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ORIGINAL ARTICLE

Impact of COVID-19 history on anxiety and complications in elective cesarean sections

Impacto del antecedente de COVID-19 en la ansiedad y las complicaciones en las cesáreas electivas

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Abstract

Objectives: *This study aims to examine the effect of COVID-19 history on pre-operative anxiety and intraoperative complications in elective cesarean section patients.* **Methods:** *A total of 200 patients undergoing elective cesarean section were divided into two groups based on COVID-19 history: Group C (n = 100, with COVID-19) and Group K (n = 100, without COVID-19). Anxiety was assessed using the state-trait anxiety inventory (STAI) I and II. Vital signs were monitored peroperatively. Intraoperative complications and APGAR scores were recorded.* **Results:** *Pregnant women with a history of COVID-19 had significantly higher state anxiety (STAI-1) scores than those without (p = 0.017). No significant difference in intraoperative or post-operative complications was observed between the groups.* **Conclusions:** *Anxiety levels were higher in pregnant women undergoing elective cesarean sections, especially those with a history of COVID-19. Managing increased anxiety is essential because of its potential effects on maternal and neonatal health outcomes.*

Keywords: *Pre-operative anxiety. COVID-19. Elective cesarean section. Intraoperative complications.*

Resumen

Objetivos: *Examinar el efecto de los antecedentes de COVID-19 sobre la ansiedad preoperatoria y las complicaciones intraoperatorias en pacientes sometidas a cesárea electiva.* **Métodos:** *Un total de 200 pacientes sometidas a cesárea electiva se dividieron en dos grupos en función de los antecedentes de COVID-19: grupo C (n =100, con COVID-19) y grupo K (n = 100, sin COVID-19). La ansiedad se evaluó mediante el Inventario de Ansiedad Estado-Rasgo I y II. Se controlaron las constantes vitales durante la operación. Se registraron las complicaciones intraoperatorias y las puntuaciones APGAR.* **Resultados:** *Las embarazadas con antecedente de COVID-19 presentaron puntuaciones de ansiedad estado (STAI-1) significativamente más altas que las que no lo tenían (p = 0.017). No se observaron diferencias significativas en las complicaciones intraoperatorias y posoperatorias entre los grupos.* **Conclusiones:** *Los niveles de ansiedad fueron mayores en las embarazadas sometidas a cesárea electiva, especialmente en aquellas con antecedente de COVID-19. Es esencial controlar el aumento de la ansiedad debido a sus posibles efectos en los resultados de salud maternos y neonatales.*

Palabras clave: *Ansiedad preoperatoria. COVID-19. Cesárea electiva. Complicaciones intraoperatorias.*

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Introduction

Pre-operative anxiety, characterized by tension toward anesthesia and surgery, typically initiates with the anticipation of hospitalization.[1] High anxiety levels can lead to emotional and physical stress, affecting post-operative recovery, pain, and potentially delaying same-day discharge. Anesthesiologists play a key role in reducing anxiety by establishing trust and guiding the patient through the process, from preparation to recovery.[2]

Pregnant women commonly experience anxiety pre-operatively due to concerns about post-operative pain, fear of not waking up from anesthesia, and worries about divulging personal information under its influence.[3] Pre-operative anxiety in pregnant women undergoing cesarean section is associated with peri-operative complications. The mental health of the pregnant woman is crucial as it can impact the emotional bond between mother and fetus and increase the likelihood of adverse neonatal outcomes such as intrauterine growth retardation, preterm delivery, and low birth weight.[4]

The COVID-19 pandemic, declared a global pandemic by the World Health Organization on March 11, 2020, has significantly impacted global health, with cases detected across 113 countries. The pandemic's widespread effects have heightened anxiety levels and increased uncertainties regarding risks, particularly impacting the mental health of pregnant individuals.[5]

Understanding pre-operative anxiety in pregnant women is essential for developing strategies to manage anxiety effectively and mitigate perioperative complications. This study aims to contribute to the literature by exploring the relationship between pregnancy data, demographic characteristics, COVID-19 history, and anxiety levels in pregnant women scheduled for elective cesarean section. In addition, we discuss factors that may influence anxiety levels and intraoperative complications in this population.

Methods

Our study included 200 volunteer patients aged between 20 and 45 years, classified as American Society of Anesthesiologists risk II-III, scheduled for elective cesarean section at the gynecology and obstetrics clinic between July 1, 2022, and May 1, 2023, following approval from the local ethics committee (2022/145). The study was conducted prospectively.

Exclusion criteria: patients with a body mass index > 35 kg/m^2, allergies to induction agents or opioids, use of medications for chronic pain, active infections, autoimmune, cardiovascular, gastrointestinal, or neurological diseases, renal or hepatic failure, chronic respiratory pathology, malignancies (colorectal, gastric, pancreatic, esophageal, lung, gynecological, etc.), chronic systemic diseases (hypertension and diabetes mellitus), hematological disorders (leukocyte and platelet diseases), and psychiatric disorders under treatment were excluded from the study. Patients who were uncooperative or unable to undergo physical and verbal performance comparisons were also excluded from the study. New participants were recruited to replace any excluded patients to achieve the planned sample size.

All patients underwent preanesthetic examinations the day before surgery. They received verbal and written information about the study and provided informed consent. Patients with a history of COVID-19, asymptomatic (no symptoms were present during the infection period), moderate (patients who had mild symptoms that did not require hospitalization), and severe (patients who required hospitalization or intensive care for their COVID-19 infection) were classified.

Pre-operative anxiety levels were assessed using the state-trait anxiety inventory (STAI), consisting of STAI-I (state anxiety) and STAI-II (trait anxiety) tests. Patients scoring 60 and above on STAI-II were excluded. Anxiety levels were categorized as follows: scores < 30 indicating little or no anxiety, 31-49 indicating moderate anxiety, and 50 and above indicating severe anxiety.

Patients were divided into two groups based on whether they had a history of COVID-19 in the past year: Group C (with COVID-19 history, n = 100) and Group K (without COVID-19 history, n = 100).

Non-invasive measurements, including mean arterial pressure (MAP), systolic arterial pressure (SAP), diastolic arterial pressure (DAB), heart rate (HR), peripheral oxygen saturation (SpO_2), and electrocardiogram were recorded. Intravenous access was established with an 18-G catheter, and 0.9% NaCl infusion was administered at 5-10 mL/kg/h. Spinal anesthesia was performed using 12 mg bupivacaine with a 25 g spinal needle. Oxygen supplementation was provided through a transparent mask as needed.

Data collection

Vital signs (SAB, DAB, MAP, HR, and blood pressure) were recorded during ward follow-up, pre-operative waiting period, intraoperative periods (0 min, 15 min, 30 min, 45 min, 60 min, 90 min after surgical incision), and post-operative period. SpO_2 values were documented accordingly. Intraoperative complications and APGAR scores of newborns were also noted.

Following surgery, patients were transferred to the post-anesthesia care unit (PACU). Vital signs (SAB, DAB, MAP, HR, and SpO_2) upon PACU admission and discharge were recorded. Stable patients were then transferred to the obstetrics and gynecology service.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences 23.0. Descriptive statistics were presented as numbers/percentages for categorical variables and as mean, standard deviation, minimum, and maximum for numerical variables. To control for confounding variables such as age, gestational week, previous cesarean history, and chronic illness, multivariate regression analysis was performed. Normal distribution was assessed using the Kolmogorov-Smirnov test. Parametric tests (Student's t-test, analysis of variance) were used for normally distributed data, whereas non-parametric tests (Mann-Whitney U test, Kruskal-Wallis test) were used otherwise. Chi-square analysis was employed for categorical data. *Post hoc* analysis evaluated differences between groups. Significance level was set at $p < 0.05$.

Sample size calculation

The Open Epi 3.01 program was used to calculate the sample size. Based on previous studies, 25% of pregnant women without severe acute respiratory syndrome coronavirus 2 infection were reported to have anxiety. Assuming a 45% anxiety rate in pregnant women with COVID-19, with a type 1 error of 5% and power of 80%, the study required a total of 196 participants (98/group).

Results

The study initially involved 304 pregnant women. Of these, 61 were excluded due to emergency situations, 24 due to chronic diseases, and 19 declined to participate, resulting in a final analysis of data from 200 patients.

Demographic characteristics, including age, weight, education level, income-generating employment, smoking status, infant gender, gestational week, history of miscarriage, and history of *in vitro* fertilization (IVF), were compared between the groups with and without a history of COVID-19 infection. Statistical analysis (Table 1) showed no significant differences between the groups ($p > 0.05$).

The intraoperative MAP follow-up values were analyzed based on the history of COVID-19 infection. Graph 1 illustrates that there was no statistically significant difference in MAP values between patients with and without a COVID-19 history ($p > 0.05$) (Fig. 1).

STAI-1 (state anxiety) and STAI-2 (trait anxiety) scores were evaluated in relation to COVID-19 history among pregnant participants. Table 2 reveals that STAI-1 scores were significantly higher in Group C (with COVID-19 history) compared to Group K (without COVID-19 history) ($p = 0.017$). However, there was no significant difference in STAI-2 scores between the two groups.

Complications during the perioperative period were compared between patients with and without COVID-19 history. Table 3 shows that there was no statistically significant difference in the development of specific complications between the groups, except for bradycardia ($p > 0.05$). Complications occurred in 67 (33.5%) of the pregnant women, with the most common being nausea and vomiting in 47 (23.5%) patients.

Apgar scores at 1st and 5th min were analyzed according to COVID-19 history. Table 4 indicates that there were no statistically significant differences in APGAR scores between the groups at the 1st min and 5th min ($p > 0.05$).

Discussion

In this study, we investigated the pre-operative anxiety levels in pregnant women undergoing elective cesarean section with and without a history of COVID-19 infection. We found a significant difference in state anxiety (STAI-1) between the two groups, suggesting that a history of COVID-19 may contribute to higher levels of acute anxiety in pregnant women facing surgery. We also identified factors such as a history of IVF and non-active employment status that influenced anxiety levels in pregnant women with COVID-19 history.

Table 1. Comparison of demographic characteristics between groups with and without a COVID-19 history

Variables	Total (n = 200)		Group C (n = 100)		Group K (n = 100)	
Age (years), mean ± SD	32.0 ± 5.5		32.6 ± 5.7		31.4 ± 5.4	
Weight (kg), mean ± SD	81.7 ± 12.9		81.0 ± 12.1		82.4 ± 13.8	
COVID-19 symptoms, n (%)						
Asymptomatic	82		82 (72)		NA	
Moderate	13		13 (20.0)		NA	
Severe	5		5 (51.0)		NA	
Working status, n (%)						
Yes	47		29 (29.0)		18 (18.0)	
No	153		71 (71.0)		82 (82.0)	
Smoking status, n (%)						
None	175	87.5	89	89.0	86	86.0
Before pregnancy	14	7.0	6	6.0	8	8.0
Before and during pregnancy	11	5.5	5	5.0	6	6.0
Gestational week, mean ± SD	37.4 ± 2.1		37.2 ± 1.8		37.6 ± 2.3	
Baby gender, n (%)						
Female	105		52 (52.0)		53 (53.0)	
Male	95		48 (48.0)		47 (47.0)	
History of miscarriage, n (%)						
Yes	43		19 (19.0)		24 (24.0)	
No	157		81 (81.0)		76 (76.0)	
History of *in vitro* fertilization, n (%)						
Yes	7		4 (4.0)		3 (3.0)	
No	193		96 (96.0)		97 (97.0)	

SD: standard deviation; NA: not applicable.

Table 2. Comparison of STAI-1 and STAI-2 scores according to COVID-19 history

Variables	Group C	Group K	p
STAI-1 score	50.9 ± 13.0	47.0 ± 10.2	0.017*
STAI-2 score	46.4 ± 9.1	44.9 ± 7.7	0.142

*p < 0.05 indicates statistical significance.
STAI: state-trait anxiety inventory.

Table 3. Comparison of complication development according to COVID-19 history

Complications	Group C n (%)	Group K n (%)	p
Any complication present			
Yes	34 (34.0)	33 (33.0)	1.000
No	66 (66.0)	67 (67.0)	1.000
Nausea-vomiting			
Yes	23 (23.0)	24 (24.0)	1.000
No	77 (77.0)	76 (76.0)	1.000
Mask oxygen requirement			
Yes	8 (8.0)	5 (5.0)	0.568
No	92 (92.0)	95 (95.0)	1.000
Spinal block level increase			
Yes	5 (5.0)	5 (5.0)	1.000
No	95 (95.0)	95 (95.0)	1.000
Bradycardia			
Yes	1 (1.0)	5 (5.0)	0.097
No	99 (99.0)	95 (95.0)	1.000
Bleeding			
Yes	2 (2.0)	2 (2.0)	1.000
No	98 (98.0)	98 (98.0)	1.000

Pregnancy inherently involves physiological and psychological changes, often accompanied by increased levels of fear and anxiety, particularly in the context of impending surgery.[6] Studies by Rubertsson et al. and Morris et al. have consistently shown high anxiety levels among pregnant women scheduled for cesarean sections, with a significant portion experiencing severe anxiety.[7,8] Our findings align with these studies, indicating that pre-operative anxiety remains a prevalent concern among pregnant women.

The COVID-19 pandemic has significantly influenced global mental health, exacerbating anxiety and depression in the general population.[4] Our study aimed to evaluate this impact specifically among pregnant women who had experienced COVID-19. Studies by Khubchandani et al. and Ayaz et al. highlighted increased psychological distress and anxiety symptoms in COVID-19 survivors and pregnant women during the pandemic.[9,10] Similarly, our findings indicate

Table 4. Comparison of APGAR scores (1st and 5th min) according to COVID-19 history

Variables	Group C	Group K	p
APGAR 1st min (mean ± SD)	6.3 ± 1.4	6.6 ± 1.4	0.098
APGAR 5th min (mean ± SD)	7.8 ± 1.1	7.8 ± 1.3	0.743

SD: standard deviation.

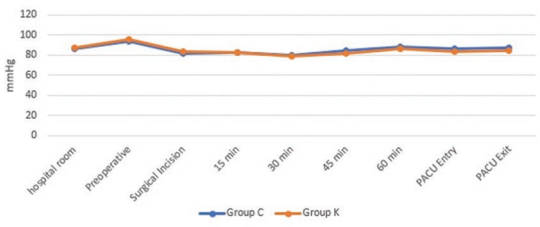

Figure 1. *Intraoperative mean arterial pressure follow-up values according to COVID-19 history.*

that pregnant women with a history of COVID-19 exhibited significantly higher state anxiety levels compared to those without such a history.

In a survey study conducted by Zainiyah and Susanti among 70 pregnant women during the coronavirus pandemic, it was shown that 31.4% of pregnant women experienced very severe anxiety, and 12.9% experienced severe anxiety. It was emphasized that anxiety during the coronavirus pandemic is an important issue that should be addressed in pregnant women to prevent negative effects on the mother and unborn child.[11] In our study, the STAI-1 (state) score of pregnant women with a history of COVID-19 was statistically significantly higher than that of those without a history of COVID-19. In terms of STAI-1 levels, severe anxiety level was found to be statistically significantly higher than moderate and mild anxiety levels in pregnant women with a history of COVID-19 compared to those without a history of COVID-19.

Literature reports varying impacts of COVID-19 on perioperative complications among pregnant women.[12] Studies like those by Zhang et al. have observed higher incidences of complications such as hypotension in COVID-19-positive pregnant women undergoing cesarean sections.[13] However, our study, consistent with findings from Kho et al., did not find significant differences in complication rates between pregnant women with and without a history of COVID-19.[14]

The relationship between COVID-19 during pregnancy and neonatal outcomes remains an area of active investigation. There are studies that found a significant association between low Apgar scores and neonatal intensive care unit admission in pregnant women with active COVID-19 infection, as well as studies showing that pregnancy-related anxiety increased during the COVID-19 pandemic, but this did not have a direct effect on neonatal outcomes after cesarean section.[15-18] In our study, we did not find significant differences in Apgar scores at 1st and 5th min between groups with and without COVID-19 history, likely due to the absence of active infection and emergency cases in our study cohort.

Previous research has established a link between maternal anxiety levels and neonatal outcomes, including lower Apgar scores.[19,20] Our study also found that higher state anxiety levels (STAI-1) were associated with lower Apgar scores at both 1st and 5th min. This underscores the importance of managing maternal anxiety to potentially improve neonatal outcomes.

Limitations

This study has limitations, including its single-center design and exclusion criteria that may limit generalizability. In addition, the study did not assess long-term maternal mental health outcomes beyond the immediate perioperative period. Future studies could benefit from larger, multicenter designs and longitudinal follow-up to comprehensively evaluate these relationships.

Conclusions

Our study highlights the heightened anxiety levels among pregnant women with a history of COVID-19 undergoing elective cesarean section. The pandemic context has exacerbated anxiety, which may impact perioperative and neonatal outcomes. Effective management of pre-operative anxiety is crucial to mitigate potential complications and improve maternal and neonatal health outcomes. Future research should continue to explore the long-term impacts of the COVID-19 pandemic on maternal mental health and pregnancy outcomes.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study. Ethical approval for this study (Ethical Committee 2022/145) was provided by the Local Ethical Committee.

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

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ORIGINAL ARTICLE

Impact of psoas muscle area measurement in complex open abdominal aortic aneurysm repair

Impacto de la medición del área del músculo psoas en la reparación de aneurismas de aorta abdominal complejos

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Abstract

Objective: *Cross-sectional psoas muscle area (PMA), measured by computed tomography images, is a surrogate of the muscle mass. We aimed to evaluate the impact of PMA and length of stay (LOS) after complex open abdominal aortic aneurysm repair (OAAAR).* **Methods:** *A retrospective review between January 2013 and January 2017 was conducted. The main outcome was to assess the PMA as a predictor of LOS. Demographics and clinical variables were collected, and Spearman's rank coefficient was used to define the correlation of PMA and LOS.* **Results:** *A total of 72 patients were studied with a mean age of 72 (standard deviation ± 10.3) years, and 54 (75%) were males. The median post-operative LOS was 10 (7-14) days; lower PMA was correlated with longer LOS ($R = -0.47$, $p \leq 0.001$). Thirty-six patients (50%) had a PMA < 17 cm^2, which was associated with greater post-operative 30-day complications ($p = 0.004$). There was no difference in 30-day mortality between patients with PMA < 17 cm^2 and those with PMA > 17 cm^2 ($p = 0.147$).* **Conclusions:** *Lower PMA was associated with longer LOS and a higher rate of 30-day complications; however, no statistically significant difference was found in mortality.*

Keywords: *Psoas muscle area. Length of stay. Abdominal aortic aneurysm. Open repair. Clinical outcomes.*

Resumen

Objetivo: *Evaluar el impacto de la medición del área del músculo psoas (AMP) en la estancia hospitalaria (EH) posterior a la reparación abierta de los aneurismas de aorta abdominal (RAAAA) complejos.* **Métodos:** *Revisión de pacientes que fueron sometidos a RAAAA entre enero de 2013 y enero de 2017. El objetivo principal fue la evaluación de la medición del AMP como predictor de EH. Se documentaron variables demográficas y clínicas, y se utilizó el coeficiente de Spearman para correlacionar el AMP y la EH.* **Resultados:** *Se incluyeron 72 pacientes con una media de edad de 72 años (DE: 10.3), de los que 54 (75%) eran hombres. La mediana de EH fue de 10 (7-14) días. Un AMP baja se correlacionó con una EH prolongada ($R = -0.47$; $p < 0.001$). Treinta y seis pacientes (50%) tuvieron AMP < 17 cm^2, y se asoció con mayor tasa de complicaciones a 30 días ($p = 0.004$). No se observaron diferencias en cuanto a mortalidad ($p = 0.147$).* **Conclusiones:** *Un AMP baja se asoció a una EH más larga y a mayores tasas de complicaciones a 30 días; sin embargo, no hubo diferencia significativa en cuanto a mortalidad.*

Palabras clave: *Área del músculo psoas. Estancia hospitalaria. Aneurisma de aorta abdominal. Reparación abierta. Resultados clínicos.*

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Introduction

The proportion of older adults is expected to increase within the next few years, particularly in countries where the demographic transition is accelerated.[1] By 2050, almost 23% of the total population will be 60 years or older, 3 times greater than what it was in 2010. Regrettably, this has seemed to be accompanied by an increase in chronic diseases.[1] Due to the increased prevalence of arterial hypertension and diabetes, there will also be an increase in the incidence of arterial diseases; therefore, more vascular interventions in the elderly population will be needed. Age-related changes have demonstrated a negative impact on outcomes in the older population, such as increased mortality and complications after abdominal surgery, and some others related just to hospitalization. Some age-related complications, such as delirium, urinary incontinence, pressure ulcers, depression, infection, and decline in functionality, can influence post-operative outcomes.[2,3] In terms of surgery decision making, the eligibility of older adults has become an important issue, and the need for objective parameters that could help to identify patients at higher risk of post-operative complications and hospitalization length of stay (LOS) is still necessary.[4]

Sarcopenia is a geriatric syndrome characterized by a decline in skeletal muscle mass and decreased strength,[5] it has been studied in multiple scenarios. It is known to be related to higher mortality and post-operative complications in older adults after abdominal and cardiovascular surgeries.[2,6,7] There are many ways to identify sarcopenia, and the choice of measurement depends on the patient and the resources that each hospital can access. Psoas muscle area (PMA) measured by computed tomography (CT) has been used to identify sarcopenia in pre-operative patients.[5] Some authors have found PMA association with adverse outcomes in cardiovascular surgeries.[8] This study aims to determine the association of PMA and LOS after open aortic aneurysm repair, and whether PMA has an impact on post-operative complications in these patients.

Methods

We performed a retrospective perioperative CT scan analysis of patients who underwent open abdominal aortic aneurysm repair (OAAAR) at our third-level referral center in Mexico City. The PMA was measured at the level of the L3 vertebrae; this was defined as the CT slice including the most inferior portion of the L3 vertebral body. Data of patients with an OAAAR treated between January 2013 and January 2017 were collected. Patients with an acute rupture were excluded because of higher morbidity and mortality. Demographic characteristics, complications, and outcomes were obtained from medical records.

Patients were divided into two groups to compare LOS, we defined the cut-off point, as the median of days after surgery in all patients. As a secondary outcome, we divided the patients by their mean PMA into two groups for comparison. This research project follows the regulations of an institution and the generally accepted guidelines governing this work. For this study, informed consent was not required.

PMA determination

CT scans were performed before all procedures for clinical evaluation, and Osirix MC (Pixmeo SARL, Geneva, Switzerland) multiplanar reformatting software was used to measure the right and left PMA in an axial plane. (Fig. 1) The L3 level was selected in accordance with the European Working Group on Sarcopenia in Older Adults recommendations for the diagnosis of sarcopenia.[5] Interobserver mean differences were assessed in two observers researches by measuring the PMA in 20 randomized patients. PMA values were represented as continuous variables with a mean PMA in the study group.

Statistical analysis

Categorical variables are shown as frequencies and continuous variables as mean ± standard deviation or as median and interquartile range. Spearman's rank correlation coefficient was used to assess the linear correlation between PMA and LOS. Distribution of categorical variables was compared using the X^2 test. Continuous variables were compared with a univariate test, and statistical significance was considered at a two-sided $p < 0.05$. Data were collected and analyzed using the Statistical Package for the Social Sciences (IBM SPSS, version 22, IBM Corp., NY, USA).

