciona que «no es correcto permitir que la gente se deteriore en semiceguera porque no podemos organizarnos para proporcionar un procedimiento en forma oportuna»[19]. Aunque el autor hace énfasis en los costos, optimizar el proceso representa la posibilidad de mejorar significativamente el estado de salud general, y conviene esforzarse para ello.

Conclusiones

En este estudio, el 60% del tiempo que se consume entre la evaluación oftalmológica inicial y la cirugía correspondió a las valoraciones preoperatorias de riesgo y a los estudios auxiliares oftalmológicos; intervenir sobre estos elementos del proceso de atención (equipos de diagnóstico, valoraciones cardiovasculares), abreviando su duración al disponer de acceso oportuno a ellos, haría factible reducir el tiempo de espera para cirugía de facoemulsificación.

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Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

Consideraciones éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad, consentimiento informado y aprobación ética. El estudio no involucra datos personales de pacientes ni requiere aprobación ética. No se aplican las guías SAGER.

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LETTER TO THE EDITOR

Comment on: the relationship between systemic inflammation response index and gastric cancer features

Comentario sobre: la relación entre el índice de respuesta inflamatoria sistémica y el cáncer gástrico

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To the editor,

We read with great interest the article by Pehlevan-Özel et al., in which authors evaluated the prognostic significance of the Systemic Inflammation Response Index (SIRI) among patients with gastric adenocarcinoma undergoing elective gastric surgery[1]. Investigating inflammation-based biomarkers in oncology is undoubtedly a clinically relevant topic. However, several methodological aspects of the study warrant clarification to better assess the validity and generalizability of the findings.

While authors indicate they aimed to explore the association between SIRI and 3- and 5-year survival, as well as various demographic, clinical, and pathological features, the manuscript does not clearly state a primary objective. This omission is critical, as the absence of a prespecified primary endpoint raises concerns regarding the statistical power of results. In studies involving survival outcomes, clearly defining a primary endpoint is crucial for calculating an appropriate sample size and conducting hypothesis testing.

Furthermore, the methodology used to define the optimal SIRI cutoff raises essential concerns. Authors appear to have constructed a receiver operating characteristic (ROC) curve using mortality as the outcome and subsequently applied the resulting threshold to generate Kaplan-Meier survival curves for the same endpoint. This approach introduces a form of analytical circularity, as the cutoff is derived and tested on the same dataset using the same outcome variable. Without external validation or appropriate statistical correction (e.g., cross-validation), this strategy may overestimate the prognostic value of SIRI. Moreover, standard ROC analysis is suboptimal for survival data, as it does not account for censoring or time-to-event information. The use of time-dependent ROC curves or Cox-based modeling would provide a more robust assessment of the discriminatory capacity of SIRI in this context.

In addition, the generalizability of the proposed cutoff value deserves further discussion, as numerous studies have reported different SIRI thresholds depending on tumor type, patient population, and analytic method. For instance, Li et al. identified a cutoff of greater than 0.82 using ROC analysis to predict disease-free survival in patients with localized or regional gastric cancer[2]. In contrast, Gao et al. used X-tile software to determine a cutoff of $\geq$ 1.2 in a similar population[3,4]. These discrepancies illustrate that SIRI cutoffs are not universally applicable and underscore the importance of external validation. Acknowledging this variability and its implications would enhance the study's relevance to broader clinical practice.

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In conclusion, Pehlevan-Özel et al., contribute valuable data to the growing literature on systemic inflammation markers in gastric cancer. Nonetheless, clarifying the study's primary objective, detailing the methodology used to derive the SIRI cutoff, and addressing the issue of generalizability would enhance the clarity and clinical utility of their findings. In addition, we question whether Kaplan–Meier analysis was the most appropriate method to evaluate survival differences based on the SIRI cutoff, given that the threshold was derived from the same cohort using the same endpoint[5]. A multivariate Cox regression model would offer a more rigorous assessment of SIRI's independent prognostic significance. We hope these comments are received as constructive and helpful for ongoing discussions in this field.

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Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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LETTER TO THE EDITOR

Difficulties in the use of cost-effective mouse models of atrial fibrillation

Dificultades en el uso de modelos murinos costo-efectivos para fibrilación auricular

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To the editor,

In the past 10 years, the number of studies claiming to induce atrial fibrillation (AF) in mice has increased. These studies include a substrate, such as structural heart disease, pressure overload, obesity, diabetes mellitus, inflammation, ethanol exposure, or the use of selective targets identified through genome-wide association studies, as well as genetic mutations in ion channels[1].