Results

A total of 72 patients were included in this study, with a mean age of 72 ± 10 years, and 75% (54 patients)

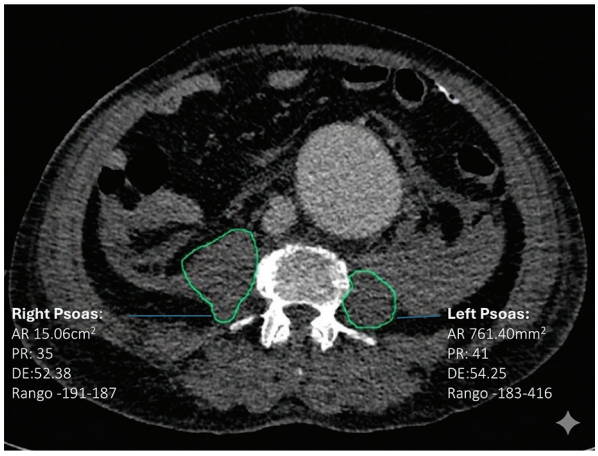

Figure 1. *Cross-sectional view of the computed tomography with the Psoas muscle area measurement in a patient with an abdominal aortic aneurysm.*

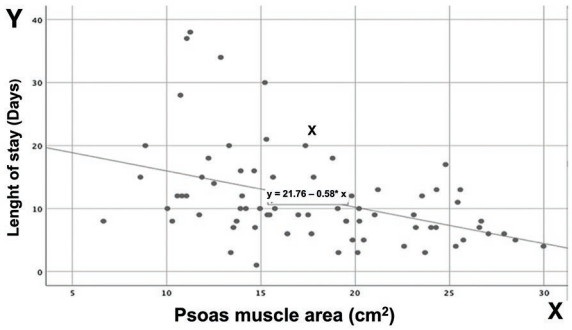

Figure 2. *Spearman correlation of length of stay and psoas muscle area. R = –0.47 (p < 0.001).*

Table 1. Demographic and clinical characteristics of the study population

Characteristics	n = 72
Age (years)	72 ± 10
Sex male, n (%)	54 (75)
Diabetes, n (%)	15 (20)
Hypertension, n (%)	48 (66)
CAD, n (%)	12 (16)
Chronic kidney insufficiency, n (%)	15 (20)
Smoke, n (%)	62 (86)
Height (cm)	163 (153-171)
Weight (kg)	67 ± 13
Aortic aneurysm diameter (cm)	64 (55-74)
Creatinine (mg/dL)	1.08 (0.8-1.3)
Albumin level g/dL	3.7 ± 0.66
Psoas muscle area (cm²)	17 ± 5.8
LOS (days)	10 (7-14)
30-day complication	40 (55)

LOS: length of stay; CAD: coronary artery disease.

were male. Regarding comorbidity, 66% had hypertension, 20% diabetes, and 86% had a history of smoking. The median abdominal aortic aneurysm (AAA) diameter in centimeters was 64 (55-74) (Table 1).

The mean interobserver PMA difference found (one radiology fellow and one vascular surgeon fellow) in 20 patients was 0.4 cm² (95% confidence interval [CI] –0.9-1.2 cm²), and the mean interobserver difference was 0.5 cm² (95% CI –1.3-2.1 cm²). The correlation obtained by the Spearman test between PMA and postoperative LOS was negative (R = –0.47, p < 0.001), supporting the fact that patients with lower PMA were more likely to have longer LOS after surgery (Fig. 2).

The median LOS for the 72 patients included in the study was 10 (7-14) days, after dividing groups by their median, the first group included 42 patients (58.3%) who stayed < 10 days after OAAAR, with a median age at surgery of 73 (68-78) years, 33 patients (79%) were males, with median AAA diameter of 65 (56-75) cm and a median PMA of 19 (14-23) cm². After comparing the PMA between groups, those patients who stayed more than 10 days after surgery had a smaller PMA compared to those who stayed < 10 days - 14 (11-19) versus 19 (14-23) cm², p = 0.004 (Table 2).

As a secondary outcome, 30-day complications were assessed using PMA for the comparison between groups. The cut point used to separate groups was the mean PMA obtained in the 72 patients (17 cm²) (Table 3). We observed that complications after 30 days were present in 71% (26 patients) in the < 17 cm² PMA group compared to 39% in patients with PMA > 17 cm² (p = 0.004) (Table 3). None of the complications required surgery intervention. The most common complications that we found were: respiratory complications (30%) as pulmonary embolism and pneumonia; cardiac complications (25%) as arrhythmias, myocardial infarction, and cardiac failure; renal complications (15%) as acute renal failure, urinary retention, and urinary tract infections; and other complications (30%) such as incisional hernia, small bowel obstruction or wound infection. There was no significant difference in death between groups (p = 0.147); however, those patients with PMA < 17 cm² had longer LOS 12 (9-17) versus 8 (5-11) days (p = 0.001).

Table 2. Comparison of patients divided by length of stay in the post-operative

Characteristics	LOS < 10d n = 42	LOS > 10d n = 30	p
Age (years)	73 (68-78)	74 (67-80)	0.468
Sex male, n (%)	33 (79)	21 (70)	0.408
Diabetes, n (%)	9 (21)	6 (20)	0.888
Hypertension, n (%)	29 (69)	19 (63)	0.612
CAD (%)	7 (17)	5 (17)	1.0
Chronic renal failure, n (%)	8 (19)	7 (23)	0.659
Smoke, n (%)	38 (90)	24 (80)	0.205
Height (cm)	161 (150-172)	165 (156-170)	0.441
Weight (kg)	68 ± 13	65 ± 13	0.392
Aortic aneurysm diameter (cm)	65 (56-75)	61 (55-72)	0.355
Creatinine (mg/dL)	1.08 (0.8-1.3)	1.08 (0.8-1.5)	0.918
Albumin g/dL	3.8 ± 0.63	3.5 ± 0.68	0.065
Psoas muscle area (cm^2)	19 (14-23)	14 (11-19)	0.004*

*p < 0.05.
LOS: length of stay; CAD: coronary artery disease.

Table 3. Comparison of patients divided by Psoas muscle area in the post-operative

Characteristics	PMA < 17cm^2 (n = 36)	PMA > 17cm^2 (n = 36)	p
Age (years)	75 (69-81)	71 (66-77)	0.32
Sex male, n (%)	20 (56)	34 (94)	0.000*
Diabetes, n (%)	8 (22)	7 (19)	0.772
Hypertension, n (%)	22 (61)	26 (72)	0.317
CAD, n (%)	6 (17)	6 (17)	1.0
Chronic renal failure, n (%)	6 (17)	9 (25)	0.384
Smoke, n (%)	28 (78)	34 (94)	0.041*
Height (cm)	161 (152-165)	168 (158-175)	0.062
Weight (kg)	61 ± 11.5	73 ± 12	0.000*
Aortic aneurysm diameter (cm)	67 (55-80)	62 (57-71)	0.460
Creatinine (mg/dl)	1.0 (0.8-1.3)	1.1 (0.8-1.4)	0.288
Albumin g/dL	3.6 ± 0.7	3.8 ± 0.6	0.214
Mortality	10 (28)	5 (14)	0.147
30-day complications	26 (71)	14 (39)	0.004*
LOS	12 (9-17)	8 (5-11)	0.001*

*p < 0.05.
PMA: psoas muscle area; CAD: coronary artery disease; LOS: length of stay.

Discussion

Once an aneurysm in the abdominal aorta has been diagnosed and after it reaches the threshold for elective repair, the risk for post-operative complications and death must be assessed against the risk of rupture.[9] Consequently, many prediction models have been described to estimate morbidity and mortality; however, many of these include poor suitability variables for OAAAR.[10,11] Frailty is a geriatric syndrome where low muscle mass and strength play an important role, contributing to a diminished homeostatic capability and leading patients to a higher vulnerability to stressors such as surgical interventions and post-operative time.[11-16] This syndrome becomes more prevalent with increasing age, and sarcopenia, which is defined as a loss of muscle mass and strength, is an important characteristic of the latter.[5,17] In addition, as it has been reported as an easy component to measure by imaging techniques such as CT[9] and due to the relevant association that sarcopenia has with post-operative outcomes such as LOS and major adverse complications, it has gained interest by many authors in the surgical field.[12,16,18-22]

Nowadays, there is growing evidence that PMA can predict negative post-operative outcomes such as an increasing patient morbidity and mortality.[12,16,19-22] In regard to the proposed threshold to define low PMA in these patients, there is no universally accepted cutoff point, since some authors have chosen to stratify their patients in percentiles[7,14,16,18] and others have chosen a random cut point.[12,20,23] As no threshold value for sarcopenia exists currently in the literature regarding PMA,[21,22] we decided to stratify our post-operative patients into those above the mean PMA obtained from patients' CT scans reviewed (mean = 17 cm^2). Using our proposed threshold, 36 patients (50%) were defined as having a low PMA, showing a statistically significant association (p = 0.004) with greater post-operative 30-days complications as well as an increased LOS (> 10 days) (p = 0.001) identifying PMA as a radiologic biomarker of frailty, helping in the prediction of post-operative morbidity in patients considered for complex abdominal aortic aneurysm open repair.

Clinical research has been growing, focusing on the association of a low PMA with an increased post-operative morbidity and mortality, as stated in a systematic review by Antoniou and colleagues[24] confirming the relevance of low skeletal muscle mass as a prognostic factor for survival. LOS then becomes a

crucial post-operative outcome to consider for a physician when deciding on the best course of treatment for patients, as an increased LOS leads to higher costs for patients and the healthcare system. We found in the present study that a lower PMA was significantly associated with longer LOS, which supports the evidence from previous studies. Our results are in concordance with those reported by Zuckerman et al.,[12] who reported an increased LOS in patients with a lower PMA.

Limitations of the present study are those inherent in the retrospective nature of our work and possible selection bias.

Conclusion

Patients with the lower PMA (below 17 cm^2) were associated with longer LOS and a higher rate of 30-day complications. However, no statistically significant difference was found in mortality. PMA measurement might assist as a postoperative predictor of LOS in major vascular surgery

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 subjects and animals. The authors declare that the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the World Medical Association and the Declaration of Helsinki. The procedures were authorized by the Institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable 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 or creation of the content of this manuscript.

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ORIGINAL ARTICLE

Predictors of postoperative neurological deficits in traumatic thoracolumbar fractures

Predictores de déficits neurológicos posoperatorios en fracturas toracolumbares traumáticas

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Abstract

Objective: *The goal of this retrospective study was to assess the outcomes of vertebral stabilization following acute traumatic thoracolumbar (TL) fractures.* **Methods:** *The study examined the mechanism and location of trauma, pre-operative and post-operative neurological deficits, stabilization level, screw malposition, cerebrospinal fluid fistula, development of post-operative infections, additional pathological findings, mobilization times, and follow-up durations.* **Results:** *The study included 55 patients. Falls were the leading cause of trauma (75%), and L1 was the most common fracture site (30.9%). A4 was the most common fracture type (61.8%), with T11-L3 being the most frequently stabilized level (32.7%). Screw malposition occurred in 3.6% of cases, and CSF fistula was more common in types B and C. The presence of pre-operative neurodeficits and TL American Orthopedic Spine Injury Score (AOSIS) type B and C significantly increased the risk of post-operative neurological complications. Univariate analysis showed that pre-operative neurodeficits (odds ratio [OR]: 396, 95% confidence intervel [CI]: 22-6935, p < 0.001) and TL AOSIS types B (OR: 11.78, 95% CI: 1.88-73.58, p = 0.008) and C (OR: 9.9, 95% CI: 1.31-74.73, p = 0.026) significantly increased the risk of post-operative neurodeficits.* **Conclusions:** *This study, therefore, takes into consideration the strong impact of pre-operative neurological deficit and injury severity with respect to TL classifications on post-operative outcomes for patients undergoing surgical stabilization for traumatic fractures.*

Keywords: *Traumatic spine fracture. Thoracolumbar fracture. Trauma.*

Resumen

Objetivo: *Evaluar los resultados de la estabilización vertebral tras fracturas traumáticas agudas toracolumbares.* **Métodos:** *Se evaluaron el mecanismo y la localización del trauma, los déficits neurológicos preoperatorios y posoperatorios, el nivel de estabilización, la mala posición de los tornillos, la fístula de líquido cefalorraquídeo, el desarrollo de infecciones posoperatorias, los hallazgos patológicos adicionales, los tiempos de movilización y las duraciones del seguimiento.* **Resultados:** *El estudio incluyó 55 pacientes. Las caídas fueron la principal causa de trauma (75%), L1 fue el sitio de fractura más común (30.9%), el tipo de fractura más frecuente fue A4 (61.8%) y T11-L3 fue el nivel estabilizado con mayor frecuencia (32.7%). La mala posición de los tornillos se observó en el 3.6% de los casos y la fístula de líquido cefalorraquídeo fue más común en los tipos B y C. La presencia de déficits neurológicos preoperatorios y tipo B, C de la clasificación TL AOSIS aumentó significativamente el riesgo de complicaciones neurológicas posoperatorias. El análisis univariado mostró que los déficits neurológicos preoperatorios (OR: 396; IC 95%: 22-6935; p < 0.001) tipo B (OR: 11.78; IC 95%: 1.88-73.58; p = 0.008) y tipo C (OR: 9.9; IC 95%: 1.31-74.73; p = 0.026) de TL AOSIS aumentaron significativamente el riesgo de déficits neurológicos posoperatorios.* **Conclusiones:** *Este*

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estudio toma en consideración el fuerte impacto del déficit neurológico preoperatorio y la gravedad de la lesión con respecto a clasificaciones toracolumbares en resultados posoperatorios de pacientes sometidos a estabilización quirúrgica por fracturas traumáticas.

Palabras clave: *Fractura traumática de columna. Fractura toracolumbar. Trauma.*

Introduction

Traumatic thoracolumbar (TL) fractures are one of the most significant causes of disability, deformity, and neurological deficits among working-age individuals in both industrialized and developing countries.[1-4] These fractures most commonly affect men between the ages of 20 and 40, and in approximately 50% of cases, they can lead to significant medical, social, and economic consequences.[2,3,5] It is estimated that 50-60% of TL fractures occur in the transition zone between T11 and L2, 25-50% in the thoracic region, and only 10-14% in the lumbar and sacral regions.[6-8] According to various studies, compression fractures (type A) account for 63-82% of all traumas, distraction injuries (type B) for 14-21%, and rotational injuries (type C) for 4-16%.[9,10] The likelihood and extent of neurological deficits vary depending on the type of fracture, with an incidence of up to 55% in the latest AO classification's type C fractures.[7,11] Spinal cord injuries are often the result of high-energy blunt trauma, with 56-67% associated with motor vehicle accidents and falls from great heights. These injuries are commonly associated with other injuries, such as rib fractures and pneumothorax, due to the high-speed nature of the trauma.[11,12] In addition, the incidence of concurrent intra-abdominal injuries can be as high as 50%. Over time, many classifications have been developed to assist clinicians in treatment selection; however, while there is consensus on surgery for flexion-distraction and rotational injuries, a definitive recommendation on how to treat compression injuries is still lacking.[11,13] Although various approaches and surgical techniques have been described for the treatment of TL fractures, scientific evidence is still insufficient to support the selection of one surgical technique as being more effective than others.[7,14,15]

The goal of this retrospective study was to assess the outcomes of vertebral stabilization following acute traumatic TL fractures. We aimed to examine these outcomes with patient clinical data, the type and location of the fracture, the presence of neurological damage, and neurodeficit risk factor analysis.

Methods

A retrospective analysis was conducted on 55 patients who underwent surgery in our clinic between 2018 and 2024 (Fig. 1). The study examined the mechanism and location of trauma, pre-operative and post-operative neurological deficits, stabilization level, screw malposition, cerebrospinal fluid (CSF) fistula, development of post-operative infections, additional pathological findings, mobilization times, and follow-up durations. All patients underwent an imaging study of the vertebral column, which included anteroposterior and lateral X-rays, computed tomography, and magnetic resonance imaging. The purpose was to outline the exact morphology of the lesion and the possible spine involvement. Fractures were radiologically classified using the AO spine injury scores, and the findings were evaluated in the context of the existing literature (Fig. 2).

This study was approved by the non-interventional ethics committee of Sancaktepe Training and Research Hospital. This study was conducted in accordance with the principles of the Declaration of Helsinki, as revised in 2013. Before surgery, written informed consent was obtained from all patients or their legal guardians.

Patients who presented to the emergency department due to trauma and were determined to require surgery were included in the study. Patients diagnosed with osteoporosis who developed fractures, as well as those who sustained fractures due to trauma but did not require surgical intervention, were excluded from this study.

In this study, spine injuries were classified according to the AOSpine TL spine injury classification system. In response to the limitations of previous classification systems in gaining global acceptance, Vaccaro et al. developed the AOSpine TL spine injury classification system in 2013.[16] This new system incorporates elements from both the Magerl classification and the TL injury classification and severity score. The morphologic classification is a simplified version of the Magerl system, featuring a total of nine injury patterns. These injuries are categorized into three

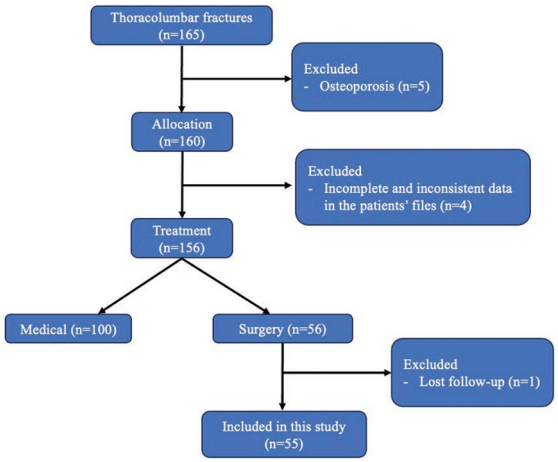

Figure 1. *Patient flow chart.*

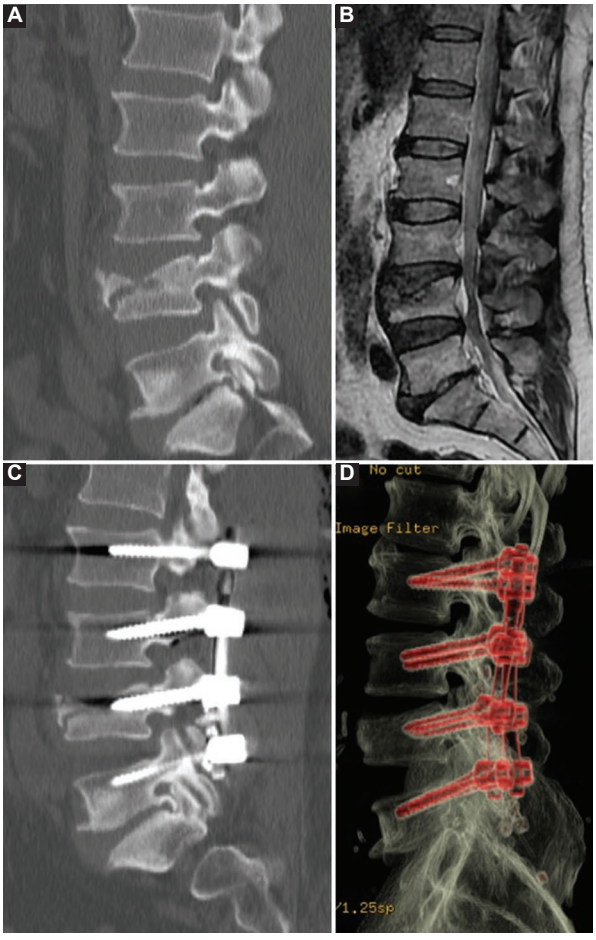

Figure 2. *Radiological image.* **A** *and* **B:** *pre-operative magnetic resonance imaging image.* **C:** *post-operative MRI image,* **D:** *post-operative 3D computed tomography image.*

primary types: Type A – compression injuries, Type B – tension band injuries, and Type C – translation injuries. Type A and Type B injuries are further divided into five and three subtypes, respectively (Table 1).

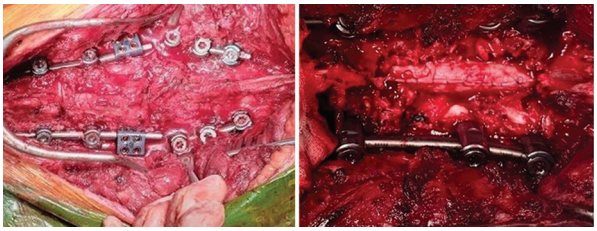

Figure 3. *Intraoperative view.*

All patients underwent surgical stabilization of the fracture site, utilizing a posterior approach under general anesthesia.[7,11,14,17] The number of levels fused varied depending on the type and location of the fracture, as well as the difficulty in realigning the spinal column, with the goals of restoring sagittal alignment and ensuring implant stability. In cases involving spinal canal compromise with neurological deficits, spinal cord decompression was also performed. For patients where pedicle screws alone could not provide sufficient stability due to osteoporosis, bone cement and fenestrated screws were used (Fig. 3).

The data for our study were analyzed using Jamovi software version 2.4.1. Descriptive statistics were presented as counts and percentages for categorical variables and as means with standard deviations for continuous variables. The Pearson Chi-square test was applied to determine differences between groups for categorical variables. To assess the normality of the distribution for continuous variables, the Shapiro–Wilk test was utilized. For comparisons between two groups, the independent t-test was employed. A binary logistic regression test was used to test the predictors. A $p < 0.05$ was considered statistically significant.

Results

The study included 55 patients with a mean age of 42.1 years (min-max: 12-83). The majority of the patients were male (69%). The primary cause of trauma was falls, accounting for 75% of the cases, followed by motor vehicle accidents at 18%, and other injuries at 7%. Vertebral fractures were most commonly observed at the L1 level, representing 30.9% of the cases. Other frequently affected levels included L2 (16.3%), T12 (14.6%), L3 (14.4%), and L2-L4 (7.2%). Preoperatively, 18.2% of the patients presented with neurodeficits, with 5.5% having paraparesis and 12.7% experiencing plegia. Postoperatively, the incidence of neurodeficits remained consistent, with 18.2% of the patients displaying neurological

Table 1. TL AOSIS types

Subgroup	Description	TL AOSIS
Type A: compression fractures		
A0	An injury that has no possibility of affecting the structural integrity of the spine (ie, fracture of the spinous or transverse process)	0
A1	A fracture through a single endplate that does not extend into the posterior wall	1
A2	A fracture through both endplates that does not extend into the posterior wall	2
A3	A fracture through a single endplate that does extend into the posterior wall (incomplete burst)	3
A4	A fracture through both endplates that does extend into the posterior wall (complete burst)	5
Type B: Tension band injury		
B1	A completely osseous tension band injury (ie, a bony chance fracture)	5
B2	An injury that disrupts the posterior tension band	6
B3	An injury that disrupts the anterior tension band	7
Type C: Translational injuries		
C	Any injury that results in translation of the vertebral body	8

TL: thoracolumbar.

impairment, distributed equally between paraparesis (5.5%) and plegia (12.7%). Screw malposition was noted in 3.6% of the cases, while a CSF fistula and infections occurred in 1.8% of the patients. The mean time to mobilization post-surgery was 1.2 days (min-max: 1-5). The mean follow-up period was 3.3 years (min-max: 1-6), during which the outcomes of the surgical interventions were closely monitored. During the follow-up period, no patients required reintervention (Table 2).

The TL injury classification for the 55 patients included in the study revealed that the majority of cases were categorized as A4, accounting for 61.8% of the total. This was followed by B2 injuries, which comprised 21.8% of the cases, and C injuries, representing 14.5%. A2 injuries were the least common, with only 1.8% of the cases falling into this category (Table 3).

The analysis of stabilization levels among the 55 patients revealed that the most common stabilization level was T11-L3, accounting for 32.7% of the cases. This was followed by the L1-L5 stabilization level, which was observed in 9.1% of the patients. Other frequently stabilized segments included T10-L2 (7.3%), T12-L4 (5.5%), and L2-L5 (5.5%) (Table 4).

The average age differed among the groups, with patients classified as type A having a mean age of 45.8 years, while those in groups B and C were younger, with mean ages of 38.3 years and 31.5 years, respectively, though this difference was not statistically significant ($p = 0.059$). Gender distribution did not differ significantly across the groups ($p = 0.546$). A significant difference was observed in the presence of pre-operative neurodeficits, which were rare in type A injuries (2.9%) but more common in types B (41.7%) and C (50%) ($p < 0.001$). Post-operative neurodeficits followed a similar pattern, with higher rates in type B (41.7%) and C (37.5%) compared to type A (5.7%) ($p = 0.006$). The cause of trauma did not show a significant difference across the injury types ($p = 0.617$). Screw malposition was only observed in the type A group (5.7%) ($p = 0.553$). However, CSF fistula occurrence showed a significant difference, being more common in types B (25%) and C (25%) compared to type A (2.9%) ($p = 0.040$). Infection rates did not differ significantly among the groups ($p = 0.748$) (Table 5).

The univariate analysis revealed that the presence of pre-operative neurodeficit and the TL AOSIS type were significantly associated with post-operative neurodeficit occurrence. Specifically, having a pre-operative neurodeficit significantly increased the risk of developing a post-operative neurodeficit (OR: 396, 95% CI: 22-6935, $p < 0.001$). In addition, patients with TL AOSIS type B had a significantly higher risk of post-operative neurodeficit compared to those with type A (OR: 11.78, 95% CI: 1.88-73.58, $p = 0.008$). Similarly, those with type C also demonstrated an increased risk (OR: 9.9, 95% CI: 1.31-74.73, $p = 0.026$) (Table 6).

Discussion

In this study, we found that pre-operative neurodeficits and the type of TL injury, as classified by the AOSpine

Table 2. Basic characteristics of the patients

Basic characteristics	n = 55	%
Age (year; mean ± SD, min-max)	42.1 ± 18.3	12-83
Gender (M)	34	69
Cause of trauma		
Falls	41	75
Motor vehicle accidents	10	18
Other injuries*	4	7
Vertebral fracture levels		
T4-T5	1	1.8
T7	1	1.8
T10-T11	1	1.8
T12	8	14.6
T12-L1	1	1.8
L1	17	30.9
L2	9	16.3
L2-L4	4	7.2
L3	8	14.4
L3-L4	1	1.8
L3-L5	1	1.8
L4	3	5.5
Pre-operative neurodeficit (yes)	10	18.2
Type of neurodeficit (pre-operative)		
Paraparesis	3	5.5
Plegia	7	12.7
Post-operative neurodeficit	10	18.2
Type of neurodeficit (post-operative)		
Paraparesis	3	5.5
Plegia	7	12.7
Screw malposition (yes)	2	3.6
Infections	1	1.8
CSF fistula (yes)	1	1.8
Time for mobilization (day; mean ± SD, min-max)	1.2 ± 0.6	1-5
Follow-up (year; mean ± SD, min-max)	3.3 ± 1.5	1-6

*Other injuries: assault, epileptic seizure, gunshot.
SD: standard deviation; CSF: cerebrospinal fluid; M: male; T: thoracal; L: lumbar.

Table 3. TL AOSIS type of fracture

TL AOSIS	n	%	Cumulative %
A2	1	1.8	1.8
A4	34	61.8	63.6
B2	12	21.8	85.5
C	8	14.5	100
Total	55	100	100

TL: thoracolumbar.

Table 4. Frequencies of stabilization level

Stabilization level	n	%
L1-L3	1	1.8
L1-L4	2	3.6
L1-L5	5	9.1
L2-L5	3	5.5
L2-S1	1	1.8
L3	1	1.8
L3-L5	1	1.8
T10-L1	1	1.8
T10-L2	4	7.3
T10-L3	2	3.6
T10-T12	1	1.8
T10-l2	1	1.8
T11-L5	2	3.6
T11-L6	1	1.8
T11-L3	18	32.7
T11-L3	1	1.8
T11-L4	1	1.8
T12-L3	1	1.8
T12-L4	3	5.5
T12-L5	2	3.6
T2-T7	1	1.8
T5-T9	1	1.8
T8-T12	1	1.8

system, were significant predictors of post-operative outcomes. Patients presenting with pre-operative neurodeficits had a markedly higher risk of developing post-operative neurodeficits, emphasizing the critical impact of early neurological impairment on surgical outcomes. Furthermore, injury types B and C were associated with significantly higher risks of post-operative neurodeficits compared to type A injuries, underscoring the severity of these injury patterns.

Despite significant advancements in diagnostic techniques and spinal instrumentation, there remains no clear consensus on the optimal treatment approach for TL fractures.[11,18-20] Treatment options vary widely, ranging from conservative management with orthotic external bracing to more invasive surgical procedures, such as instrumented fusions.[11,13,15] Recently, percutaneous fixation has emerged as a minimally invasive alternative, providing a middle ground between these two extremes. Neeley et al. compared deformity correction and surgical outcomes between

Table 5. Comparative analysis of items regarding TL AOSIS

Characteristics	A (n = 35)	B (n = 12)	C (n = 8)	p
Age (year)	45.8 ± 18.6	38.3 ± 17.8	31.5 ± 13	0.059
Gender (M), n (%)	20 (57)	9 (75)	5 (62.5)	0.546
Any pre-operative neurodeficit, n (%)	1 (2.9)	5 (41.7)	4 (50)	< 0.001
Any post-operative neurodeficit, n (%)	2 (5.7)	5 (41.7)	3 (37.5)	0.006
Cause of trauma, n (%)				0.617
Falls	26 (74.3)	8 (66.7)	7 (87.5)	
Motor vehicle accidents	7 (20)	2 (16.7)	1 (12.5)	
Other injuries*	2 (5.7)	2 (16.7)	0 (0)	
Screw malposition	2 (5.7)	0 (0)	0 (0)	0.553
CSF fistula	1 (2.9)	3 (25)	2 (25)	0.040
Infections	1 (2.9)	0 (0)	0 (0)	0.748

*Other injuries: assault, epileptic seizure, gunshot.
CSF: cerebrospinal fluid; M: male.

Table 6. Binary logistic regression analysis

Characteristics	Univariate analysis		p	OR	95% CI	Multivariate analysis		p
	Estimate	SE				Estimate	SE	
Age (year)	–0.0163	0.0202	0.419	0.984	0.945-1.02			
Gender (ref: Female)	1-0.442	0.754	0.558	0.643	0.147-2.189			
Any pre-operative neurodeficit	5.98	1.46	< 0.001	396	22-6935	39.44	6763	0.995
Cause of trauma								
Motor vehicle accidents - falls	–0.617	1.133	0.586	0.540	0.058-4.970			
Other injuries* - falls	1.580	1.083	0.144	4.857	0.581-40.55			
Screw malposition	–15.11	1696	0.993		0.39-16.44			
CSF fistula	0.942	0.948	0.321	2.563				
Infections	–15.08	2399	0.995					
TL AOSIS type (ref: A)								
B-A	2.47	0.934	0.008	11.78	1.88-73.57	–16.33	4619	0.997
C-A	2.29	1.031	0.026	9.9	1.31-74.73	–34.85	6763	0.996

*Other injuries: assault, epileptic seizure, gunshot.
CSF: cerebrospinal fluid. OR: odds ratio; SE: standard error; CI: confidence interval.

percutaneous instrumentation and open fusion in patients with traumatic TL fractures, highlighting the evolving landscape of treatment options.[15] Reinhold et al. reported using a posterior approach in approximately half of their cases, with the remainder divided between combined anteroposterior and exclusively anterior approaches.[14] Similarly, Muratore et al. emphasized a tailored approach, choosing between posterior and combined anteroposterior methods based on the anatomical and overall clinical status of each patient.[11] In our study, we employed a uniform strategy, performing surgical stabilization using the posterior approach in all patients. This choice was guided by our clinical experience and the specific characteristics of the fractures observed, reinforcing the utility of a consistent approach in achieving reliable outcomes.

According to a meta-analysis, the most commonly injured vertebra was L1, with an incidence rate of 34.4% (95% CI 18.2%, 50.3%).[21] The most frequently injured non-junctional vertebra was T7, at 3.9% (95% CI 2.81%, 4.99%), while T2 was the least affected, with an incidence of 0.26% (95% CI 0, 0.56%). The same meta-analysis found that the leading cause of TL fractures was motor vehicle collisions, accounting for

36.7% (95% CI 31.35%, 42.0%) of cases, followed by high-energy falls at 31.7% (95% CI 25%, 38.4%). Motorcycle collisions accounted for 10.05%, other causes for 9.06%, and pedestrian accidents for 4.83%. Muratore et al.[11] reported that fractures predominantly involved the TL region, between T11 and L2, while Neeley et al.[15] found the highest incidence at the T12-L1 level. In contrast, our study identified falls as the most common cause of fractures, with the most frequent fracture levels occurring between T11 and L3.

Katsuura et al. identified type A3 or A4 fractures as the most prevalent trauma patterns.[21] Similarly, Reinhold et al. demonstrated that type A fractures were the most common, with over half of their patients presenting with polytrauma.[14] Their findings also revealed an increasing incidence of neurological deficits as the fracture severity escalated from type A to type C. Neeley et al. also observed a predominance of type A fractures.[15] In our study, type A fractures were the most frequently encountered. In addition, post-operative neurodeficits in our cohort exhibited a comparable trend, with significantly higher rates observed in type B (41.7%) and type C (37.5%) fractures compared to type A fractures (5.7%).

In their meta-analysis, Azizi et al. reported a pooled spinal cord injury (SCI) event rate of 15.81% among patients with TL fractures.[22] Similarly, Muratore et al. found that the probability of medullary involvement increased with the severity of the primary fracture type, showing a significant difference between type A and type C fractures, but not between type A and type B.[11] Katsuura et al. conducted a meta-analysis involving seven studies, which included 3,146 patients, to assess the rate of neurologic SCI in TL fracture patients.[21] One study, which differentiated between a polytrauma group and a specific TL trauma group, was analyzed as two separate cohorts.[23] The overall rate of SCI in these patients was found to be 26.5% (95% CI 15.8%, 37.2%).[21] In our study, neurological deficits were observed in 18.2% of the patients. Furthermore, univariate analysis revealed that the presence of pre-operative neurodeficits and the TL AOSIS type were significantly associated with the occurrence of post-operative neurodeficits.

While this study provides valuable insights into the surgical outcomes of traumatic TL fractures, it is not without limitations. First, the retrospective nature of the study introduces potential biases, including selection and recall bias, which may affect the accuracy of the data. Second, the relatively small sample size limits the generalizability of the findings, particularly when stratifying patients by injury type and analyzing subgroup outcomes. The study did not account for potential confounding factors such as the patients' comorbidities, the timing of surgery, and variations in surgical techniques, all of which could influence the outcomes. In addition, the follow-up period, though adequate, varied among patients, which might have affected the assessment of long-term outcomes such as late-onset complications and functional recovery. Finally, the lack of randomization and a control group limits the ability to establish causality between the interventions and observed outcomes.

Conclusions

This study, therefore, takes into consideration the strong impact of pre-operative neurological deficit and injury severity with respect to TL classifications on post-operative outcomes for patients undergoing surgical stabilization for traumatic fractures. Patients who have pre-operative neurological deficits and those whose injury types are more serious, the B and C types, have a higher likelihood of having post-operative neurological deficits. This study's results bring out the importance of early and accurate assessment of injuries, further pinpointing the need for individualized surgical approaches to improve patient outcomes. However, more prospective studies on larger populations are needed to confirm these observations and sharpen clinical decision-making.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the World Medical Association and the Declaration of Helsinki. The procedures were authorized by the Institutional Ethics Committee.

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

confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study. Ethical approval was obtained from the Sancaktepe local ethical committee.

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

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ORIGINAL ARTICLE

Arthroscopic treatment with absorbable bone cement for intra-articular comminuted fracture of the distal radius

Tratamiento artroscópico con cemento óseo reabsorbible para la fractura intraarticular conminuta del radio distal

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Abstract

Objective: *The objective of this study was to explore the clinical application value of arthroscopic injection of absorbable calcium sulfate bone cement in the treatment of distal radius intra-articular comminuted fractures.* **Methods:** *A total of 15 patients with distal radius intra-articular comminuted fractures treated in the Department of Hand Surgery I of our hospital from January 2020 to October 2021 were selected as the research subjects, including nine males and six females, aged 25-55. Closed reduction was performed first, followed by arthroscopic-assisted fracture reduction to eliminate step-off caused by the fracture and to inspect and repair damaged ligaments. Absorbable bone cement was injected into the fracture gap under fluoroscopy or arthroscopic guidance. The Mayo wrist score and Gartland-Werley score were used to assess wrist pain and joint function of the patients.* **Results:** *In the latest follow-up, 12 cases achieved excellent results in the Mayo score, and three cases achieved good results; Gartland-Werley score: 11 cases were excellent, and 4 cases were good.* **Conclusions:** *Arthroscopic injection of calcium sulfate bone cement for distal radius intra-articular comminuted fractures is effective, with the advantages of minimal trauma, satisfactory reduction, fewer post-operative complications, and the ability for early functional exercise in patients.*

Keywords: *Wrist arthroscopy. Calcium sulfate bone cement. Distal radius intra-articular comminuted fracture. Traumatic arthritis.*

Resumen

Objetivo: *Explorar el valor clínico de la inyección artroscópica de cemento de sulfato de calcio reabsorbible en el tratamiento de la fractura conminutas intraarticular del radio distal.* **Métodos:** *Se seleccionaron 15 pacientes (9 hombres y 6 mujeres), de entre 25 y 55 años, con fractura conminuta intraarticular del radio distal tratados en nuestro hospital entre enero de 2020 y octubre de 2021. Primero se realiza una reducción cerrada y luego una reducción de fractura asistida por artroscopia para eliminar la dislocación causada por la fractura, examinar y reparar los ligamentos dañados. Bajo guía de fluoroscopia o artroscopia, el cemento óseo reabsorbible se inyecta en el espacio de fractura. Para evaluar el dolor de muñeca y la función articular del paciente se utilizaron la puntuación Mayo de muñeca y la puntuación de Gartland y Werley.* **Resultados:** *En el seguimiento reciente, 12 pacientes alcanzaron una excelente puntuación Mayo y 3 alcanzaron una buena puntuación de Gartland y Werley: 11 casos excelentes y 4 casos buenos.* **Conclusiones:** *La inyección de cemento óseo de sulfato de calcio bajo artroscopia es efectiva en el tratamiento de fracturas conminutas en la articulación del radio distal, con pocas complicaciones posoperatorias y ejercicio funcional temprano en los pacientes.*

Palabras clave: *Artroscopia de muñeca. Cemento de sulfato de calcio. Fractura conminuta intraarticular del radio distal. Artritis traumática.*

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Introduction

Distal radius fractures are the most common fractures in adults, with an incidence rate of 0.35%, and this rate is showing an upward trend.[1] These fractures are typically caused by high-energy trauma and can manifest as sheare, compression, burst, or avulsion fractures. In addition to osseous structural damage, they are often accompanied by carpal bone fractures.[2] Non-surgical treatment is suitable for stable fractures, whereas displaced or unstable fractures usually require surgical intervention to restore upper limb alignment, functionality, and prevent post-traumatic arthritis.[3,4] Currently, the use of the volar approach and volar locking plates for treating distal radius fractures has been widely accepted. Although it can address most extra-articular and simple intra-articular fractures, treating comminuted intra-articular fractures, such as AO type C fractures, remains a challenge in surgery. Harness pointed out that the unique anatomical structure of the distal radius fracture area with volar bone fragments makes it challenging to support the entire volar surface using standard plates for fixation, due to the proximity of the fracture line to the joint surface, presenting treatment difficulties.[5] For elderly individuals with accompanying osteoporosis, bone deficiency is also a factor that must be considered. Moreover, distal radius intra-articular fractures often involve damage to ligaments and other structures. Without timely intervention, post-operative chronic wrist pain or wrist instability might persist.[6] How to reduce intra-articular comminuted fractures and repair ligament damage are critical aspects of surgically treating intra-articular fractures, and the emphasis on anatomical reduction and early functional exercises in the context of accelerated recovery concepts places higher demands on surgical techniques.[7,8] From January 2020 to October 2021, our department utilized wrist arthroscopy in combination with calcium sulfate bone cement for the treatment of 15 patients with distal radius fractures and intra-articular comminuted fractures. The results are reported as follows.

Methods

General information

Between January 2020 and October 2021, 45 patients underwent surgery for distal radius intra-articular comminuted fractures in our trauma center. Retrospective study subjects were identified according to inclusion and exclusion criteria, and 15 patients were included in the study.

Inclusion criteria

- Age 18-65 years and met the diagnostic criteria for a distal radius fracture;
- AO type C fractures;
- Patient's informed consent and signed informed consent;
- Patients were treated with arthroscopic treatment with absorbable bone cement;
- A minimum follow-up of 12 months after surgery.

Excluded patients

- Patients with a history of wrist joint surgery;
- Lost to follow-up.

There were 9 males and 6 females, aged between 40 and 65 years. Causes of injury included falls in 12 cases and collisions in 3 cases. The fractures were classified according to the AO classification as follows: C1 in 4 cases, C2 in 10 cases, and C3 in 1 case. This study was approved by the Medical Research Ethics Board of blinded for review. All patients were informed in detail before surgery, and consent was obtained from both the patients and their families. All surgeries were performed by the author.

Surgical procedure

Patients were administered brachial plexus nerve block anesthesia and placed in a supine position. Closed reduction was performed initially, with traction and compression to achieve closed reduction, aiming to restore radial height and avoid ulnar deviation. Fracture alignment was corrected, and palmar tilt, ulnar variance, and rotational deformity were restored. The affected limb was placed in a wrist arthroscopy tower, providing 3-4 kg of traction force. Dry arthroscopy was used intraoperatively. Arthroscopy was used for exploration, primarily involving intra-articular fracture reduction to eliminate step-off caused by the fracture. Subsequently, the integrity of the triangular fibrocartilage complex (TFCC) and the lunate ligament was further examined. Any injuries were repaired under arthroscopy. Passive wrist joint movement and

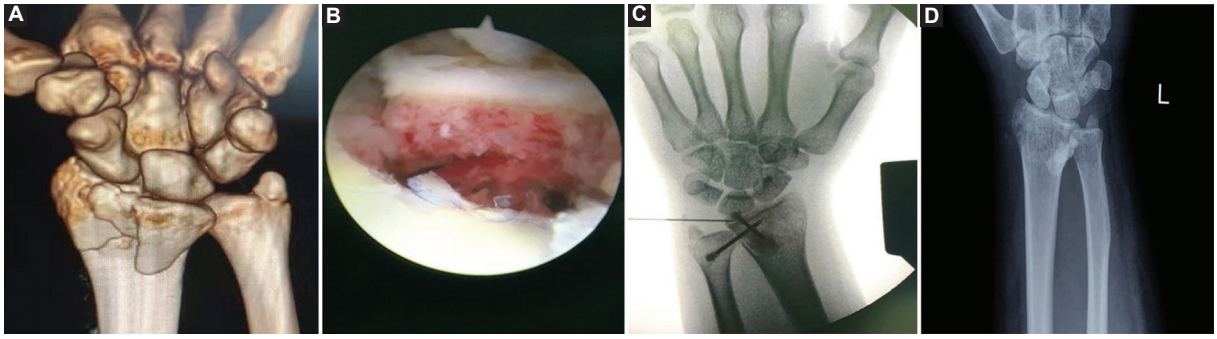

Figure 1. A: *patient, female, 34 years old, suffered from a left distal radius intra-articular fracture due to violence. The fracture was classified as AO type C3 with joint surface depression.* **B:** *under direct vision of wrist arthroscopy, articular surface fractures with step formation, triangular fibrocartilage complex (TFCC) injury, probe prying reduction, Kirschner wire fixation, reduction of articular surface, and repair of TFCC can be seen.* **C:** *post-operative fluoroscopy shows anatomical reduction of the joint surface, correction of ulnar variance angle, palmar tilt angle, and radial height. Injectable absorbable bone cement was injected into the fracture gap under fluoroscopic guidance.* **D:** *6 weeks after the operation, an X-ray of the wrist joint was taken. The fracture has basically healed, the articular surface has not collapsed, and the bone cement has been partially absorbed.*

ulnar-radial and radial-ulnar collision tests were performed during the surgery to assess joint stability. A Kirschner wire or cap screw was used for temporary intraoperative fixation. Once satisfactory exploration was achieved, the wrist joint was positioned under a fluoroscopy machine, and a needle was inserted into the fractured gap under fluoroscopy or arthroscopic guidance. Absorbable injectable calcium sulfate bone cement (STIMULAN, BIOCOMPOSITES, UK) was prepared with a ratio of 2 g calcium sulfate bone cement to 5 mL of normal saline using a 5 mL syringe. The cement was injected immediately and allowed to naturally solidify, with a solidification time of about 3 min. Postoperatively, the wrist joint was carefully immobilized in a plaster functional position.

Post-operative management and efficacy evaluation

Active and passive functional exercises for interphalangeal and metacarpophalangeal joints were initiated on the first day after surgery. At 3 weeks post-surgery, the plaster was removed, and patients were guided to perform passive wrist flexion-extension training. Resistance and weight-bearing training began at 4 weeks post-surgery. The Kirschner wire was pulled out at 4 weeks post-surgery. These patients began resistance and weight-bearing training at 6 weeks post-surgery.

Follow-up was conducted for at least 1 year. X-ray evaluation was performed to assess fracture healing and the occurrence of arthritis. General wrist conditions were assessed, including stability, range of motion, tendon irritation, wrist pain, and other complications. The Mayo wrist score and Gartland-Werley score were used to assess wrist pain and joint function.

Results

The average time from injury to operation was 3.5 days (range 2-7 days). All 15 patients in this group were successfully followed up, with a follow-up period ranging from 12 to 23 months, averaging 14.5 ± 4.1 months (Fig. 1). Two patients exhibited TFCC grade I injuries, which were cleaned and repaired intraoperatively. Two patients presented with injuries to the lunotriquetral ligament, which were managed through intraoperative fixation of the lunotriquetral joint. One patient experienced radial nerve symptoms 1 week after surgery, which disappeared after oral administration of methylcobalamin. Minimal cement leakage occurred in one case, requiring no specific treatment. All patients achieved anatomical restoration of the radiocarpal, radioulnar, and distal radioulnar joints. No complications such as infection, non-union, carpal tunnel syndrome, ulnar impaction syndrome, cement intolerance, or tendon rupture were observed.