The mouse atrial surface area is < 35 mm^2, and this limited size makes it difficult to sustain atrial tachyarrhythmias. In fact, the most effective models for AF typically involve large animals. Some research groups report that it is possible to sustain a micro-reentrant circuit in mouse models, even though the atrial tissue does not meet the critical mass requirement of > 100-200 mm^2 to induce AF[2]. Garrey postulated in 1914 that Garrey postulated in 1914 that "Any small auricular piece will cease fibrillating3". In studies reporting positive AF induction in mouse models, carbachol and electrical stimulation are often included as cost-effective methods for inducing AF, despite the limitation that such arrhythmias are non-spontaneous.

As a cost-effective alternative, and based on the positive results reported by Chiba and Hashimoto (1971) in beagle dogs using carbachol and epinephrine, induction of AF through pharmacological protocols appears feasible. In a pilot study, we utilized nine wild-type mice divided into three groups. Administration of carbachol combined with epinephrine at higher doses in one group resulted in sinus pause, sinus bradycardia, and severe bradycardia when delivered by epicardial drip (thoracotomy and mechanical ventilation were used). First-degree atrioventricular block was observed in one out of three mice, but no mouse developed AF. Fig. 1 shows representative electrocardiograms illustrating each observed effect.

Carbachol is a potent compound with a longer duration of action compared to acetylcholine. In the study performed by Chiba and Hashimoto, carbachol alone was sometimes insufficient to trigger AF; therefore, epinephrine was administered to enhance the adrenergic response. Cholinergic stimulation shortens the action potential, and carbachol, as a muscarinic receptor agonist, is reported to reduce atrial refractoriness and facilitate reentrant circuits. Furthermore, it has been proposed that epinephrine can help trigger AF by increasing adrenergic activity[4].

In recent decades, research on acute AF in mice has commonly employed protocols that combine carbachol administration with high-frequency electrical stimulation of the atrium to induce AF, potentially altering the activity of intrinsic cardiac ganglia. In 2022, Fu et al. compared various murine AF models, including those using carbachol and burst pacing. Using optical mapping, they observed that the induced atrial

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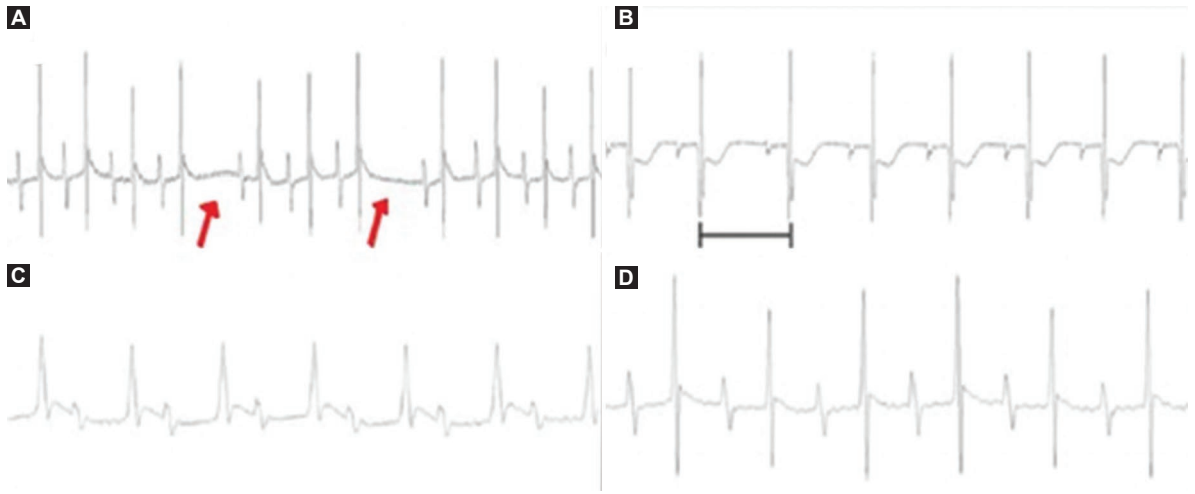

Figure 1. A*: Sinuses pause (red arrows).* **B***: Bradycardia.* **C** *and* **D***: first-degree atrioventricular block.*

tachyarrhythmias more closely resembled atrial flutter-like arrhythmias rather than typical AF[5].

Genetically modified mice, which provide a more physiologically relevant model, have proven to be the most effective for developing spontaneous AF, although they are not the most cost-effective option. The literature suggests that the combination of carbachol and electrical stimulation remains the most cost-effective method to induce AF to date, despite its limitations of producing non-spontaneous arrhythmias and challenges in interpreting positive AF cases[5]. However, this method is not always affordable for researchers in underdeveloped countries. Therefore, exploring alternative pharmacological and instrumental approaches is crucial to advancing arrhythmia research, as well as improving access to modern techniques for verifying AF in mice, such as optical mapping.