Fracture healing time ranged from 8 to 15 weeks, with an average of 12.2 ± 2.7 weeks. The bone cement gradually absorbed around 4 weeks after surgery, with complete absorption occurring between 10 and 13 weeks, averaging 13.5 ± 1.9 weeks. At the latest follow-up, all patients exhibited stable wrist joints. Range of motion values were as follows: extension 36-45°, averaging 38 ± 3.5°; flexion 40-52°, averaging 45.2 ± 4.1°; pronation 65-80°, averaging 75.3 ± 5.3°;

supination 60-77°, averaging 69.1 ± 4.9°; palmar tilt angle 9-17°, averaging 12.5 ± 1.7°; ulnar variance angle 15-27°, averaging 22.5 ± 3.2°. In the latest follow-up, 12 cases achieved excellent results in the Mayo score, and 3 cases achieved good results. The Gartland-Werley score showed excellent results in 11 cases and good results in 4 cases.

Discussion

The distal radial articular surface is composed of different combinations of fracture fragments, including the radial column fragment, volar lip fragment of the lunate fossa, ulnar dorsal corner fragment, dorsal wall fragment, and intra-articular fragment. The specific location affected by distal radial fractures corresponds to the arrangement of these five fracture fragments. In addition, soft-tissue structures such as the radial collateral ligament, TFCC, and extensor carpi radialis brevis tendon are often damaged during traumatic events.[9,10] Achieving anatomical reduction is a treatment principle that can significantly reduce the risk of adverse effects such as traumatic arthritis.

Commonly used distal radius plates are volar plates. Soong reported that placing the distal radius plate at a 2nd position is necessary to fix fractures beyond the watershed line.[11] Traditional open surgery entails greater disruption and often requires incisions that sever the pronator quadratus muscle and involve traction of the median nerve. Fixation of dorsal fracture fragments may necessitate additional dorsal incisions, and exploring internal wrist joint structures can be challenging, particularly in cases of TFCC damage and injuries to the lunotriquetral ligament.[12-14]

The technique of arthroscopic-assisted injection of absorbable bone cement for fixation offers advantages such as minimal trauma, excellent outcomes, rapid recovery, and reduced discomfort.[15] Following reduction, step-off and fracture gaps on the joint surface should not exceed 1mm. Otherwise, residual wrist pain or functional impairment may occur postoperatively. However, it has been observed that fluoroscopy during surgery is often inadequate in detecting step-offs or gaps of around 1 mm.[15] Arthroscopy provides a direct view of fractures and soft-tissue injuries, allowing for direct repair of damaged joint surfaces and soft tissue structures. Yin et al.[10] used arthroscopy-assisted Kirschner wire fixation in combination with external fixation for treating fractures of the extreme distal radius in 21 patients. Intraoperative arthroscopy was utilized for initial exploration of the joint space, revealing TFCC tears in six cases. Arthroscopy can repair joint soft-tissue injuries and effectively address wrist joint dysfunction and persistent pain caused by soft-tissue damage.[10] In our study, two patients experienced TFCC injuries, and two patients had lunotriquetral ligament injuries, all of which were promptly repaired during surgery. Postoperative recovery met expectations, and no significant wrist pain was observed. Arthroscopy facilitates the removal of impurities such as blood clots and bone fragments from gaps while emphasizing the protection of damaged soft tissues. Anatomical reduction of the wrist joint surface was pursued during surgery, and arthroscopy holds unique advantages for certain fractures, such as those within the lunate fossa, dorsal wall fragments, and distal radioulnar joint fractures. In our procedures, we performed closed reduction, followed by meticulous arthroscopic repair and bone cement injection, striving to achieve maximal anatomical reduction. Adhesive fixation with bone cement can reduce the invasiveness of open surgery, aligning more closely with surgical principles[16] established in the field.

Subarticular bone defects often require bone grafting. Calcium sulfate bone cement material has good biocompatibility, degradability, and osteogenesis, and is widely used in the treatment of bone defects caused by vertebral compression fractures and trauma.[17] Calcium sulfate can produce a local micro-acid environment *in vivo*, which can increase the local calcium ion concentration, which is conducive to the aggregation and growth of osteoblasts. During the degradation and absorption, a large number of new bone trabeculae are formed, and the undegraded bone cement acts as a bone conduction scaffold. Bone cement absorption and bone tissue formation are synchronous, and the degradation and absorption rate of calcium sulfate is close to the rate of new bone formation.[18] Previous studies have shown that calcium sulfate bone cement can allow early wrist joint movement after the treatment of distal radius fractures, which can avoid wrist pain, stiffness, traumatic arthritis, and muscle atrophy caused by post-operative fixation, and has a good effect on comminuted fractures of the distal radius, unstable fractures, and osteoporotic fractures in the elderly. In addition, muscle contraction during early post-operative activity can produce axial stress at the fracture end, which can promote bone healing.[18] In this study, the minimally invasive injection method can effectively avoid periosteal injury and facilitate fracture healing. Calcium sulfate cement is used to fill bone

defects, which is an important factor in restoring the articular surface and maintaining radial height. Calcium sulfate is acidic, which can increase the local calcium ion concentration and the activity of osteoblasts. At the same time, bone cement absorption and bone tissue formation are synchronized, and the degradation and absorption rate of calcium sulfate is close to the rate of new bone formation.[19] In this group of cases, the follow-up found that a small amount of bone cement leakage occurred in one case; without special treatment, the bone cement was gradually absorbed after about 4 weeks, and the average time of fracture healing was 13.5 ± 1.9 weeks. The fracture healing time was 8-15 weeks, the average time of fracture healing was 12.2 weeks, and the bone cement absorption and healing time were almost the same, which was basically consistent with the previous reports of healing time. This suggests that cement may not increase the risk of delayed union. The absorbability of bone cement could avoid secondary surgery, and all patients had no rejection reaction. After an average follow-up of 14.5 months, all patients had no chronic wrist pain or wrist arthritis, and wrist joint function recovered well. The authors used manual reduction, wrist arthroscopy, and the use of bone cement for injection to obtain reliable clinical results. Under the arthroscopic, the author examined and repaired TFCC injury, and used bone cement to repair the intra-articular steps and fill the bone defect. The combination of the three can effectively restore the length of the radius, fill the bone defect, and address the problem of articular surface reduction. Subarticular bone defects often require bone grafting. Calcium sulfate bone cement material has good biocompatibility, degradability, and osteogenesis, and is widely used in the treatment of bone defects caused by vertebral compression fractures and trauma.[17] Calcium sulfate can produce a local micro-acid environment *in vivo*, which can increase the local calcium ion concentration, which is conducive to the aggregation and growth of osteoblasts. During the degradation and absorption, a large number of new bone trabeculae are formed, and the undegraded bone cement acts as a bone conduction scaffold. Bone cement absorption and bone tissue formation are synchronous, and the degradation and absorption rate of calcium sulfate is close to the rate of new bone formation.[18] Previous studies have shown that calcium sulfate bone cement can allow early wrist joint movement after the treatment of distal radius fractures, which can avoid wrist pain, stiffness, traumatic arthritis, and muscle atrophy caused by post-operative fixation, and has a good effect on comminuted fractures of the distal radius, unstable fractures, and osteoporotic fractures in the elderly. In addition, muscle contraction during early post-operative activity can produce axial stress at the fracture end, which can promote bone healing.[18] In this study, the minimally invasive injection method can effectively avoid periosteal injury and facilitate fracture healing. Calcium sulfate cement is used to fill bone defects, which is an important factor in restoring the articular surface and maintaining radial height. Calcium sulfate is acidic, which can increase the local calcium ion concentration and the activity of osteoblasts. At the same time, bone cement absorption and bone tissue formation are synchronized, and the degradation and absorption rate of calcium sulfate is close to the rate of new bone formation.[19] In this group of cases, the follow-up found that a small amount of bone cement leakage occurred in one case; without special treatment, the bone cement was gradually absorbed after about 4 weeks, and the average time of fracture healing was 13.5 ± 1.9 weeks. The fracture healing time was 8-15 weeks, the average time of fracture healing was 12.2 weeks, and the bone cement absorption and healing time were almost the same, which was basically consistent with the previous reports of healing time. This suggests that cement may not increase the risk of delayed union. The absorbability of bone cement could avoid secondary surgery, and all patients had no rejection reaction. After an average follow-up of 14.5 months, all patients had no chronic wrist pain or wrist arthritis, and wrist joint function recovered well. The authors used manual reduction, wrist arthroscopy, and the use of bone cement for injection to obtain reliable clinical results. Under the microscope, the author examined and repaired the scapholunate ligament, TFCC injury, and other soft-tissue injuries, and used bone cement to repair the intra-articular steps and fill the bone defect. The combination of the three can effectively restore the length of the radius, fill the bone defect, and address the problem of articular surface reduction.

Early exercise is key to joint function recovery. Among the 15 cases in this group, active and passive flexion and extension exercises for the fingers and metacarpophalangeal joints were initiated 24 h post-operatively, whereas active wrist flexion, extension, and rotational exercises were started at 4 weeks post-operatively. No complications of refracture or deformity healing were observed. The surgical technique involving a plaster cast combined with injectable

calcium sulfate bone cement not only met the requirements for anatomical reduction of fractures but also fulfilled the need for early rehabilitation exercises. During the procedure, the following points should be noted: (a) for cases where the central column fracture fragment of the radius cannot be reduced by flipping, Kirschner wires should be used to lever the fragment into position under arthroscopy; (b) as a supplementary material, bone cement can adhere to small bone fragments that are difficult to fix or free-floating fragments, such as smaller Die-punch fractures; (c) for cases involving ulnar styloid fractures, TFCC injuries are often present. After reduction, exploration of the TFCC injury can be conducted.

This study has several limitations: a limited number of cases. During the initial exploratory stage of surgery, the operation time was longer, and surgical techniques were less mature, which may have influenced post-operative recovery and data statistics. In addition, all surgeries were performed by one team of doctors, potentially introducing subjective factors influencing therapeutic outcomes. There is limited research on the optimal concentration ratio and injection timing of absorbable bone cement, and there is a lack of quantitative biomechanical studies.

Conclusions

Minimally invasive wrist joint surgery aligns with the concept of rapid recovery. It features small incisions and minimal tissue damage while serving both diagnostic and therapeutic purposes. This approach is particularly effective for repositioning joints with unique anatomical structures. The technique of injectable absorbable calcium sulfate bone cement provides a new perspective for surgeons in choosing treatment options. The combination of these two approaches serves as a beneficial supplement to traditional treatments, offering clinicians new avenues for therapy. In summary, the use of wrist arthroscopy combined with injectable calcium sulfate bone cement for treating distal radius intra-articular fractures results in minimal trauma, satisfactory reduction, and fewer post-operative complications. It allows patients to engage in early flexion-extension exercises, facilitating quicker restoration of wrist joint function.

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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 all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study. This study was approved by the Medical Research Ethics Board of Zhengzhou Orthopedic Hospital.

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

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ORIGINAL ARTICLE

The effect of ethyl pyruvate administration on intestinal mucosal damage in neonatal rat models of necrotizing enterocolitis

Efecto de la administración de piruvato de etilo sobre el daño de la mucosa intestinal en modelos de enterocolitis necrosante en ratas neonatas

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Abstract

Objective: *The purpose of this study was to determine whether intraperitoneal administration of ethyl pyruvate (EP) affects intestinal mucosal damage in neonatal rats with a model of necrotizing enterocolitis (NEC).* **Methods:** *The study comprised 46 Sprague-Dawley newborn rats delivered on the 21st gestational day. The rats were divided into four groups: Sham Group (n = 10), EP Group (n = 10), NEC Group (n = 13), and NEC + EP Group (n = 13).* **Results:** *The mean body weights of rats in Sham and EP groups significantly increased ($p < 0.05$), whereas those in NEC groups significantly decreased ($p < 0.05$). The changes were similar between groups ($p > 0.05$). There was no significant difference in the clinical sickness score (CSS) between groups ($p > 0.05$). The CSS in the NEC groups showed an increase from day 1 to day 4. Based on the histopathological grading, there was a statistically significant difference ($p < 0.001$) observed between the Sham Group, the NEC Group, and the NEC + EP Group. The differences in biochemical values among the other groups were found to be statistically significant ($p < 0.05$) for all variables.* **Conclusions:** *The application of EP in high-mortality diseases such as NEC is expected to reduce surgical needs, establishing a basis for future studies on EP as an innovative anti-inflammatory agent.*

Keywords: *Necrotizing enterocolitis. Neonate. Ethyl pyruvate. Interleukin 6. Malondialdehyde. Sprague-Dawley rat.*

Resumen

Objetivo: *Determinar si la administración intraperitoneal de piruvato de etilo (PE) afecta al daño de la mucosa intestinal en ratas neonatas con un modelo de enterocolitis necrosante (ECN).* **Métodos:** *El estudio incluyó 46 ratas recién nacidas Sprague-Dawley entregadas en el día gestacional 21. Las ratas se dividieron en cuatro grupos: grupo simulado (n = 10), grupo PE (n = 10), grupo ECN (n = 13) y grupo ECN + PE (n = 13).* **Resultados:** *El peso corporal medio de las ratas en los grupos simulado y PE aumentó significativamente ($p < 0.05$), mientras que en los grupos ECN disminuyó significativamente ($p < 0.05$). Los cambios fueron similares entre grupos ($p > 0.05$). No hubo diferencia significativa en el puntuación clínica de enfermedad (PCE) entre grupos ($p > 0.05$). El CSS en los grupos ECN mostró un aumento del día 1 al día 4. Según la clasificación histopatológica, se observó una diferencia estadísticamente significativa ($p < 0.001$) entre el grupo simulado, el grupo ECN y el grupo ECN + PE. Las diferencias en los valores bioquímicos entre los otros grupos resultaron ser estadísticamente significativas ($p < 0.05$) para todas las variables.* **Conclusiones:** *La aplicación de PE en enfermedades de alta mortalidad como la ECN se espera que reduzca las necesidades quirúrgicas, estableciendo una base para futuros estudios sobre el PE como un innovador agente antiinflamatorio.*

Palabras clave: *Enterocolitis necrotizante. Neonato. Piruvato de etilo. Interleucina 6. Malondialdehído. Rata Sprague-Dawley.*

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Introduction

Necrotizing enterocolitis (NEC) is a pathological condition characterized by inflammation of the intestines that primarily affects neonates. It is sometimes observed in conjunction with sepsis, leading to the occurrence of intestinal perforation, peritonitis, and ultimately, mortality. The etiology of NEC encompasses various factors, including hypoxia, hyperosmolar enteral nutrition, intestinal immaturity, and intestinal dysbiosis.[1] Hypoxia and disruption of the intestinal epithelial barrier due to failure to provide enteral nutrition play an important role in premature infants.[2]

Studies in the past have shown that ethyl pyruvate (EP) has anti-inflammatory benefits.[3,4] EP is a derivative of pyruvic acid and serves as an intermediary compound in the process of energy metabolism. Under anaerobic conditions, it facilitates the conversion to lactic acid through the process of dehydrogenation, thereby contributing to energy generation. Consequently, it exhibits antioxidant properties and diminishes the concentration of free radicals.[5] EP is a chemical compound that serves as a derivative of pyruvic acid. It functions as an intermediary molecule in the process of energy metabolism. In anaerobic conditions, it facilitates the conversion of pyruvate to lactic acid by dehydrogenation, thereby contributing to energy generation. Previous research has demonstrated that EP possesses therapeutic properties in the treatment of intra-abdominal sepsis and colitis by modulating intestinal permeability and fortifying the mucosal barrier systems. According to reports, EP has been found to possess a mitigating impact on intestinal inflammation through the inhibition of toll-like receptor 4 (TLR-4).[6] The experimental colitis model has demonstrated that EP exhibits beneficial effects by suppressing the "T Helper 1" immune response.[7] The study investigated the impact of *Escherichia coli* lipopolysaccharide-induced sepsis and septicemia on arterial hypotension in a shock model. The researchers found that the administration of EP solution during resuscitation in rats led to a reduction in arterial hypotension, resulting in prolonged survival. Furthermore, it was observed that the concentrations of interleukin-6 (IL-6) and nitrite/nitrate exhibited a decrease; however, the levels of IL-10 were found to be elevated.[8-10]

The applications of EP are currently being investigated in the experimental study phase, with administration occurring through various channels such as intravenous, intraperitoneal, and intrapulmonary methods.[9,11-13] There is no experimental research on the intraperitoneal administration of EP in NEC models in the literature.

The purpose of this study was to determine whether intraperitoneal administration of EP affects intestinal mucosal damage in neonatal rats with a model of NEC.

Methods

After the approval of the Acibadem University Experimental Animals Local Ethics Committee (January 08, 2020–2020/01), the study was approved by the Scientific Research Projects Unit in the University of Health Sciences, Turkey, which is in accordance with legislation for the protection of animals used for scientific purposes.

To create newborn rats, male and female Sprague-Dawley rats were housed together. If the veterinarian observed sperm in the vaginal smear between 08:30 and 09:30 am, this was considered the start of the 1st gestational day. The mother rats were provided with unlimited access to food at a standard room temperature of 24.5°C. They were kept in a controlled environment with a 12-h cycle of darkness and light.[10] On the 21st gestational day, a total of 46 Sprague-Dawley rats were born by cesarean section and were randomly divided into four groups. The study consisted of four groups: Sham Group (n = 10), NEC Group (n = 13), EP Group (n = 10), and NEC + EP Group (n = 13). The rats in the sham group were allowed to stay with their mothers and were given unlimited access to food. To eliminate the protective effect of breast milk against NEC, the rats designated for the NEC model were isolated from their mother. They were then placed in an incubator set at a temperature of 32°C with 60% humidity.[11]

Sham group

The newborn rats were immediately given to their mother after birth and began to be nourished with breast milk. A total of 0.02 mL of 0.9% NaCl (saline) was administered intraperitoneally into the left lower quadrant at 1:00 p.m. for the initial 4 days.

EP group

Newborn rats, who were being fed breast milk and staying close to their mother for the first 4 days after birth, were given 50 mg/kg of EP intraperitoneally. This was administered as a solution in 0.9% NaCl, with a dosage of 0.02 mL.

NEC group

The newborn rats were fed a hyperosmolar formula consisting of 15 g of formula mixed with 75 mL of puppy or canine milk. This mixture was administered every 4 h using a 24 Gauge orogastric catheter, starting from the 3rd h. The feeding schedule was maintained every 4 h, with an increase of 0.1 mL/day in the subsequent days. The rats used in the NEC model experiment were subjected to specific conditions. They were exposed to hypoxia for a duration of 90 s inside a box filled with nitrogen gas flowing at a rate of 10 L/min. Following this, they were exposed to cold temperatures of 4 °C for a period of 10 min. In addition, the rats were placed in an incubator twice a day, specifically at 9:00 a.m. and 5:00 p.m., for a total of 3 days. A total of 0.02 mL of 0.9% NaCl (saline) was administered intraperitoneally from the left lower quadrant at 1:00 pm for the initial 4 days.[10]

NEC + EP group

The initial steps were identical to those in Group C. During the initial 4 days, a dose of 50 mg/kg of EP, in the form of a solution in 0.9% NaCl, was administered intraperitoneally from the left lower quadrant at 1:00 pm.

Histopathological evaluation

Two double-blind observers evaluated the daily weight and clinical sickness scores (CSSs) of rats in all groups.[14] On the 4th day, following hypothermic sedation with an ice pack and 200 mg/kg phenobarbital, the surgical site was cleaned with povidone-iodine. A 3 cm segment of the terminal ileum was extracted through a 2 cm median incision above the umbilicus. Subsequently, all rats were euthanized.

Evaluation of the macroscopic appearance of the intestines was made by double-blind observers according to the "Macroscopic Gut Score"[12] (Table 1). Histopathological evaluation is based on the "NEC Grading Score" after 10% formaldehyde fixation and Hematoxylin and Eosin staining (Intact villus Grade 0, villi deletion 1, mild villus damage 2, complete villus necrosis 3, and transmural necrosis 4) performed by pathologists. Grades 2, 3, and 4 were accepted as NEC.[13]

Tissue samples of 3 cm in length, obtained from the terminal ileum, were subjected to storage at a temperature of −80°C. Subsequently, these samples were homogenized in a phosphate-buffered saline solution at a weight-to-volume ratio of 1/10. The tissue homogenates underwent centrifugation at a speed of 3000 revolutions/min (rpm) at a temperature of +4°C. Subsequently, the supernatants obtained were gathered and put into polypropylene tubes. The levels of IL-6 and Malondialdehyde (MDA) were quantified using the Rat-IL-6 Enzyme-Linked Immuno Sorbent Assay (ELISA) kit (Catalog Number E0135Ra) and the Rat-MDA ELISA kit (Catalog Number E0156Ra), respectively.[14,15]

Table 1. Scoring system for macroscopic gut assessment

	Macroscopic gut assessment		
Score	**Gut consistency**	**Gut colour**	**Gut dilatation**
0	Normal	Normal	Normal
1	Moderately Friable	Patchy discoloration	Patchy dilatation
2	Extremely Friable (jelly-like)	Extensive discoloration	Extensive dilatation

Macroscopic Gut assessment, from Zani et al.[12].

Statistical analysis

The data was documented using the Microsoft Office 2019 Pro-Excel software. The data were analyzed using the IBM Statistical Package for the Social Sciences 26.0 software (IBM, Armonk, New York, US). The data are presented as means and standard deviations, or as counts and percentages (n%). The Shapiro-Wilk test was used to assess the normality of the data distribution. To assess the distinctions between groups, analysis of variance tests and *post hoc* tests were employed. In order to examine temporal variance, the Friedman and Wilcoxon tests were utilized. The results were assessed using a 95% confidence interval and a statistical significance level of $p < 0.05$.

Results

Nine rats survived in both the sham group and the EP group. One rat from each group could not be found in the cage, leading to the assumption that the mother rat might have eaten the baby rat. Six of 13 rats in the NEC group were euthanized on day 3 due to deterioration in their general condition and increased clinical disease scores. One rat in the NEC + EP group was excluded from the study due to its unfortunate demise in the cage on the 2nd day. Three of them were sacrificed on the 3rd day and included in the study due to

Table 2. Clinical sickness score

Clinical sickness score				
Score	**Appearance**	**Natural activity**	**Response to touch**	**Body color**
0	Tonic and well hydrated	Moving normally in the cage	Alert (without stimulation)	Pink
1	Slimmer but still tonic and hydrated	Able to wriggle if put supine	Responding to mild stimulation	Pale (just at the extremities)
2	Skinny, floppy, and dehydrated	Not able to wriggle if put supine	Responding to vigorous stimulation	Pale (whole body)
3	Gasping and in agony	Not moving limbs and lying still	Unresponsive notwithstanding vigorous stimulation	Grey

deterioration in general condition and an increase in CSSs on the 3rd day (Table 2).

The mean body weights of rats in Sham and EP groups significantly increased ($p < 0.05$), while those in NEC groups significantly decreased ($p < 0.05$). The changes were similar between groups ($p > 0.05$) (Fig. 1).

There was no statistically significant difference between the groups in terms of the CSS values on the 1st day ($p > 0.05$). The CSS was consistent across all groups on day 1. The results showed that there was no significant difference between the groups on day 1 ($p > 0.05$), but there was a significant difference on days 2-4 ($p < 0.05$). There was no significant difference in the CSS between groups ($p > 0.05$). The CSS in the NEC groups showed an increase from day 1 to day 4 (Fig. 2).

The average macroscopic bowel assessment score for all groups of rats was 1.58. There was no significant difference in macroscopic bowel scoring between the Sham and the EP Group. However, there was a statistically significant difference between all other groups ($p < 0.05$). Figure 3 displays the macroscopic bowel appearances of the different groups.

During the histopathological examination, it was observed that 78% of the rats in the sham Group had grade 0 NEC, while the remaining 22% had grade 1 NEC. Within the NEC group, 7.7% of the rats exhibited grade 1, while another 7.7% displayed grade 2. The majority, 30.7%, had grade 3 NEC, and the highest proportion, 53.8%, exhibited grade 4 NEC. All rats in the EP Group exhibited no signs of NEC, as they were assigned a grade of 0. In the NEC+EP Group, the distribution was as follows: 1 in 8.4%, 2 in 33.3%, 3 in 33.3%, and 4 in 25%. The histopathological microscopic images are displayed in figure 4. Based on the histopathological grading, there was a statistically significant difference ($p < 0.001$) observed between the Sham Group, the NEC group, and the NEC + EP Group. There was a statistically significant difference ($p < 0.001$) between the NEC Group and the EP Group. A statistically significant difference ($p < 0.001$) was observed between the EP and NEC + EP Group. There was no statistically significant difference observed in the histopathological evaluation between the NEC group and the NEC + EP group. However, when considering the distribution, it was observed that the percentage of grade 3 and 4 rats in the treatment group was lower compared to the untreated NEC group. Table 3 presents the statistical results pertaining to the differences between groups.

Table 3. Histopathological changes

Group (n)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Sham (9)	7 (77.8)	2 (22.2)	0	0	0
EP (9)	9 (100)	0	0	0	0
NEC (9)	0	1 (7.69)	1 (7.69)	4 (30.7)	7 (53.8)
NEC+EP (12)	0	1 (8.3)	4 (33.3)	4 (33.3)	3 (25)

Statistically significant differences were observed between Sham vs NEC, Sham vs NEC + EP, NEC vs EP, and EP vs NEC + EP groups ($p < 0.001$). No statistically significant difference was observed between NEC and NEC + EP groups.
NEC: necrotizing enterocolitis; EP: ethyl pyruvate.

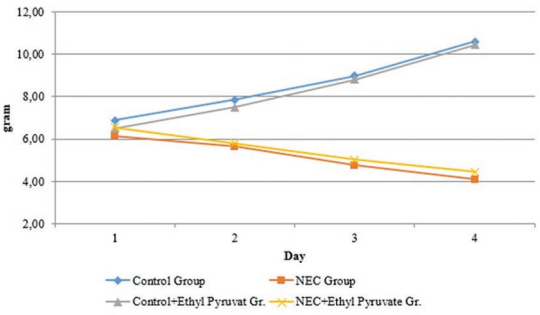

Figure 1. *Time change of mean body weights of the groups.*

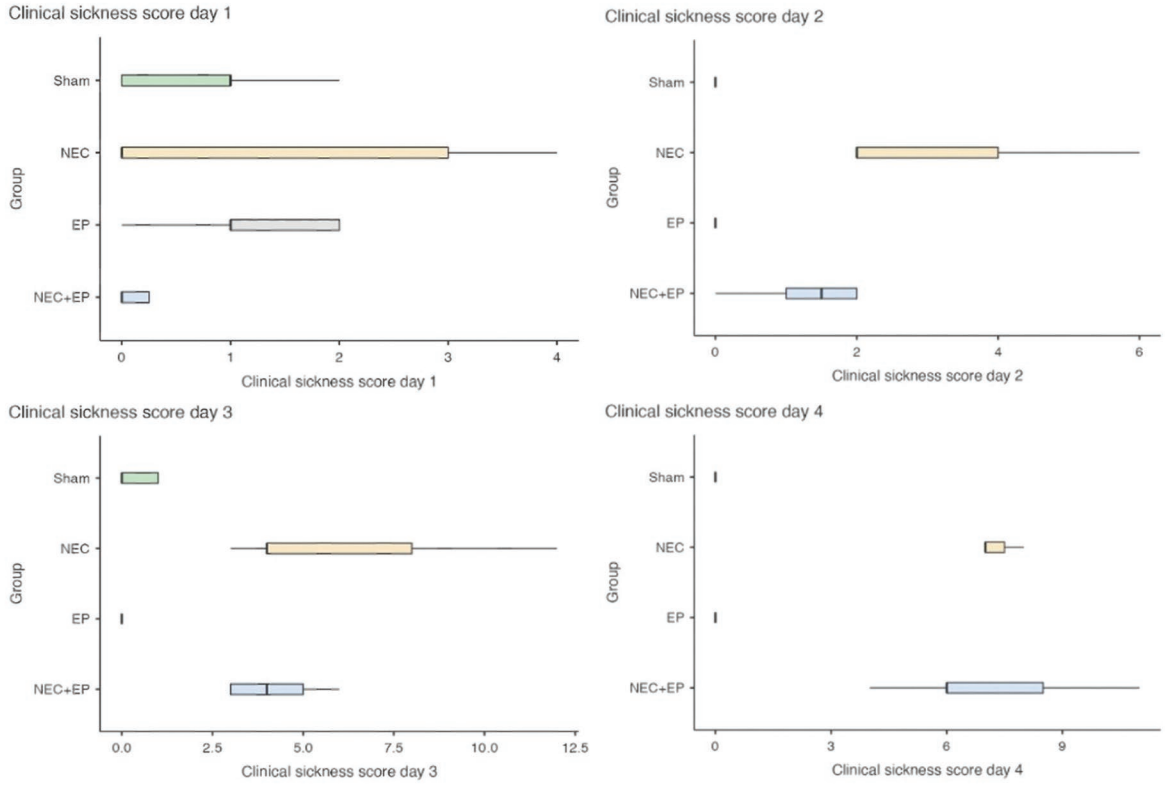

Figure 2. *Change of clinical sickness scores over time.*

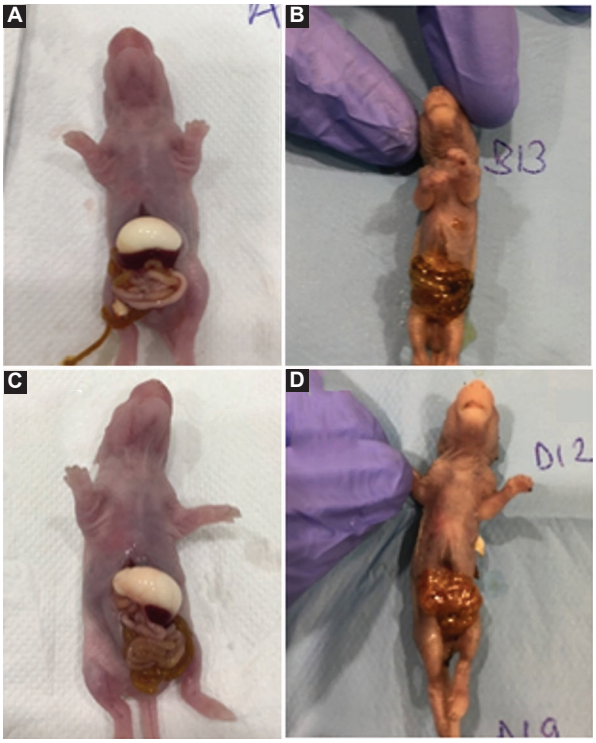

Figure 3. *Macroscopic bowel appearance. (**A**) Sham group, (**B**) necrotizing enterocolitis (NEC) group, (**C**) ethyl pyruvate (EP) group, (**D**) NEC + EP group.*

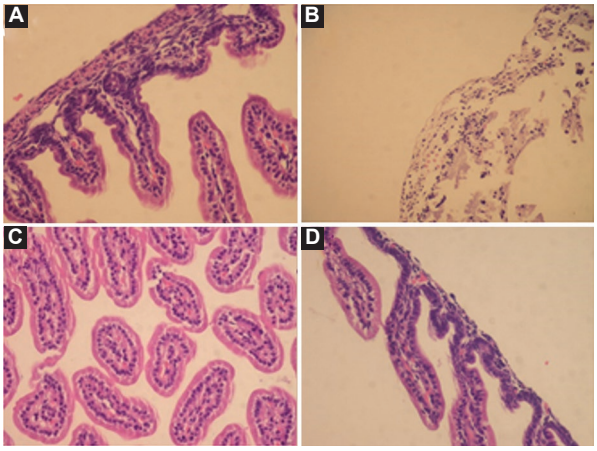

Figure 4. *Histopathological changes. (**A**) Sham (Grade 1), (**B**) necrotizing enterocolitis (NEC) (Grade 3), (**C**) ethyl pyruvate (EP) (Grade 0), (**D**) NEC + EP (Grade 1).*

There was no statistically significant difference in the biochemical values of the Sham Group and the EP Group when comparing the results of IL-6 level and tissue MDA level. The differences in biochemical values among the other groups were found to be

Table 4. Cytokine levels of groups

Cytokines	Sham (n = 9)	EP (n = 9)	NEC (n = 9)	NEC+EP (n = 12)	p
IL-6 (pg/mg tissue)	0.21 ± 0.02	0.21 ± 0.02	0.43 ± 0.06[a]	0.28 ± 0.05[a]	0.0001
MDA (pg/mg tissue)	0.06 ± 0.01	0.05 ± 0.01	0.12 ± 0.02[a]	0.08 ± 0.02[a]	0.0001

[a]Statistically significant difference between group NEC versus NEC + EP p = 0.001.
NEC: necrotizing enterocolitis; EP: ethyl pyruvate; IL-6: interleukin-6; MDA: malondialdehyde.

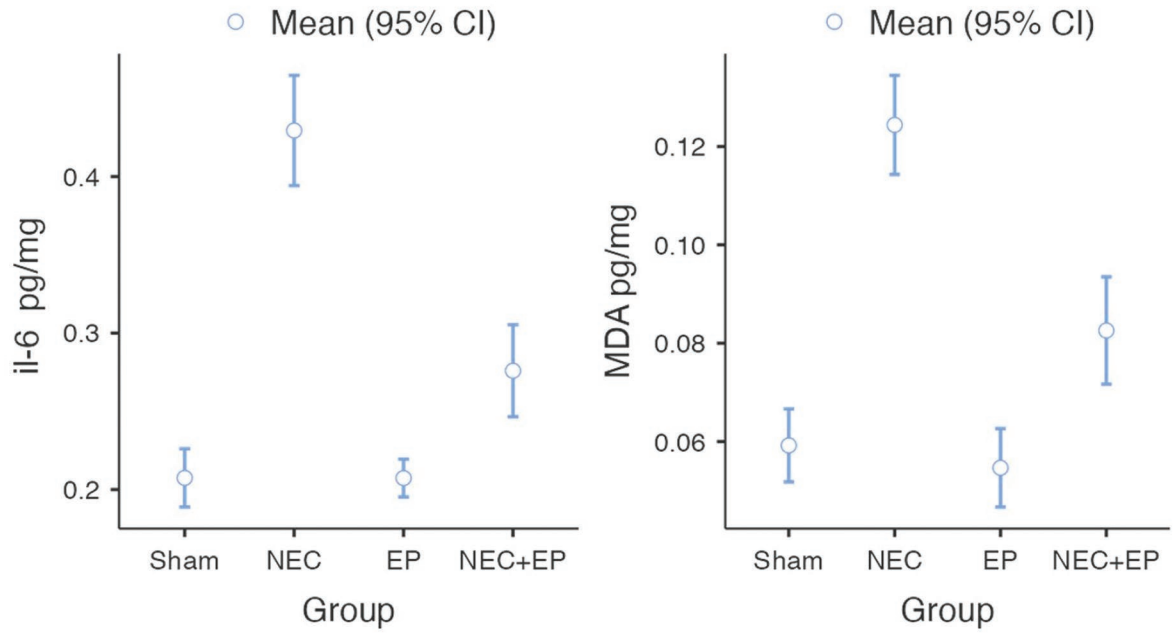

Figure 5. *Comparison of the cytokine levels.*

statistically significant ($p < 0.05$) for all variables (Table 4 and Fig. 5).

Discussion

The advancement of neonatal intensive care units has highlighted NEC as a major concern due to its high rates of illness and death in premature infants. In preventing NEC, administering EP intraperitoneally may play a key role in lessening intestinal harm by reducing intestinal necrosis. This study is the first to examine the impact of EP on neonates with an NEC model. Our research aimed to shed light on NEC's causes and development, as well as on strategies for its prevention. The insights gained from this study lay the groundwork for further research in this field.

Different animal models have been developed for NEC research, but they vary in mechanism and pathophysiology. The human and animal immune systems differ; for example, humans get immunoglobulins via the placenta, while pigs get them through the gastrointestinal tract. Barlow and Santulli's 1974 NEC model, the first successful one, focuses on altered intestinal bacteria and the lack of breast milk. Its creation involved formula feeding, hypoxia, and cold exposure.[16]

Numerous agents have undergone investigation in experimental animal models to explore their potential for preventing and treating NEC.[17-19] EP is a pyruvic acid derivative and has been reported to provide improvement in conditions such as ischemia-reperfusion injury, organ dysfunctions, hemorrhagic shock, sepsis, acute respiratory distress syndrome, acute pancreatitis, and skin burns.[9] EP has the ability to reduce the action of peritoneal macrophages by decreasing the secretion of HMGB1 protein.[4] Previous studies have demonstrated that EP possesses therapeutic effects in the treatment of intra-abdominal sepsis and colitis by targeting the intestinal permeability

and mucosal barrier systems.[6,7] In the colitis model induced by 2,4,6-trinitrobenzene sulfonic acid, it has been demonstrated that intraperitoneal administration of EP at a dose of 50 mg/kg for 1 week improves pathological damage and reduces T-helper-17 cells in the local tissue.[7]

Yurttutan et al.'s study showed newborn rats with an NEC model gained more weight with etanercept, a tumor necrosis factor alpha (TNF-α) blocker.[17] Another study found increased weight in NEC rats fed growth factor-enriched formula.[15] Our study observed normal growth in breastfed control groups and significant weight loss in NEC groups, with no difference in weight gain from intraperitoneal EP application.

The CSS was used to assess the clinical condition of newborn rats with NEC.[14] Korkut et al.'s study showed lower scores in rats treated with obestatin.[11] Another study found improvement with mesenchymal stem cell therapy.[18] Our research observed worsening conditions and increased scores in the NEC and NEC + EP groups, with significant deterioration by the 4th day. No difference in scores was noted between these groups, aligning with high morbidity and mortality rates in NEC models.

The macroscopic gut assessment method evaluates bowel appearance in the NEC model newborn rats.[14] A study found that cytidine 50-diphosphocholine significantly reduced macroscopic bowel scores in treated rats.[20] Our study, using double-blind observers, showed that EP treatment in NEC rats led to improved bowel appearance and lower scores, indicating potential reduction in intestinal damage.

A grading system has been established to determine the histopathological diagnosis of NEC. The histopathological grading is assessed using the NEC grading score. This scoring system assigns a value of 0 for intact villi, 1 for villi deletion, 2 for mild villus damage, 3 for complete villus necrosis, and 4 for transmural necrosis.[13] In a study performed by giving pentoxifylline to newborn rats, for which the NEC model was created, it was shown that histopathological NEC findings were milder.[21] Previous studies similar to ours have reported a morbidity rate of 75% in the experimental NEC model.[10] A study was conducted to investigate the effects of pioglitazone, a peroxisome proliferator-activated receptor-γ agonist, on an NEC model. The study compared a control group with a treatment group. The results showed that the treated group had a lower macroscopic bowel score and exhibited milder intestinal damage in histopathological examinations. The study found that there was no difference between the two groups in terms of the amount of IL-6 and TNF-α messenger RNA (mRNA) in the tissue.[17] In our study, we observed histopathological findings in newborn rats. Specifically, we found that 53% of rats in the NEC Group had grade 4 NEC, whereas 30% had Grade 3 NEC. In the group treated with NEC+EP, the distribution of rat grades was as follows: 33% were Grade 2, 33% were Grade 3, and 25% were Grade 4 NEC. There was no statistically significant difference between the two groups; distributionally, there was a decrease in the severity of NEC in the NEC + EP Group. In grades 3 and 4, NEC was detected in 83% of the rats in the NEC group. There was a significant difference between the control groups and the NEC groups in relation to the increase in histopathological grading. There was no statistically significant difference observed in histopathological grading between the NEC group and the NEC + EP group. However, the percentage of rats in the treatment group with Grade 3 and 4 distributions was lower compared to the untreated NEC group. In order to achieve statistical significance, it may be necessary to increase the sample size. The results indicate that the therapeutic effect of EP on NEC can be observed through intraperitoneal administration, as seen in the histopathological findings.

NEC is linked with increased levels of IL-6, a proinflammatory cytokine, which correlates with NEC severity. IL-6 stimulates C-reactive protein release and is regulated by nuclear factor kappa-light-chain-enhancer of activated B cells.[22] Studies in rats show that interventions can impact IL-6 levels.[23,24] Fecal microbiota transplantation normalized systemic IL-6, IL-1β, and TNF-α in a Wistar albino rat NEC model. Another study using an NEC model induced by formula feeding, lipopolysaccharide injection, and hypoxia found that subcutaneously administered glucagon-like peptide-2 significantly lowered TNF-α and IL-6 levels.[25] Ulinastatin treatment also significantly decreased tissue IL-6 levels.[26] N-Acetyl Cysteine given antenatally and postnatally reduced IL-6 and its mRNA expression in intestinal tissue.[27,28] Our study focused on the effect of EP on IL-6 levels in NEC rats. While control groups showed no significant IL-6 difference, NEC groups had higher IL-6, which was significantly reduced by EP treatment, suggesting EP's effectiveness in reducing NEC severity by lowering IL-6 in intestinal tissue.

EP has been found to be an effective agent in combating free oxygen radicals during instances of oxidative stress. Previous studies have reported that the

administration of EP reduces the levels of MDA, a free oxygen radical, in conditions such as hemorrhagic shock and ischemia-reperfusion injury.[29] In the case of NEC, oxidative stress leads to the formation of free oxygen radicals, which in turn causes an increase in tissue MDA levels.[23] A study was conducted to investigate the effects of quercetin, a flavonoid derivative known for its antioxidant properties, on newborn rats with NEC. After creating the NEC model, quercetin was administered to one group of rats while another group did not receive any treatment. The results revealed a decrease in oxidative stress parameters, specifically MDA levels, in the tissues of the treated group compared to the non-administered group.[30] A study conducted by Guven et al. demonstrated that the rats with the NEC model who were administered melatonin exhibited a decrease in the oxidative stress parameter, MDA, compared to the group that did not receive melatonin.[31] In our study, we did not find any significant difference in MDA levels in intestinal tissues between the two control groups. However, we did observe a significantly higher level of MDA in the NEC groups compared to the control groups. In the NEC group that received EP, it was observed that the levels of tissue MDA decreased significantly compared to the NEC group that did not receive EP.

This study is the first to examine the impact of EP on neonates with an NEC model. The study demonstrated that when EP was administered intraperitoneally to newborn rats with an NEC model, it did not have any impact on the clinical status or body weight of the rats. However, it did lead to an improvement in the macroscopic appearance of the bowel. Although the application of EP did not have a statistically significant effect on the histopathological improvement in the NEC group, it was observed that it improved the overall histopathological condition. It has been found that administering EP intraperitoneally to rats with an NEC model resulted in a reduction in the severity of NEC. This was achieved by decreasing the level of IL-6 in the intestinal tissue and reducing oxidative stress by lowering the MDA level.

This is a pioneering study to investigate the effects of EP on the NF-kB activation pathway and the TLR-4 inhibition pathway in the pathogenesis of NEC. Due to financial difficulties, this research could not be carried out. It may be necessary to enlarge the sample sizes to obtain more statistically significant results. These situations are the limitations of the study.

Conclusions

It is predicted that the application of EP in diseases with high mortality, such as NEC, can decrease the necessity for surgery. This finding will serve as the foundation for future phase studies exploring the use of EP as a new-generation anti-inflammatory agent.

Funding

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the World Medical Association and the Declaration of Helsinki. The procedures were authorized by the Institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. This study did not involve human participants. All experimental animal procedures were approved by the Acibadem University Experimental Animals Local Ethics Committee (Approval date: January 08, 2020; Approval number: 2020/01) and were conducted in accordance with institutional and applicable ethical guidelines. The ethics committee approval document is attached for editorial records."

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

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ARTÍCULO ORIGINAL

La comunicación como la habilidad no técnica más importante en el quirófano

Communication as the most important non-technical skill in the operating room

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Resumen

Objetivo: *Realizar una revisión de la literatura acerca de la complementariedad entre la comunicación en el área quirúrgica como una habilidad no técnica y su aspecto fundamental en la práctica quirúrgica.* **Métodos:** *Se realizó una búsqueda bibliográfica consultando las bases de datos de la National Library of Medicine, PubMed, SciELO y Google Académico. Se consideraron como criterios de inclusión artículos publicados en los últimos 10 años, en idiomas inglés y español, de acuerdo con una serie de palabras clave.* **Resultados:** *La búsqueda inicial proporcionó 2597 títulos, los cuales fueron sometidos a cribaje y se recuperaron 22 artículos para el análisis del estudio.* **Conclusiones:** *El proceso del comunicar no es tan sencillo y lineal; la comunicación debe ser clarificada por los partícipes de la interacción, ya que deben superar ciertas variables internas y externas para que esta logre desarrollarse adecuadamente. La comunicación en el quirófano debe ser asertiva y efectiva, que todos se sientan importantes y sean capaces de comprender lo que está ocurriendo con capacidad de presentar sus propias opiniones como factor clave para la seguridad del paciente durante el tiempo quirúrgico.*

Palabras clave: *Habilidades no técnicas. Comunicación. Competencia quirúrgica.*

Abstract

Objective: *To carry out a review of the literature about the complementarity between communication in the surgical area as a non-technical skill and its fundamental aspect in surgical practice.* **Methods:** *A bibliographic search was carried out by consulting the databases of the National Library of Medicine, PubMed, SciELO and Google Scholar. Articles published in the last 10 years, in English and Spanish, were considered as inclusion criteria, according to a series of keywords.* **Results:** *The initial search provided 2597 titles, which were screened and 22 articles were recovered for study analysis.* **Conclusions:** *The process of communicating is not so simple and linear; communication must be clarified by the participants in the interaction since they must overcome certain internal and external variables for it to develop properly. Communication in the operating room must be assertive and effective, where everyone feels important and is able to understand what is happening with the ability to present their own opinions as a key factor for patient safety during the surgical time.*

Keywords: *Non-technical skills. Communication. Surgical competence.*

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Introducción

La comunicación se define como el intercambio o retroalimentación de información, ideas y sentimientos, que promueve el trabajo en equipo como un todo, en el que se asegura que todos los miembros compartan la misma visión durante el cumplimiento efectivo de las tareas[1]. Las habilidades no técnicas a su vez son definidas como aspectos cognitivos, sociales y personales que complementan la experiencia y el conocimiento. Son cinco los pilares fundamentales de las habilidades no técnicas: conciencia de la situación, toma de decisiones, liderazgo, trabajo en equipo y comunicación[2].