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Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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LETTER TO THE EDITOR

The role of omega-3 fatty acids in modulating inflammatory response after surgery

El papel de los acidos grasos omega-3 en la modulación de la respuesta inflamatoria despues de cirugía

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To the editor:

Surgical trauma induces an immunological response, characterized by the activation of cytokines during the post-operative period. Cytokines play a crucial role in coordinating the inflammatory response at the injury site, aiding the wound healing process. However, excessive cytokine production can lead to systemic effects, potentially causing complications and mortality after surgery. Major abdominal surgeries, in particular, can provoke a systemic inflammatory response, leading to significant complications such as organ damage and failure. Numerous studies have highlighted the predictive value of post-operative inflammatory markers for complications and mortality. For instance, higher post-operative interleukin (IL)-6 levels on the 1st day after surgery are significant predictors of post-operative complications[1,2].

Natto et al. in 2014, investigated C-reactive protein (CRP) levels post-major surgeries (cardiac, neuro, vascular, thoracic, or abdominal) in approximately 150 patients, finding that patients with post-operative complications had higher baseline CRP levels. This suggests that reducing post-operative inflammation through anti-inflammatory mechanisms could improve outcomes[3]. Polyunsaturated fatty acids (PUFAs), particularly omega-3 fatty acids, are vital components of cell membranes and precursors for various inflammatory mediators. Omega-3 PUFAs, including α-linolenic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), have been recognized for their immune-modulating properties and potential to reduce chronic inflammation in diseases such as coronary artery disease and diabetes[4].

Research on rodents and humans has demonstrated the anti-inflammatory effects of omega-3 fatty acids, particularly their ability to inhibit IL-6 production by venous endothelial cells in response to endotoxins. For instance, Kiecolt-Glaser et al. found that omega-3 supplementation significantly reduced IL-6 levels in overweight, inactive, middle-aged adults. In addition, Natto et al.'s analysis concluded that omega-3 supplementation was associated with reduced inflammatory markers in individuals with diabetes and cardiovascular diseases[4,5].

EPA and DHA inhibit the production of arachidonic acid (AA)-derived eicosanoids, which regulate inflammation. The EPA/AA ratio influences inflammatory pathways, potentially impacting cancer and chronic inflammatory disorders such as atherosclerosis and cardiovascular disease. Given omega-3 fatty acids' anti-inflammatory properties, their potential benefits in the context of abdominal surgery warrant investigation.

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DHA and EPA reduce inflammation primarily by decreasing eicosanoid synthesis from AA. They compete with AA for incorporation into cell membrane phospholipids, thereby reducing AA availability. This reduction is partly due to the suppression of COX-2 and 5-LOX enzymes, which are involved in AA metabolism. In addition, DHA and EPA inhibit the activation of the proinflammatory transcription factor nuclear factor kappa by preventing the phosphorylation of its inhibitory subunit, I-κB. Furthermore, DHA and EPA promote the synthesis of Resolvin E and D, which possess anti-inflammatory properties by preventing neutrophil migration and IL-1β production[6].

In conclusion, the immunomodulatory effects of omega-3 fatty acids, particularly EPA and DHA, represent a promising area for mitigating post-operative inflammation and improving surgical outcomes. Further research is essential to elucidate their potential benefits in the context of major abdominal surgeries. The integration of omega-3 supplementation into post-operative care protocols could revolutionize our approach to managing inflammation and enhance patient recovery. Despite evidence supporting the anti-inflammatory effects of omega-3 fatty acids, their impact on reducing inflammation after major abdominal surgery remains inconclusive.

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LETTER TO THE EDITOR

Comments on "Morbidity and mortality of emergency surgery in octogenarian patient"

Comentarios a "Morbimortalidad de la cirugía de urgencia en el paciente octogenario"

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To the Editor,

I reviewed the study by Morales-García et al.[1] The elderly population is increasing due to advancements in health-care services and improvements in socioeconomic conditions. Consequently, there has been an increase in surgical procedures performed on octogenarians and nonagenarians. In this frail patient population, diminished organ reserves reduce surgical tolerance and contribute to increased morbidity and mortality. In emergency surgeries, the uncertainty regarding organ reserves particularly heightens the risk of unforeseen post-operative complications.

First, although frailty increases with advancing age, post-operative morbidity and mortality are more closely associated with frailty than with chronological age. It has been reported that using different frailty assessment tools for various types of surgeries may be appropriate for detecting this condition[2]. Therefore, utilizing frailty indices rather than chronological age is likely to yield more accurate results.