En la última década se considera que los eventos adversos en cuidados de la salud, especialmente en el área quirúrgica, están originados por fallas en aspectos conductuales más que por falta de experticia. En este sentido, se ha reportado que hasta un 86% de los acontecimientos adversos en cirugía están relacionados con habilidades no técnicas, siendo el 43% atribuidos solo a fallas en la comunicación[3].

A través del análisis sistemático del estudio de los factores humanos relacionados con la cirugía es posible observar que una atención de buena calidad no se reduce únicamente a la interacción técnica del cirujano y el paciente en la mesa quirúrgica; de esta manera, los errores pueden explicarse entendiendo también la interacción de las condiciones ambientales y las habilidades personales, tanto técnicas como no técnicas, que permiten al cirujano interactuar y reaccionar a este sistema dinámico[3,4].

El objetivo del presente artículo es realizar una revisión sistemática de la literatura disponible acerca de la complementariedad entre la comunicación como una habilidad no técnica y su aspecto fundamental en la práctica quirúrgica.

Métodos

Se realizó una búsqueda bibliográfica consultando las bases de datos de la National Library of Medicine, PubMed, SciELO y Google Académico. Se consideraron como criterios de inclusión artículos publicados en los últimos 10 años (2014-2024), en idiomas inglés y español. Se utilizaron las siguientes palabras clave: “non-technical skills”, “communication in surgery”, “competencias médicas”, “habilidades no técnicas en cirugía”, “comunicación en cirugía” y sus combinaciones con el uso de los operadores booleanos AND y OR. Se excluyeron los artículos cuyo texto no estuviera disponible.

Resultados

La revisión inicial en las bases de datos mencionadas proporcionó 2597 resultados, de los cuales fueron excluidos 2403 por tratarse de estudios duplicados, no relacionados con el tema seleccionado, referirse a patologías específicas o enfocados en otra habilidad no técnica. En el cribado por título, de los 194 estudios recopilados se excluyeron 152. Se revisaron los resúmenes de 42 artículos y finalmente se seleccionaron 22 relacionados con el tema de estudio.

Discusión

La formación de los cirujanos siempre se ha centrado en el desarrollo de conocimientos, experiencia clínica y habilidades técnicas; otros aspectos, como la toma de decisiones, la comunicación efectiva y el liderazgo, se desarrollan de manera informal y tácita en lugar de ser abordados durante la capacitación. La comunicación se considera la base del trabajo en equipo y uno de los factores más importantes a tener en cuenta en la formación y la evaluación[5].

La comunicación y su relación con la destreza quirúrgica

El quirófano es un ambiente lleno de potenciales situaciones, muchas de las cuales no pueden controlarse. Sin embargo, aquellas que sí pueden serlo, incluyendo el lenguaje verbal y gestual, y el tono de voz, de los miembros del equipo deben ser manejadas. Estableciendo una comunicación clara y efectiva se asegura que todos los integrantes de un equipo compartan una visión en común y, de esta manera, puedan completar sus tareas de manera adecuada[3].

Estudios que respaldan la comunicación en cirugía

Se ha demostrado que gran parte de los eventos adversos que se producen en cirugía se basan en problemas con la comunicación que tienden a repetirse sistemáticamente, por lo que, si mejora la comunicación, mejorará el trabajo en equipo[5]. Los datos recolectados por la Comisión Conjunta de

Acreditación de Organizaciones de Salud sugieren que la mala comunicación contribuyó al 70% de los eventos centinelas reportados en 2005[6].

Lingard et al.[7] identificaron 421 eventos de comunicación y clasificaron casi un tercio de ellos como fracasos. En el análisis de Greenberg et al.[8] sobre reclamos por negligencia quirúrgica se identificaron patrones recurrentes y contribuyentes a la falta de comunicación que resultaron en lesión a los pacientes. En un estudio de Sánchez et al.[9] se evidenció falla en la comunicación de los profesionales en el acto operatorio, evidenciando en 35 cirugías la ocurrencia de 179 errores, variando el número de estos de manera individual entre 1 (12.8%), 2 (7.8%), 3 (7.8%) y más de 3 (71.5%), con distintos tipos de causas en el origen de los errores comunicativos por parte del equipo quirúrgico.

Actualmente, apenas estamos empezando a comprender la importancia de la comunicación y su contribución para el desempeño eficiente y seguro del equipo durante el acto quirúrgico[10].

Cómo alcanzar la comunicación y su impacto en la competencia quirúrgica del cirujano

Realizar reuniones de trabajo previo y posterior al acto quirúrgico permite a los miembros del equipo discutir el desenvolvimiento intraoperatorio, la evolución esperada y las oportunidades para mejorar, llegando a una retroalimentación efectiva. De igual manera, comunicar y discutir cualquier complicación, elemento sorpresa o evento no esperado (como fallas de equipos) que pudieron darse durante la cirugía. Esta rutina de comunicación se convierte en una herramienta que permitirá al equipo mantener una buena relación y una preparación para la siguiente cirugía, y le ayudará a desarrollar en conjunto sus habilidades y evitar que se repitan los mismos errores[9].

Desafíos y recomendaciones para la práctica quirúrgica y la comunicación en cirugía

Un paso importante en la creación de equipos altamente efectivos radica en enseñar al personal a cómo ser parte de ese equipo. Sin capacitación, solo serán grupos de personas que trabajan en el mismo lugar, pero no un verdadero equipo. La capacitación moldeará a este grupo de personas en una sola entidad que enfrentará problemas y trabajará unida en la atención del paciente[11].

La comunicación por parte del equipo es un factor clave para la seguridad del paciente en el tiempo quirúrgico, puesto que este es un espacio en el que intervienen múltiples factores, se toman decisiones y se comparten y discuten ideas en pro del paciente. Sin embargo, el proceso del comunicar no es tan sencillo y lineal; la comunicación debe ser clarificada y negociada por los partícipes de la interacción, puesto que se encuentran influenciados por variables internas y externas. Además, es importante mencionar que la comunicación puede ser subdividida en tres vertientes: la primera es la verbal, que contempla la palabra (sea oral o escrita); luego está la no verbal, que comprende el complejo kinésico (lenguaje corporal) y proxémico (asociado a la distancia corporal); y finalmente, la línea paralingüística (hace referencia a la expresión con sonidos, pero sin palabras)[12].

Los miembros del equipo priorizan la familiaridad por sobre la formalidad y se ayudan unos a otros para evitar equivocaciones. Para estimular este abordaje en la atención médica, las instituciones pueden seguir distintas acciones, como[11]:

- Utilizar herramientas de comunicación estructuradas que eliminen las jerarquías.
- Brindar retroalimentación a los cirujanos.
- Capacitar el trabajo de equipo.
- Enfrentar comportamientos conflictivos.

Obstáculos comunes en la búsqueda de la práctica quirúrgica y la comunicación

Al igual que todas las habilidades, existen ciertos parámetros mínimos que deben cumplirse y superarse para lograr una comunicación efectiva en el área quirúrgica; son las denominadas barreras internas y externas.

Las barreras externas están constituidas por el ruido, el bajo volumen de voz, la distancia, el tiempo e incluso la falta de expresión visual. Las barreras internas, a su vez, son diferencias de lenguaje, cultura organizativa, estado de ánimo y afectos por parte de los involucrados[13].

Los equipos quirúrgicos habitualmente se enfrentan a los desafíos impuestos por el sofisticado instrumental que utilizan, por la necesidad de transmitir con rapidez información crítica, por la naturaleza cambiante de la condición del paciente y por la incertidumbre inherente a toda cirugía[14]. Además, los

miembros del equipo pueden conocer muy poco acerca del otro o desconocer las necesidades de un paciente o de un procedimiento determinado. Como consecuencia de esto, cuando el personal quirúrgico no se comunica eficientemente puede perderse, olvidarse o malinterpretarse información crítica, y poner en peligro la seguridad del paciente[14,15].

Estrategias para superar los desafíos y alcanzar la práctica quirúrgica y la comunicación en cirugía

Entendiendo la comunicación como un proceso de equipo combinado, multidireccional, que tiene diferentes emisores, mensajes y receptores, en donde debe existir un ciclo cerrado, partimos de lo que se quiso decir, después a lo que se dijo, a lo que se oyó y finalmente a lo que se entendió. Para que una comunicación sea efectiva, debe ser completa, precisa, no ambigua y claramente comprendida[16]. Se han descrito algunas características o aspectos que debe cumplir el proceso comunicativo para que sea efectivo, como la claridad del mensaje, la oportunidad, la asertividad y la escucha activa[17]. Para cumplir con estas metas, recientemente se ha descrito la estrategia ISAER constituida por cinco componentes: identificación, situación, antecedentes, evaluación y recomendación; ha demostrado mejorar la comunicación en equipos de trabajo, disminuyendo los errores y mejorando la satisfacción tanto de los pacientes como del personal[18].

Conclusiones

Tradicionalmente, los médicos, en especial los cirujanos, han sido entrenados para pensar más como individuos que como miembros de un equipo. Sin embargo, la seguridad del paciente requiere un abordaje en el cual individuos con diferente formación trabajen juntos, compartan información y coordinen sus esfuerzos para brindar una atención óptima[19]. Los equipos altamente efectivos no permiten que las barreras jerárquicas pongan en peligro la seguridad. Cuando se enfatizan las diferencias de jerarquía, la gente en la base de la pirámide suele sentirse incómoda o directamente temerosa de expresar problemas o preocupaciones. Las conductas groseras, agresivas o intimidantes por parte de aquellos individuos que están en el vértice de la jerarquía ponen en peligro la comunicación, haciendo que esa persona parezca inabordable. El líder del equipo es el que establece el tono de todas las interacciones perioperatorias[20].

La comunicación, tanto verbal como no verbal, tiene lugar en el quirófano para garantizar un desempeño adecuado, y se ve afectada por una serie de factores internos y externos. Los que facilitan el desarrollo de una buena comunicación son la claridad de la expresión y la escucha, el respeto, la conciencia de la situación, la experiencia y la confianza[21]. Además, la comunicación no es solo un proceso que se limite al quirófano, pues se deben generar situaciones en las que se eliminen jerarquías dentro y fuera de la cirugía, y por ende la acción individualista es rechazada; debe haber participación no solo del equipo quirúrgico, sino que hay que generar espacios donde la parte organizativa y administrativa se integren para así comprender los errores y los puntos de mejora, como a la vez galardonar aquellas acciones exitosas que el equipo realizó correctamente. Así, la comunicación en el quirófano debe ser asertiva y efectiva, buscar siempre el trabajo en equipo, que todos se sientan importantes y sean capaces de comprender lo que está ocurriendo y presentar opiniones al respecto[22].

El manejo dentro del área quirúrgica es una tarea que requiere la colaboración de profesionales de distintas disciplinas, y de ahí la importancia de la interacción para que esta sea adecuada y se mantenga una percepción similar de la situación que asegure un trabajo óptimo en equipo y se garantice la seguridad del paciente. La institución también puede destinar recursos para capacitar a los miembros del equipo quirúrgico en comunicación, algo que generalmente no se brinda en el pregrado y cuya carencia puede afectar la evolución del paciente y aumentar el riesgo de sufrir demandas por responsabilidad profesional.

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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, historias clínicas ni muestras biológicas humanas, por lo que no requiere aprobación ética. No se aplican las guías SAGER.

Declaración sobre el uso de inteligencia artificial. Los autores declaran que no se utilizó ningún tipo de inteligencia artificial generativa para la redacción ni la creación de contenido de este manuscrito.

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ORIGINAL ARTICLE

Incidence of surgical site infection in head and neck surgery: a prospective cohort study

Incidencia de infección del sitio quirúrgico en cirugía de cabeza y cuello: estudio de cohorte prospectivo

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Abstract

Objectives: *Surgical site infection (SSI) causes high morbidity. Our aim was to study the incidence of SSI and to assess its risk factors in patients undergoing head and neck surgery.* **Methods:** *A prospective cohort study was conducted, from July 2007 to June 2023, by collecting data on patient, surgery, and infection-related variables, and calculating the incidence of SSI after a maximum follow-up period of 1 year. We assessed the effect of the different risk factors on SSI, using the relative risk adjusted with a logistic regression model.* **Results:** *We included 423 patients, mean age 65.8 years (standard deviation: 12.4). The most frequent comorbidities were neoplasms (82.1%) and diabetes mellitus (29.3%). The cumulative incidence of surgical infection across the follow-up period was 6.4% (95% confidence interval: 4.1-8.7). Most infections were superficial, with the most common microorganism being Enterobacter cloacae (42.8%). Duration of surgery above the 75th percentile was the only risk factor associated with SSI in the multivariate analysis (p = 0.01).* **Conclusions:** *The incidence of infection was low in neck surgery. Infection rates must be assessed continuously, and SSI risk factors identified early through the implementation of prospective hospital surgical-infection surveillance and control programs.*

Keywords: *Epidemiological surveillance. Head and neck surgery. Surgical site infection. Incidence. Cohort studies. Risk factors.*

Resumen

Objetivo: *Estudiar la infección del sitio quirúrgico (ISQ) y los factores de riesgo relacionados en pacientes intervenidos de cirugía de cuello.* **Métodos:** *Se realizó un estudio de cohorte prospectivo desde julio de 2007 hasta junio de 2023. Se recogieron datos de los pacientes, la cirugía y las infecciones quirúrgicas. Se calculó la incidencia de ISQ tras un seguimiento de 1 año. Se evaluó el efecto de los factores de riesgo con el riesgo relativo ajustado con un modelo de regresión logística.* **Resultados:** *Se incluyeron 423 pacientes, con una edad media de 65.8 años (DE: 1.4). La comorbilidad más frecuente incluyó neoplasias (82.1%) y diabetes mellitus (29.3%). La incidencia acumulada de ISQ fue del 6.4% (IC 95%: 4.1-8.7). La mayoría de las infecciones fueron superficiales y el microorganismo más frecuente fue Enterobacter cloacae (42.8%). En el análisis*

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multivariante, la duración de la cirugía mayor que el percentil 75 se relacionó con la ISQ (p = 0.01). **Conclusiones:** *La incidencia de ISQ en la cirugía de cuello fue baja. La incidencia de infección quirúrgica y los factores de riesgo asociados deben ser evaluados de forma continuada con programas de vigilancia y control de las infecciones quirúrgicas.*

Palabras clave: *Vigilancia epidemiológica. Cirugía de cabeza y cuello. Infección del sitio quirúrgico. Incidencia. Estudio de cohorte. Factores de riesgo.*

Introduction

Healthcare-associated infections (HAIs) are those that occur during patients' healthcare processes and were neither present clinically nor incubating at the time of admission.[1] According to the latest Prevalence Study of Nosocomial Infection in Spain (*Estudio de Prevalencia de Infección Nosocomial en España/ EPINE*), 6.0% of patients present with one or more HAIs.[2]

Surgical site infections (SSIs) are infections related to a surgical procedure, which occur in the surgical incision or nearby tissue and whose development is most likely within 15-30 days following surgery. SSIs are classified in three categories: superficial, if they only affect the cutaneous and subcutaneous tissue; deep, if they involve deep soft tissue (fascia and muscle walls); and organ-space, when they affect any distal zone to the sterile incision or cavity.[3]

SSIs are one of the main causes of morbidity and mortality in hospitalized patients,[4] prolonging hospital stays, increasing readmissions, reducing the quality of life of the patient intervened, and raising the cost of healthcare processes.[5-9] Within HAIs, SSIs lead (26.3%), ranking ahead of urinary infections (16.0%) and bacteremias (14.8%).[2,10]

Within otorhinolaryngological surgery, head and neck surgery is one of the most important types, mainly encompassing surgical interventions of neoplasms that develop in topographical regions of the mouth, throat, glottis, salivary glands, and skin of the face and neck. These tumors account for around 3% of all cancers, and their incidence is on the rise.[11] Treatment of this type of neoplasm is multidisciplinary, with resection of the tumor being practically indispensable for its cure.

The development of SSIs in head and neck surgery is a relatively frequent complication. According to the literature, these figures fluctuate widely, depending on the degree of contamination of surgery, ranging anywhere from 3% to 85%[7,8,12,13] according to whether it is classed as "clean," "clean-contaminated," contaminated" or "dirty."

We sought to study the incidence of SSI and assess the risk factors that determine it in patients undergoing head and neck surgery at a University Teaching Hospital.

Methods

Study design

We conducted a prospective cohort study from July 2007 to June 2023, covering patients over 18 years of age undergoing head and neck surgery at a university teaching hospital and excluding those who at the time of surgery presented with suspicion of infection or were receiving antibiotic treatment for confirmed infection. All surgical procedures falling within the CDC's NECK category were included (Table 1). The study was approved by the Clinical Ethics Research Committee of the hospital (number 16/91), and informed consent was obtained from all subjects and/or their legal guardian(s).

Sample size and data collection

Sample size was estimated on the basis of a 95% confidence interval (CI), a precision of 5%, an estimated proportion of infection of 25%, and an envisaged 10% of losses. A necessary sample size of at least 320 patients was thus estimated. The patients were selected from surgical programming and were consecutively recruited throughout the study period.

The research data were collected on a purpose-designed form and entered onto a normalized relational database. The following were collected: sociodemographic variables pertaining to patients and their perioperative clinical situation, including date of birth, sex, presence of comorbidities (malnutrition, kidney failure, diabetes mellitus, neoplasm, chronic obstructive pulmonary disease (COPD), cirrhosis, obesity and immunodeficiency), need for transfusion or drainage during the intervention; variables relating to hospital stay, that is, date of admission, diagnosis and date of discharge; variables related with presurgical preparation and

Table 1. Surgical procedures studied (ICD-9-CM) of head and neck surgery

ICD-9-CM*	Intervention	n	%
30.1	Hemilaryngectomy	3	0.7
30.21	Epiglottidectomy	0	0
30.22	Vocal cordectomy	168	40
30.29	Other partial laryngectomy	30	7.1
30.3	Total laryngectomy	63	15
30.4	Radical laryngectomy	24	5.7
31.45	Open biopsy of larynx or trachea	24	5.7
40.40	Radical neck dissection, not otherwise specified	12	2.9
40.41	Radical neck dissection, unilateral	87	20.7
40.42	Radical neck dissection, bilateral	6	2.2
Total		423	100

*ICD-9-CM: international classification of diseases, 9th revision, clinical modification.

antibiotic prophylaxis; and surgery-related variables, such as date of intervention, duration of surgery, type of surgical procedure, degree of contamination of surgery (clean, clean-contaminated, contaminated and dirty), American Society of Anesthesiologists (ASA) anesthetic risk and the CDC National Nosocomial Infection Surveillance (NNIS) index. When a patient was diagnosed with SSI, we collected the date of diagnosis, infection site, result of culture (positive or negative), and microorganisms isolated.

SSIs were diagnosed by reference to the CDC's SSI criteria, and taking into account the patient's signs and symptoms, his/her clinical progress, surgical wound assessment, plus results of microbiological cultures where requested. Depth of infection was classified into superficial, deep, and organ-space.[3]

Patients were clinically followed up by daily visit from the date of admission to discharge, and thereafter through visits to outpatient clinics and emergency services, or from primary care through the review of electronic medical records (Selene®) or clinical information visor HORUS®. The study follow-up and total time were set in accordance with CDC criteria for implant surgery and were 1 year.

Statistical analysis

We used frequency distributions to describe the qualitative variables, which were then compared using the Pearson Chi-square test or Fisher's exact test, where the conditions of application were not met (expected values < 5). In the case of the quantitative variables, these were described using the mean and standard deviation (SD), or the median and interquartile range (IQR) in those cases where the normality criteria were not fulfilled. To compare the quantitative variables, we used the Student's t-test or the Mann–Whitney U test in those cases where the data were not normally distributed. When the quantitative variables were compared in more than two groups, we used the analysis of variance test if the variables followed a normal distribution, or the Kruskal–Wallis non-parametric test on the contrary.

The incidence of infection was estimated by calculating the cumulative incidence of surgical infection across the follow-up period. SSI incidence was calculated by stratifying the risk according to the NNIS index. We standardized the incidence of infection by the indirect method, taking into account the cumulative incidence of SSIs in our region, in our country, and those reported by the CDC. The different risk factors were evaluated by calculating the relative risk (RR) of infection, both individually and grouped, with explanatory logistic regression models being built with the "backstep" method to control for confounding and interaction among different factors. In the internal calibration of the model (goodness-of-fit), we used the Hosmer-Lemeshow test.

The sample size was calculated using the Epidat 4.2 epidemiological software program, and the analyses were performed using the Statistical Package for the Social Sciences v.27 statistical software program, with statistical significance set at $p < 0.05$.

Results

The study covered a total of 423 surgical interventions of the head and neck. The breakdown showed that the patients were 81.4% men and 18.6% women, with a mean age of 65.8 years (SD = 12.4), 68.1 years in men and 55.5 years in women ($p < 0.01$). Table 2 shows the data on the patients' perioperative clinical situation and comorbidities.

The interventions were distributed as shown in Table 1: vocal cordectomy was the most frequent type (40%), followed by unilateral radical dissection of the neck (20.7%). The median overall hospital stay was 3 days (IQR = 13): the median stay among patients who did not develop SSIs was 3 days (IQR = 12) and 26 days (IQR = 26) among those with surgical

Table 2. Preoperative clinical situation and comorbidities of patients intervened

Comorbidity	n	%
Drainage	201	47.9
Shaving	18	4.3
Transfusion	9	2.1
Kidney failure	18	4.3
Malnutrition	18	4.3
Diabetes mellitus	123	29.3
Neoplasm	345	82.1
COPD	78	18.6
Cirrhosis	15	3.6
Obesity	36	8.6
Immunodeficiency	3	0.7
Total	423	100

COPD: chronic obstructive pulmonary disease.

infection ($p < 0.001$). The mean time from admission until diagnosis of infection was 10.6 days (SD = 6.9). The earliest case was diagnosed 2 days after surgery, and the latest, 24 days after surgery.

A total of 86.7% of intervened patients received appropriate presurgical preparation (95% CI: 83.8-89.1), with the most common cause of inappropriateness being non-application of mouthwash (67.1%). Of the 228 patients who required antibiotic prophylaxis, 189 received it, and among these, it was appropriate in 162 (85.7%; 95% CI: 80.8-90.1). The principal cause of inappropriateness was the choice of antibiotic (65.0%).

For the calculation of the NNIS index, we used the variables of classification of ASA anesthetic risk, degree of contamination of surgery, and duration of surgery (75th percentile, 225 min). While most patients (47.1%) had an NNIS of 0, no patient with an NNIS of 3 underwent surgery. Table 3 shows the mean stay of patients according to the NNIS index.

There were a total of 27 infections across the follow-up period, amounting to an overall SSI incidence of 6.4% (95% CI: 4.1-8.7). Most of the infections (44.4%) occurred in patients with an NNIS index of 1. Of the 27 surgical infections, 18 were superficial (66.7%) and 9 deep (33.3%). There were no organ-space SSIs within the 16 years analyzed.

A microbiological culture was performed in all infections and tested positive in 15. The microorganism most frequently found was *Enterobacter cloacae*

Table 3. Mean stay of patients according to the NNIS index (n = 423)

NNIS index	n (%)	Days (SD)
0	199 (47.1)	3.4 (5.8)
1	160 (37.9)	11.1 (12.6)
2	64 (15.0)	19.9 (14.2)
3	0 (0)	-

NNIS: National Nosocomial Infections Surveillance System; SD: standard deviation.

(43.0%). In six cases, two microorganisms were isolated, with the microorganisms responsible for the infections being shown in figure 1.

Cumulative SSI incidence at our hospital was compared to cumulative incidences, regionally and nationwide, issued by the INCLIMECC work group (Clinical Continuous Quality Improvement Indicators) and stratified according to NNIS risk (Table 3). Furthermore, these figures were also compared to the cumulative incidence rates issued by the CDC. Indirect standardization was performed by calculating the standardized infection ratio (SIR). The SIR at the hospital was: 1.48 (95% CI: 0.51-2.45) with respect to the Region; 1.94 (95% CI: 0.67-3.21) with respect to the country as a whole; and 2.07 (95% CI: 0.72-3.42) with respect to the CDC.

SSI risk factors were studied univariate. The statistically significant variables ($p < 0.05$) were as follows: malnutrition; duration of surgery above the 75th percentile; and the presence of drainage. Table 4 shows the univariate analysis of the various SSI risk factors: it omits the risk factors which had very low prevalence and those that did not present with infection in some of the groups.

The multivariate analysis (Table 4) studied the independent SSI risk factors shown to be statistically significant by the univariate analysis. Duration of surgery above the 75th percentile was the sole factor to prove statistically significant ($p = 0.01$).

Discussion

Overall SSI incidence in our study was 6.4% (95% CI: 4.1-8.7), a figure lower than that of most of the papers reviewed.[14-16] There were no significant differences after standardization with existing data, neither for the region nor the country, nor those reported by the CDC.[12]

Surgery of the head and neck is a complex surgery that encompasses many procedures and different

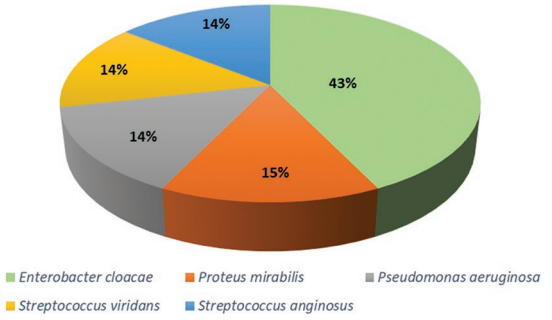

Figure 1. *Etiology of surgical site infection in head and neck surgery (%), n = 15.*

Table 4. Univariate and multivariate analysis for SSI risk factors

Univariate analysis					
Risk factors	**SSI (n: 9) n (%)**	**No SSI (n: 131) n (%)**	**RR[1]**	**95% CI[2]**	**p**
Mean age (SD[3])	65.7 (9.3)	65.8 (12.7)	1	09-1.1	0.99
Diabetes mellitus	3 (33.3)	38 (29.0)	1.22	0.3-5.1	0.52
COPD[4]	1 (11.1)	25 (19.1)	0.53	0.1-4.4	0.48
Malnutrition	2 (22.2)	4 (3.1)	9.1	1.4-58.3	0.048
Cirrhosis	1 (11.1)	4 (3.1)	4.0	0.4-39.8	0.29
NNIS[5] index					
0	2 (22.2)	64 (48.9)	Ref.		
1	4 (44.4)	49 (37.4)	2.61	0.5-14.9	0.28
2	3 (33.3)	18 (13.7)	5.33	0.8-34.4	0.08
ASA[6] > 2	4 (44.4)	57 (43.5)	1.04	0.3-4.0	0.61
Duration of surgery (> P75)	6 (66.7)	28 (21.4)	7.36	1.7-31.3	0.007
Inappropriate prophylaxis	2 (28.6) of 7	7 (12.5) of 56	2.8	0.4-17.3	0.26
Drainage	7 (77.8)	60 (45.8)	4.14	0.8-20.7	0.06

Multivariate analysis			
Risk factors	**RR**	**95% IC**	**p**
Malnutrition	6.57	0.9-49.2	0.07
Duration of surgery (> P75)	6.52	1.5-28.6	0.01

[1]Relative risk.
[2]Confidence interval.
[3]Standard deviation.
[4]Chronic obstructive pulmonary disease.
[5]National nosocomial infections surveillance system index.
[6]American Society of Anesthesiologists.

surgical techniques. It should be stressed here that there is great variability in the diagnosis of SSIs in this type of patient, for example, due to the possibility that different complications might arise as a result of partial/total flap compromises or vascular failures, which could account in part for the wide variability in SSI incidence rates found in the literature.[7,8,12,13]

In our study, patients with SSIs had hospital stays longer than patients who did not present with surgical infections, in line with the literature.[17,18] The 23-day increase in hospital stay was higher than that reported by Al-Qurayshi et al.[7] for surgeries of the head and neck, estimated at 8 days, with our case being more in line with that described by Badia et al.,[5] who found wide variability in the six countries included in their systematic review, with hospitalization always being longer in patients with surgical infection.

The microorganisms isolated in infections of head and neck surgery vary widely, particularly the common bacterial colonization of the respiratory tract. In our study, there were a very small number of infections, with the pathogens most frequently encountered being *E. cloacae* and gram-negative bacteria, a finding that agrees with other studies of surgical infection at this site.[19-22]

The risk of developing a surgical infection depends on various factors, some of them of intrinsic to the patient him/herself (age, sex, obesity, nutritional status, or comorbidities), and others extrinsic (presurgical preparation, antimicrobial prophylaxis, use of drainage or transfusion, duration of intervention, appropriate instrumental sterilization or surgical technique used).[14,23] Updated antibiotic prophylaxis and surgical preparation protocols based on the existing literature have been implemented at our teaching hospital and are periodically reviewed by the Infections Committee. Based on these, prophylaxis and preparation were rated appropriate or inappropriate in each case, citing the reason for inappropriateness where this existed.

Antibiotic prophylaxis failed to prove statistically significant in terms of reducing SSIs, probably due to the negligible number of infections found. We found studies that did not reflect a reduction in incidence of infection, despite appropriate antibiotic prophylaxis, such as those by Mitchell et al.[24] and Sepehr et al.,[25] though the majority tended to corroborate the existence of a lower incidence of SSIs in head and neck surgery when such prophylaxis was performed correctly,[26-28] including systematic reviews and meta-analyses in clean-contaminated surgeries.[29]

When it came to the percentage of presurgical preparation of patients, this was also very high (86.7%), as in the case of prophylaxis, with the main cause of inappropriateness being the non-administration of

mouthwash, which prevents post-operative pneumonia but has no influence on the development or lack of development of surgical infection.

While ASA anesthetic risk,[30] age,[31] obesity[14] and diabetes[32-34] are risk factors described in the literature for this type of surgery, in our study, they failed to achieve statistical significance. Other risk factors for the development of SSIs, such as the patient's sex, use of drainage, or comorbidities such as COPD and cirrhosis, or described in other types of interventions[35-39] were also not statistically significant in our study.

The study's univariate analysis displayed two significant variables: duration of surgery above the 75th percentile; and presence of malnutrition in the patient. Duration of surgery is a risk factor reported in other studies for this same surgical site;[8,31] in our study, its RR was 6.5 (95% CI: 1.5-28.6) following the multivariate analysis. The rise in risk among such patients may be due to a more prolonged exposure to the wound's contaminants, longer duration of oropharyngeal secretions in the field, or increased difficulty of the surgical act. In this respect, an important factor for the appearance of SSIs is the surgeon's experience, as highlighted by McHugh et al.[40] or Mallol et al.[41] This variable was not evaluated in the study, since ours is a university teaching hospital where there is thus a higher turnover of surgeons and physicians in training during interventions.

In the multivariate logistic regression analysis, the RR associated with malnutrition was 6.6 (95% CI: 0.9-49.2). Malnutrition was assessed at our hospital using body mass index (BMI), with malnutrition being deemed to exist if BMI < 18. In this study, the percentage of patients who presented with malnutrition was lower than in others consulted:[21,42] this may be due to the fact that malnutrition was measured with the BMI, whereas other authors considered malnutrition to exist if there was a loss of weight > 10% in the 3 months prior to surgery, or with measurement of serum albumin. Our study shows a higher risk of suffering SSIs if the patient is malnourished, a finding in line with other papers.[21,30]

There are studies in which the association between malnutrition and SSIs has been seen, and hence Basset and Dobie[43] report the relationship between malnutrition and worse prognosis in neck cancer. In this type of neoplasm, there may be a deficit of food intake due to gastrointestinal tract occlusion, plus the placement of tracheotomies for lengthy periods of time, which could entail severe malnourishment. Moreover, there are tumor factors that promote endocrine alterations and systemic responses, such as the release of cytokines, which trigger the protein catabolism and stages of cachexia. Malnutrition also affects the wound-healing process, favoring the development of septic complications.

Accordingly, we feel that a prior nutritional assessment should be made of all patients undergoing head and neck surgery, due to its close relationship with states of malnutrition, and that other anthropometric and specific biochemical parameters should be assessed, and not only BMI. A number of studies have sought to counteract malnutrition by means of enteral formulae (with arginine, glutamine, omega-3 fatty acids, and nucleotides), with evidence of a reduction in SSI and hospital-stay figures following the use of such formulae.[44-46]

One of our study's possible limitations is that the incidence of infection may have been underestimated due to some mild cases of superficial SSIs with minimal symptoms having been missed, where the patient might not have made use of the emergency, outpatient ear, nose, and throat, or primary care services. We would expect the infections missed to be negligible, in view of the fact that patients were followed up after discharge and over the course of a year. Similarly, the identification of some risk factors for surgical infection, detected through the patient's clinical history, may not be wholly accurate: for instance, if there are different forms of measurement (such as malnutrition) that pose problems when it comes to making comparisons with other studies in the literature which use different measurements. Finally, though the sample size was calculated for the assessment of SSI incidence, some of the risk factors studied may not be represented because they are factors with a very low prevalence. We endeavored to control for losses to follow-up by estimating a percentage of possible losses in the pre-calculation of sample size, in order not to lose statistical power.

Conclusions

Incidence of SSIs in head and neck surgery at our hospital during the study period was low. According to the results of this study, in order to reduce the risk of infection among the patients intervened, special attention should be paid to optimizing surgical time and ensuring an improvement in the nutritional status of patients who undergo these types of interventions.

A low SSI incidence rate is a good measure for assessing surgical practice and, by extension, quality in healthcare; hence, it is essential for infection rates to be evaluated and the possible risk factors identified. In this regard, prospective hospital surgical infection surveillance and control programs should be implemented, thereby allowing for continuous assessment of SSI incidence and the adoption of early preventive measures targeting potentially modifiable risk factors.

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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. The study was approved by the Clinical Ethics Research Committee of the Fundación Alcorcón University Teaching Hospital (number 16/91). All research activities conformed to the principles embodied in 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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ORIGINAL ARTICLE

Ethical considerations in dietary supplement consumption behaviors

Consideraciones éticas en los comportamientos de consumo de suplementos dietéticos

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Abstract

Objective: *This study examines the dietary supplement consumption behaviors and ethical attitudes aiming to contribute to a more conscientious and ethical consumption culture within the health industry.* **Methods:** *A descriptive cross-sectional study was conducted from October to December 2019 with a sample size of 384 individuals aged 20-65 in Turkey. Analysis was performed using the Statistical Package for the Social Sciences 22.0, including exploratory factor analysis and statistical tests.* **Results:** *About 55.5% of participants used dietary supplements, with Vitamin D, Vitamin B, Omega-3, and multivitamin complexes being common. Ethical concerns included inadequate label information, price discrepancies, and legal oversight issues. Statistically significant differences were observed in gender regarding the dimensions of meeting needs and promotion, in age regarding the legal dimension, and in the reasons for visiting a dietitian in the other four dimensions, except for the legal dimension ($p < 0.05$).* **Conclusions:** *This study revealed that factors such as gender, age, and dietary preferences influence individuals' supplement choices. Men were found to be more inclined toward the meeting needs and promotion aspects of dietary supplement purchases than women. In addition, age group and dietary preferences were found to affect the sensitivity of individuals in their supplement choices.*

Keywords: *Dietary supplements. Consumer behavior. Health ethics. Supplement regulation.*

Resumen

Objetivo: *Examinar los comportamientos de consumo de suplementos dietéticos y las actitudes éticas con el objetivo de contribuir a una cultura de consumo más consciente y ética dentro de la industria de la salud.* **Métodos:** *Se realizó un estudio descriptivo transversal de octubre a diciembre de 2019 con un tamaño de muestra de 384 individuos de entre 20 y 65 años, en Turquía. El análisis se realizó utilizando SPSS 22.0, incluido el análisis factorial exploratorio y las pruebas estadísticas.* **Resultados:** *El 55.5% de los participantes utilizaron suplementos dietéticos, siendo comunes la vitamina D, la vitamina B, los ácidos grasos omega-3 y los complejos multivitamínicos. Las preocupaciones éticas incluían información inadecuada en las etiquetas, discrepancias en los precios y problemas de supervisión legal. Se observaron diferencias estadísticamente significativas en el sexo en relación con las dimensiones de satisfacción de las necesidades y promoción, en la edad en relación con la dimensión legal, y en los motivos para acudir al dietista en las otras cuatro dimensiones, excepto en la dimensión legal ($p < 0.05$).* **Conclusiones:** *Este estudio reveló que factores como el sexo, la edad y las preferencias dietéticas influyen en la elección de suplementos por parte de los individuos. Se observó que los hombres se inclinaban más que las mujeres por los aspectos de satisfacción de las necesidades y promoción de la compra de suplementos dietéticos. Además, se encontró que el grupo de edad y las preferencias dietéticas influían en la sensibilidad de los individuos en el momento de elegir suplementos.*

Palabras clave: *Suplementos dietéticos. Comportamiento del consumidor. Ética de la salud. Regulación de suplementos.*

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Introduction

Today, people in pursuit of healthy living and longevity are turning to various food supplements to support their diets. Food supplements are generally defined as products containing nutrients such as vitamins, minerals, amino acids, herbs, or herbal dietary ingredients. The use of these products has increased due to successful sales strategies, advertisements, and the widespread use of the internet.[1] However, the ethical use of food supplements is an important issue in terms of public health and safety. One area of particular focus for ethical questions about food supplements is their impact on intake behavior. Factors such as consumers' reasons for using food supplements, their level of trust in these products, and their reactions to health claims are important factors shaping consumer purchasing behavior. Therefore, ethically evaluating the purchasing behavior of food supplements is an important step that can affect both the health and well-being of individuals and the overall health of society. In this context, food safety and ethical principles should be active at every stage of agriculture and food systems.[2]

Based on this idea, the aim of this study was to determine the intake behaviors of individuals taking food supplements and to examine their ethical attitudes in this field. The results of this study aim to contribute to the creation of a more conscious and ethical consumption culture in the health industry by shedding light on the ethical evaluations of consumers regarding the use of food supplements. In addition, the results of this research will be a valuable source of information for health policy makers and marketing experts.

Conceptual framework

Food supplement use in other countries

Food supplements are carbohydrates, protein, fat, minerals, vitamins, herbs, and nectars. Many studies have shown that the characteristics of people who use food supplements are that they tend to be older, have a low body mass index, exercise, do not smoke, and have a high level of education.[3-9] and are more preferred by those who strongly believe in the importance of treating certain diseases and athletes.[10-12]

In the last 30 years, there has been a great increase in the types and sales of food supplements. The Ministry of Food, Agriculture, and Livestock is the main regulator in Turkey, and the total sales of food supplements in 2020 are estimated to be 885 million TL. The National Health and Nutrition Examination Survey began to investigate motivations for the use of food supplements for the first time in 2007. The purpose of this analysis was to examine the types of food used as well as the motivations for food supplement use by adults.[13] A search of the Web of Science database with the keyword "Dietary Supplements" yielded 2,666 publications. The distribution of these publications by country is shown in the figure below.

Figure 1 shows that 1,320 of the 2,666 studies on dietary supplements were published in the USA. This is followed by the UK with 154 publications, Germany with 111 publications, Australia with 107 publications, and Italy with 98 publications.

As a result of the search of the Web of Science database on food supplements, the top 10 most cited studies were analyzed. Among these studies, the study "Standard methods for the determination of antioxidant capacity and phenolics in foods and dietary supplements" by Prior et al. in 2005 ranks first with 2579 citations. This is followed by "Cellular antioxidant activity assay for evaluating antioxidants, foods and dietary supplements" by Wolfe and Liu in 2007, with 571 citations, and "Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids" by Haller and Benowitz in 2000, with 557 citations.

In Turkey, in a study conducted by Çoşkun and Turan in Istanbul on 1000 people representing four different sociocultural groups, 34.6% reported using dietary supplements. In 2017, in the study on the use of food supplements published by the Food Supplement and Nutrition Association (GTBD) and Ipsos Social Research Institute, the rate of use of food supplements was reported as 13% after a survey of 1750 people over the age of 18 with telephone support in 81 provinces. In 2019, in the study titled "Evaluation of Food Supplement Intake Behaviors and Related Factors of Individuals Between the Ages of 18-65 Applying to the Family Health Center" conducted by Karadağ, 32.3% of the participants reported that they took supplements.

Ethical dimension of food supplements use behaviors

Ethics are principles, values, and standards that define how individuals behave correctly toward other

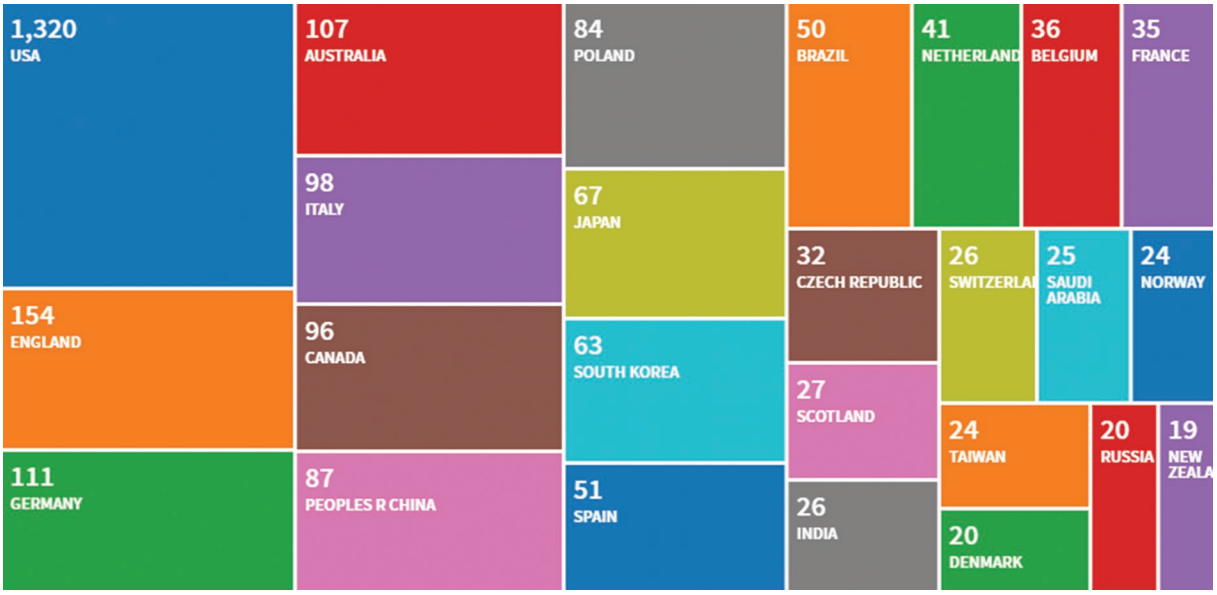

Figure 1. *Number of studies on dietary supplements by countries.*

beings[14] Professional ethics, which is a sub-branch of ethics, can be expressed as the sum of ethical principles and standards that guide behaviors in professional life and guide what to do and what not to do. Businesses feel the need to behave ethically and make decisions in order to increase their reputation and thus gain profit in the medium and long term, and it is beneficial to see the expenditures made for this purpose as one of the most valuable asset items of the business.[15]

Related to this issue, Torok and Murray in their 2008 study "Using the sword of professional ethics against misleading dietary supplements," tried to understand how dietary supplements are currently regulated for scientists who want to take a more prominent role in protecting the integrity of the interests of science and society. In general, the Food and Drug Administration (FDA) oversees safety, manufacturing, labeling, and product literature for drugs and medical devices, while the Federal Trade Commission (FTC) regulates how products are marketed. Mannatech Inc. is a publicly traded multinational multi-level marketing company founded in 1993 by Samuel Caster that markets dietary supplements and personal care products.[16] Due to consumer complaints filed with the FDA and unethical use of credit advertising, Mannatech's sales declined by 50% after 2006. Scientists should provide informational materials to consumers to prevent misuse and unethical production. The FTC and agencies such as the FDA and the Office of Dietary Supplements should have supplement manufacturers and contact information on their websites, and consumers should be able to check whether a supplement has been tested for safety and efficacy through the government.

Proactive steps are needed to prevent public mistrust of food supplements. One such measure could be to develop educational materials and training activities that can be used by medical schools and professional associations, such as the American Medical Association, to ensure that doctors and medical students are effective in countering suspicious claims. Doing so would not only address the lack of reliable information on dietary supplements available to the public, but would also give the science community a level of respectability to other professionals. In establishing standards for the proper labeling and manufacture of food supplements, the FDA has been confronted with the lack of information on the efficacy of some supplements and the lack of data to determine adequate dosage for children. Children are not just small adults in terms of dosage; untested mold supplements pose the potential for harm when administered to children. Moreover, it is clear that even benign substances such as vitamins taken in excessive amounts can be harmful.[17]

Methods

In this section of the study, the purpose and importance of the study, the data collection tool, and the analysis of the data will be discussed.

Purpose and hypothesis of the study

The aim of this study is to determine the intake behaviors of individuals taking food supplements to examine their ethical attitudes in this field. For this purpose, the following hypotheses were tested to determine the ethical dimension of dietary supplement use behaviors in the areas of needs satisfaction, ethics, monitoring, promotion, and legal areas.

- Hypothesis 1. Gender differs according to (a) Meeting needs (b) Ethical dimension (c) Monitoring dimension (d) Promotion dimension (e) Legal dimension of individuals' food supplement use behaviors
- Hypothesis 2. Age differs according to (a) Meeting needs (b) Ethical dimension (c) Monitoring dimension (d) Promotion dimension (e) Legal dimension of individuals' food supplement use behaviors
- Hypothesis 3. Dietitian Visiting Status differs according to (a) Meeting needs (b) Ethical dimension (c) Monitoring dimension (d) Promotion dimension (e) Legal dimension of individuals' food supplement use behaviors.

Population and sample of the study

The descriptive and cross-sectional study was conducted in October 2019 and December 2019. The research population consisted of individuals between the ages of 20 and 65 residing in Turkey. At the end of 2017, the population between the ages of 20 and 65 in Turkey was 48,355,065 (TÜİK, 2017); the sample size that can represent the research population was determined as 384 people with a 95% confidence interval. Convenience sampling method was used among the sampling methods.