Second, it has been shown that among geriatric patients, the prevalence of hip fractures can reach up to 29.6% in nonagenarians[1]. However, a study by Reguant et al. demonstrated that, in elderly patients with hip fractures, delaying surgery in favor of a multidisciplinary approach to improve overall health status resulted in reduced morbidity and mortality compared to performing emergency surgery[3].

Finally, in acute abdominal surgery, variations in etiology (such as mesenteric ischemia, acute appendicitis, and volvulus) will result in variable morbidity and mortality outcomes for the different surgical procedures performed. A study has shown that in perioperative exploration, a contaminated or dirty surgical site and a delta neutrophil index ≥ 0.05 are independent risk factors for mortality in the octogenarian and nonagenarian populations[4]. Therefore, in abdominal surgery, it is crucial to specify the contamination status of cases and whether patients are in a septic state.

I congratulate the authors for their valuable contribution to the literature and look forward to their responses with great anticipation.

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LETTER TO THE EDITOR

Leveraging the power of microbiota for enhanced surgical recovery: new perspectives on probiotics and pre-biotics supplementation

Aprovechando el poder de la microbiota para una recuperación quirúrgica acelerada: nuevas perspectivas sobre la suplementación con probióticos y prebióticos

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To the Editor,

Research on the gut microbiome has been gaining momentum for a long time. The term "probiotics" was first used in 1992 to describe "a preparation of or a product containing viable, defined microorganisms in sufficient numbers, which alter the microflora (by implantation or colonization) in a compartment of the host and by that exert beneficial health effects in this host". Pre-biotics, defined as "non-digestible food ingredients (fiber) that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon", have recently attracted a lot of attention. The fiber is converted into short-chain fatty acids by these bacteria, which have positive benefits both locally and systemically[1,2]. Probiotics and pre-biotic fiber are two examples of dietary supplements that may rapidly alter the gut flora. Actually, the microbiome can undergo a dramatic shift in just 24 h in response to a dietary fiber increase or decrease.

Prebiotics and probiotics exhibit anti-inflammatory properties, among other effects. The inflammatory response elicited by surgical procedures necessitates an investigation into the potential role of pre-biotics and probiotics in modulating immune responses during the perioperative period, as well as their impact on surgical outcomes[3].

The immune system constitutes a complex network of pathways regulated by binary signaling molecules. An inadequate or excessive concentration of any of these molecules can result in considerable downstream effects. The existing evidence linking specific inflammatory mediator concentrations to surgical outcomes is limited; nonetheless, the necessity to reduce excessive inflammation is unequivocal. Increased levels of inflammatory cytokines correlate with post-operative delirium, heightened muscle catabolism, and prolonged hospital and ICU stays. Cytokines play a crucial role in increasing the permeability of the blood–brain barrier, affecting the hippocampus and potentially resulting in delirium and cognitive decline[4]. Inflammation compromises the integrity of the mucosal barrier. This issue is pertinent to surgical procedures as a compromised mucosal barrier can exacerbate systemic inflammation through the entry of bacterial metabolites, fragments, and possibly intact bacteria into systemic circulation. Studies demonstrate that pre-biotics and probiotics enhance the mucosal barrier through multiple mechanisms[5].

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If the objective is to mitigate inflammation, one may inquire about methods to regulate the immune response. The regular application of pre-biotics and probiotics may alter our inflammatory condition and could have ramifications during the perioperative phase. A recent study involved 52 colorectal cancer patients who received either a placebo or a probiotic supplement comprising lactobacillus and bifidobacterium for 6 months post-surgery. Participants in the probiotic group exhibited a substantial decrease in pro-inflammatory cytokines tumor necrosis factor-α, interleukin-6 (IL)-6, IL-10, IL-12, IL-17A, IL-17C, and IL-22. In this study, Zaharuddin et al. highlight that IL-10 and IL-12 have dual activity as both anti-inflammatory and pro-inflammatory cytokines; nevertheless, the research did not identify a significant rise in exclusively pro-inflammatory cytokines with probiotic administration[6]. Recognizing the importance of tailored nutritional strategies, the integration of personalized pro-biotic and pre-biotic regimens into perioperative protocols represents a forward-thinking approach that could redefine standard surgical care.

In conclusion, leveraging probiotics and pre-biotics during the perioperative period offers promising potential to enhance recovery outcomes by modulating immune responses, strengthening the mucosal barrier, and reducing post-operative inflammation. The anti-inflammatory and barrier-supportive effects of these supplements can mitigate complications, such as post-operative delirium, muscle catabolism, and prolonged hospitalization. Further research is warranted to solidify the clinical guidelines and optimize the supplementation strategies for specific surgical populations, ultimately improving patient care and recovery pathways.

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