Data collection tool of the study

While collecting the research data, the "Knowledge, attitude and usage behavior about food supplements" scale taken from the thesis of Karadağ, 2019, was used. After interviewing with medical representatives and pharmacies within the scope of expert opinion, the scale was answered as "I think ethical values are observed in food supplement information, I think ethical values are observed in pricing policies, I think ethical values are observed when obtaining legal permissions of food supplements, I think ethical values are observed when determining the amount of use, I think that there is not enough supervision in the production and distribution processes of food supplements, I am hesitant that the prices on the internet and pharmacy prices are not the same, and I do not find it right to advertise food supplements in print and visual media" were added and the question "Food supplements are supervised by the Ministry of Food, Agriculture and Livestock" was removed.

After the questions to be asked in the questionnaire were determined, it was determined whether the questions in the draft questionnaire were compatible with the application, the aims, and assumptions of the application. Then, the questionnaire was tested by 10 pharmacists and 3 medical representatives before it was applied to the individuals and the questions that caused misunderstandings were rearranged. The questionnaire form can be classified as follows; in the first 24 questions of the questionnaire, it is aimed to obtain information about the general health status of individuals, such as gender, body mass index, sleep levels, chronic disease status, and quality of life.

Questions 24-30 of the questionnaire aimed to find out which supplements individuals who use food supplements take, the reasons for taking supplements, where they obtain supplements, and how much they spend on supplements in a year. Finally, in the 31st question, a 3-point Likert-type scale was used to determine the behaviors and attitudes of individuals toward food supplements. The answering scale for each statement of the 31st question in the scale is a 3-point Likert; 1 = No Idea, 2 = No, 3 = Yes.

Information was collected from social media and social media platforms (LinkedIn, Facebook, etc.) through the Google form. The survey method was chosen due to its ability to collect a wide range of information, speed, and cost advantages, while the face-to-face and social media survey method was chosen due to its high response rates and the ability to eliminate misunderstandings. A total of 474 questionnaire forms were collected.

Data analysis

The data obtained at the end of the research were analyzed with the Statistical Package for the Social Sciences 22.0 package program. First, frequencies and percentages were given according to the individual and demographic characteristics of the participants. Exploratory factor analysis was applied to the scale. At this stage, the Independent Samples t-test

Table 1. Factor analysis table

Ethical	Meeting needs	Ethics	Monitoring	Promotion	Legal
I believe ethical values are observed when obtaining legal permissions for dietary supplements	0.839				
I believe ethical values are observed in pricing policies.	0.748				
I believe ethical values are considered when determining the usage amount.	0.684				
I believe ethical values are observed in dietary supplement information.	0.675				
Since I started using dietary supplements, I feel healthier.		0.814			
I am aware of which dietary supplements I need for my health.		0.788			
Dietary supplements can meet all nutritional needs.		0.543			
The information on the labels of dietary supplements is sufficient.		0.445			
I am concerned about the side effects of dietary supplements.			0.781		
Dietary supplements should be prescribed and monitored by a physician.			0.597		
Taking dietary supplements along with prescribed medications can cause drug interactions.			0.591		
Vitamin and mineral levels should be regularly monitored with laboratory tests.			0.799		
I believe there is not enough supervision in the production and distribution processes of dietary supplements.				0.818	
I do not approve of dietary supplement advertisements in print and visual media.				0.720	
The fact that internet prices and pharmacy prices are not the same makes me skeptical.				0.565	
Dietary supplements are regulated by the Ministry of Health.					0.751
Physicians should have more information about dietary supplements.					0.632
Dietary supplements should be covered by health insurance.					0.557

and One-way analysis of variance (ANOVA) test were applied since the data were normally distributed and the variances were homogeneous. After conducting the ANOVA analysis, *post hoc* tests (Tukey) were utilized to determine between which groups the differences originated.

Validity and reliability of the research scale

In the study, factor analysis with varimax rotation was applied to 18 statements to reveal the construct validity of the ethical scale of dietary supplement intake behaviors. As a result of the analysis, five dimensions were reached as meeting needs, ethical dimension, monitoring dimension, promotion dimension, and life dimension. The rate of explaining the total variance of the five factors obtained was 69.543%, the Kaiser-Meyer-Olkin value was 0.810, and the Bartlett Sphericity test value was 1240.994 and was significant ($p < 0.05$). The distribution table of the factor analysis according to the dimensions is given in table 1.

There are many methods to measure the reliability of scales. Cronbach's Alpha coefficient, which is one of them, is a method frequently used in reliability calculations of scales based on total score, such as Likert-type scales.[18] The Cronbach's Alpha value used for the research was found to be quite reliable, with 0.73.

Findings

A total of 474 people participated in this study conducted on individuals living in Turkey. Of the 474

participants, 49.6% were female, and 50.4% were male. 47.6% of the individuals participating in the study were between the ages of 21 and 30. 62% of the participants are married, and 60.3% of them live with their spouse and children. When the participants are analyzed in terms of education and occupational groups, 41.6% are university graduates, 34% are public sector employees, and 32.9% are private sector employees. 53% of the participants are Social Security Institution (SSI/SSK) members, and 37.1% of them have an income level between 2000 and 4000, 27.4% between 4000 and 6000.

When the healthy living behaviors of the individuals participating in the study were evaluated, 47.26% were normal weight, and 37.97% were slightly overweight. While 38.80% of the participants do not exercise, 38.60% do mild exercise, and 46.60% do not go to general health check-ups. The proportion of the participants who consulted a nutrition and diet specialist was 26.2%, and 56.6% of them went to lose weight. When the nutritional status of the participants is analyzed; 51.70% of them apply equal weight from carbohydrates. 36.50% of the participants consume 1-15 L of water/day, 26.60% sleep between 7 and 8 h. In addition, 67.9% do not smoke, and 84% do not consume alcohol. Only 26.2% of the participants reported having a chronic disease. The most common diseases were hypertension and migraine, with 18%, followed by asthma with 14%. Among the participants with chronic diseases, 41.9% used medication when necessary, while 39.5% reported that they used medication every day. 55.5% of the participants reported taking food supplements. Among these, 57.8% use them every day. 41.8% spend 200 TL or less on food supplements in a year, while 38.8% spend between 200 and 500 TL. 70.7% of the participants obtain food supplements from pharmacies.

Table 2 shows that 15.8% of the participants take vitamin D, 12.8% vitamin B, 11.3% Omega 3, and 9.30% multivitamin complex.

When the reasons for using food supplements are analyzed in table 3, 17.60% of the participants use food supplements to “Increase body performance and energy during the day,” 16.50% to “Promote general health,” 16.20% to “Treat specific health problems,” and 14.70% to “Increase immune power.” Weight gain (0.40%) and weight loss (0.10%) are the least preferred reasons for use.

In table 4, when the participants’ food supplement purchasing behaviors were examined in terms of ethics, 78.7% stated that physicians should have more information about food supplements, 76.8% stated that vitamin and mineral levels should be regularly monitored with laboratory tests, 72.6%

Table 2. Distribution of food supplements used by the participants

Supplements	n	%	Supplements	n	%
Vitamin D	126	15.80	Coenzyme Q10	23	2.90
Vitamin B	102	12.80	Sports drinks and foods	18	2.30
Omega-3	90	11.30	Calcium	15	1.90
Multivitamin/ multimineral complex	74	9.30	Selenium	14	1.80
Vitamin C	53	6.60	Alpha lipoic acid	9	1.10
Iron	53	6.60	Melatonin	9	1.10
Herbal supplements	52	6.50	Glucosamine	8	1.00
Probiotic	41	5.10	Protein Bar	5	0.60
Magnesium	39	4.90	Other*	4	0.50
Vitamin K	33	4.10	Amino Acid	3	0.40
Zinc	26	3.30	Protein Powder	2	0.30

*Indicates statistically significant difference ($p < 0.05$).

Table 3. Distribution of reasons for use of food supplements by participants

Reasons for use	n	%
To enhance daytime physical performance and energy	121	17.60
To promote general health	113	16.50
To treat specific health issues	111	16.20
To boost immunity	101	14.70
As recommended by a doctor	81	11.80
To improve nutrition	62	9.00
As recommended by a nutrition and diet specialist	25	3.60
To reduce stress	20	2.90
As recommended by a pharmacist	14	2.00
As recommended by a life/sports coach	14	2.00
Based on family, friends, and community recommendations	13	1.90
After seeing on social media (TV/radio/internet/phone/ads)	7	1.00
To gain weight	3	0.40
To lose weight	1	0.10

Table 4. Results of the ethical analysis of participants' food supplement ıntake behavior scale

Variables	n	%	n	%	n	%
Food supplements should be prescribed and monitored by a doctor.	176	66.9	62	23.6	25	9.5
Doctors should have more knowledge about food supplements.	207	78.7	34	12.9	22	8.4
Food supplements should be covered by health insurance.	191	72.6	46	17.5	26	9.9
Vitamin and mineral levels should be regularly monitored with laboratory tests.	202	76.8	39	14.8	22	8.4
Food supplements are regulated by the Ministry of Health.	128	48.7	76	28.9	59	22.4
I am concerned about the side effects of food supplements.	151	57.4	77	29.3	35	13.3
The information on the labels of food supplements is sufficient.	75	28.5	149	56.7	39	14.8
Food supplements may cause drug interactions when taken with prescribed medications.	141	53.6	42	16	80	30.4
I am aware of which food supplements I need for my health.	172	65.4	51	19.4	40	15.2
I feel healthier since I started using food supplements.	171	65	54	20.5	38	14.4
All nutritional needs can be met with food supplements.	57	21.7	166	63.1	40	15.2
I believe ethical values are considered in the information provided about food supplements.	81	30.8	115	43.7	67	25.5
I believe ethical values are considered in pricing policies.	58	22.1	136	51.7	69	26.2
I believe ethical values are considered when obtaining legal permits for food supplements.	77	29.3	104	39.5	82	31.2
I believe ethical values are considered when determining the dosage.	96	36.5	91	34.6	76	28.9
I believe there is not enough control in the production and distribution processes of food supplements.	127	48.5	74	28.2	61	23.3
The discrepancy between internet and pharmacy prices makes me hesitant.	189	71.9	50	19	24	9.1
I do not think it is correct to advertise food supplements in print and visual media.	142	54	89	33.8	32	12.2

stated that food supplements should be covered by health insurance, and 71.9% stated that they were hesitant about the fact that internet prices and pharmacy prices were not the same. 63.1% of the participants think that food supplements do not meet all nutritional needs, 56.7% think that the information written on the labels of food supplements is insufficient, and 51.7% think that ethical values are not observed in pricing policies.

According to this table, statistically significant differences were not found between the sub-dimensions of the scale. According to table 5, Hypotheses 1a, 1d, 2e, 3a, 3b, 3c, and 3d are accepted while the other hypotheses are rejected.

Discussion

The purpose of this study is to determine the purchasing behaviors of individuals who take dietary supplements to examine their ethical attitudes in this field. The finding that men pay more attention to the meeting needs and promotion processes when buying dietary supplements than women is supported by various literature studies. This difference reflects differences in men's and women's behaviors and motivations for supplement use. First, women generally use supplements at higher rates than men. According to a study conducted in the USA, 63.8% of women used any food supplement in the past 30 days, compared to 50.8% of men.[19] Although women have a higher propensity to use food supplements, men generally use supplements more strategically for specific health goals (e.g., increasing muscle mass or preventing a specific disease). Men generally appear to be more motivated to use supplements to achieve specific health goals. In this context, men are more careful in their choice of supplements to meet their needs and to ensure continuity of use. For example, men place more emphasis on muscle health and performance-enhancing supplements, whereas women generally prefer supplements that focus on general health and bone health.[20] Furthermore, among the factors that increase men's motivation

Table 5. Hypothesis test results

Category	Meeting needs (a)	Ethical dimension (b)	Monitoring dimension (c)	Promotion dimension (d)	Legal dimension (e)
Women Avg	2.30	1.96	2.50	2.37	2.53
Women SD	0.40	0.58	0.44	0.59	0.45
Men Avg	2.31	2.10	2.46	2.51	2.53
Men SD	0.52	0.58	0.47	0.51	0.51
T	–0.283	–1.938	0.695	–2.105	0.142
p	0.000*	0.623	0.089	0.047*	0.267
Hypothesis accepted	**1a Accepted**			**1d Accepted**	
20-30 Avg (1)	2.25	1.94	2.50	2.38	2.59
20-30 SD	0.49	0.57	0.44	0.60	0.47
31-40 Avg (2)	2.33	2.00	2.47	2.38	2.60
31-40 SD	0.43	0.58	0.43	0.53	0.38
41-50 Avg (3)	2.39	2.17	2.48	2.54	2.42
41-50 SD	0.44	0.70	0.58	0.47	0.51
51-65 Avg (4)	2.30	2.09	2.46	2.55	2.36
51-65 SD	0.43	0.46	0.41	0.54	0.52
F	1.092	1.875	0.065	1.727	3.866
p *Post hoc* test	0.35	0.13	0.98	0.16	0.010* 1-4 p = 0.03 2-4 p = 0.04
Hypothesis accepted					**2e Accepted**
Weight loss Avg (1)	2.38	2.05	2.50	2.54	2.41
Weight loss SD	0.37	0.55	0.37	0.48	0.53
Weight gain Avg (2)	1.86	1.48	1.93	1.94	2.33
Weight gain SD	0.55	0.39	0.57	0.70	0.47
Healthy eating Avg (3)	2.28	2.19	2.42	2.31	2.56
Healthy eating SD	0.45	0.50	0.49	0.48	0.38
Doctor's recommendation Avg (4	2.44	1.84	2.28	2.00	2.71
Doctor's recommendation SD	0.42	0.63	0.49	0.69	0.28
F	4.83	5.25	5.16	5.8	1.64
p *Post hoc* test	0.000* 1-2 p = 0.002 2-3 p = 0.029 2-4 p = 0.021	0.000* 1-2 p = 0.008 2-3 p = 0.001	0.000* 1-2 p = 0.001 2-3 p = 0.013	0.000* 1-2 p = 0.004 1-4 p = 0.037	0.19
Hypothesis accepted	**3a Accepted**	**3b Accepted**	**3c Accepted**	**3d Accepted**	

*Indicates statistically significant difference ($p < 0.05$)
Avg: average; SD: standard deviation.

and commitment to supplement use, scientific evidence and the desire to be informed about the efficacy of products play an important role. Men often conduct extensive research on the health effects and scientific basis of a particular supplement before choosing it.[21] This attitude increases their tendency to use supplements regularly and consistently.

Another result of this study shows that individuals aged 31-40 years are more concerned about the legal regulations of dietary supplements than other age groups. This age group may focus on legal concerns. Individuals in this age group are generally more conscious about protecting their health and improving their quality of life. This awareness is coupled with a desire to learn more about the safety and efficacy of the food supplements consumed.[22] People in the 31-40 age group are aware that legal regulations are important to ensure the quality and safety of supplements.

The study found that individuals who go on a diet to gain weight are more sensitive to the meeting of needs, ethical standards, monitoring processes, and promotion methods when choosing dietary supplements. These individuals place greater importance on these factors, which play a decisive role in their diet choices. The literature supports this finding. The study by Cialdini and Trost emphasizes the important role of social norms and the meeting of individual needs in people's diet choices.[23] Individuals who start a diet to gain weight place more importance on the meeting of their needs because it increases their motivation and adherence to the diet. The study by Puhl and Brownell shows that ethical standards play a significant role in individuals' attitudes toward diet programs and dietary supplements. Wing and Phelan highlight the importance of monitoring processes in the success of diet programs. Individuals participating in weight gain programs are more sensitive to regular monitoring and feedback processes because these processes ensure healthy and sustainable weight gain.[24] Jeffrey and Wing demonstrate that incentive methods increase individuals' adherence to diet programs. The weight gain group is more sensitive to incentive methods because they increase their motivation and strengthen their adherence to the diet.[25]

In addition, the most frequently used food supplements in the study were Vitamin D, Vitamin B, Omega 3, and multivitamin complex. A study by Bailey et al. found that multivitamin-mineral products and fish oils were the most commonly reported food supplements.[13] Supplement use was also found to be related to more appropriate health and lifestyle choices, and less than a quarter of supplements were recommended by a doctor or dietitian. For this reason, it is recommended that food supplements should be used consciously in line with the recommendation of a doctor or dietitian. Similarly, Çoşkun and Turhan argued that if individuals do not have sufficient knowledge about vitamins, they should act by getting information from experts.[26]

In the information on food supplements, pricing and obtaining legal permissions, not observing ethical values, pharmacy prices not being the same as internet prices, being sold without a prescription, and insufficient information written on it are the results reached within the scope of this study and are not ethically appropriate. Acting in line with ethical principles in this regard will prevent both individual and social damages that may occur.

Conclusions

This study revealed that factors such as gender, age, and dietary preferences influence individuals' supplement choices. Men were found to be more inclined toward the meeting needs and promotion aspects of dietary supplement purchases than women. In addition, factors such as age group and dietary preferences were found to affect the sensitivity of individuals in their supplement choices. It was found that individuals between the ages of 31-40 gave more importance to legal regulations, and those who were trying to gain weight were more sensitive to need fulfillment, ethical standards, monitoring, and promotion processes. In conclusion, a conscious and ethical use of dietary supplements should be encouraged. This can help adopt a credible approach to improving individuals' health and quality of life. The findings may also contribute to health management practices by supporting consumer awareness, ethical marketing strategies, and regulatory policy development regarding dietary supplements.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

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

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Use of artificial intelligence for generating text. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Is there any effect of lycopene's preventing peritoneal adhesion formation in rats: an experimental study

¿Tiene el licopeno algún efecto en la prevención de la formación de adherencias peritoneales en ratas? Un estudio experimental

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Abstract

Objective: *Effects of lycopene in prevention of intra-abdominal adhesion formation in a rat model.* **Methods:** *Twenty-eight rats were divided into four groups consisting of 7 rats each. Group 1 (only adhesion), Group 2 (adhesion + corn oil), Group 3 (adhesion + 5 mg/kg lycopene), Group 4 (adhesion + 20 mg/kg lycopene). Adhesion score, histopathology, vascular endothelial growth factor (VEGF) H-score, malondialdehyde (MDA), total antioxidant capacity, and VEGF values were measured.* **Results:** *There were significantly higher extent, severity, degree, and total adhesion scores in the control and corn-oil group than in the low lycopene and high lycopene group. VEGF H-scores were significantly lower in lycopene-given groups, regardless of dose. When the low lycopene and high lycopene groups were compared in terms of anti-VEGF H-score, no significant difference was observed. Malondialdehyde levels were statistically significantly lower in the control and high lycopene group.* **Conclusions:** *Biochemical parameters, histopathological examination, and adhesion scoring revealed that lycopene significantly reduced adhesion formation.*

Keywords: *Adhesion. Lycopene. Peritoneum. Rat. Vascular endothelial growth factor.*

Resumen

Objetivo: *Evaluar los fectos del licopeno en la prevención de la formación de adherencias intraabdominales en un modelo con ratas.* **Métodos:** *Veintiocho ratas se dividieron en cuatro grupos de siete cada uno: grupo 1, solo adhesión; grupo 2, adhesión más aceite de maíz; grupo 3, adhesión más 5 mg/kg de licopeno; y grupo 4, adhesión más 20 mg/kg de licopeno. Se midieron la puntuación de adherencia, la histopatología, la puntuación H del factor de crecimiento endotelial vascular (VEGF), el malondialdehído, la capacidad antioxidante total y los valores de VEGF.* **Resultados:** *Hubo puntuaciones de extensión, gravedad, grado y adhesión total significativamente más altas en los grupos control y con aceite de maíz que en el grupo con bajo y alto licopeno. Las puntuaciones VEGF H fueron significativamente más bajas en los grupos que recibieron licopeno, independientemente de la dosis. Cuando se compararon los grupos con niveles bajos y altos de licopeno en términos de puntuación H anti-VEGF, no se observaron diferencias significativas. Los niveles de malondialdehído fueron más bajos en los grupos de control y alto en licopeno, con una diferencia estadísticamente significativa.* **Conclusiones:** *Los parámetros bioquímicos, el examen histopatológico y la puntuación de adherencias revelaron que el licopeno redujo significativamente la formación de adherencias.*

Palabras clave: *Adhesión. Licopeno. Peritoneo. Rata. Factor de crecimiento endotelial vascular.*

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Introduction

Although our knowledge about peritoneal cavity physiology and peritoneal healing mechanisms is increasing, post-operative adhesions continue to be a problem for surgeons from different disciplines. In different studies, the direct relationship between intra-abdominal surgical interventions and adhesion formation has been revealed, and it has been stated that the most important cause of intestinal obstruction is adhesions due to previous surgeries.[1,2] Post-operative adhesions are fibrous connections that can be seen between organs that are not normally combined with each other and are surrounded by serous membranes following injury or surgical operations.[1] Approximately 30% of intestinal obstructions develop due to intra-abdominal adhesion, and post-operative peritoneal adhesion occurs in more than 90% of all laparotomies. In addition, they may lead to post-operative mortality, morbidity, and cost increase due to their ability to extend the length of hospital stay.[3] Despite advanced surgical techniques and medical treatment options, post-operative intra-abdominal adhesions are still an unsolved problem. When the literature is searched, it is seen that many experimental, clinical studies, and theoretical reports on adhesion prevention have been published since the beginning of the century. Various chemical agents used as adhesion inhibitors prevent fibrin organization by inhibiting fibroblastic proliferation. Therefore, many agents such as non-steroidal anti-inflammatory drugs, corticosteroids, calcium channel blockers, histamine antagonists, antibiotics, fibrinolytic drugs, antioxidants, and vitamins have been tried to inhibit this proliferation.[4] Lycopene is a pigment belonging to the carotenoid family, naturally found in vegetables and fruits. Lycopene is a potent antioxidant substance; besides protecting cells from free radical damage, it strengthens the bonds between cells and improves cell metabolism.[5-10] There have been reports supporting lycopene's effect on reduced risk of many diseases, including Alzheimer's disease, peripheral nerve damages,[11] cardiovascular disease, skin health,[12,13] and even some types of cancer (breast and uterine).[14] Lycopene also slows down the aging process with its antioxidant properties.[15] In this observational rat study, we investigated the effectiveness of lycopene use in preventing adhesions after gynecological surgery.

Methods

Ethical statement

This study was approved by our University Animal Experiments Local Ethics Committee (April 26, 2017, Protocol No: 2017/011).

Study design

Twenty-eight female Wistar albino rats were included in the study. Inclusion criteria in the study were as follows: the animals were female Wistar albino species, weighing between 160 and 250 g, and survived from the beginning to the end of the study. The exclusion criteria were as follows: the animals were out of the female Wistar albino species, their weight was not between 160 and 250 g, and they died before the study was completed. Experimental animals were kept in our University Animal Laboratory at a room temperature of 24°C and a 12/12 h day and night cycle. Fed with standard rat food and water without restrictions. Each rat was anesthetized with ketamine hydrochloride (40 mg/kg IV). Before surgery, the abdominal area of the rats was shaved and wiped with 1% povidone iodine and prepared for the operation. Approximately 4 cm lower midline laparotomy was performed on the umbilical region. Before surgery, the rats were randomly divided into four groups each consisting of 7 rats. The operations performed on groups of rats were as follows:

- Control group (CG): a standard adhesion was created; no adjuvant was given. Corn oil group (CoG): After the injury, 1 mL of corn oil was administered daily by direct intraperitoneal injection method. The same dose was continued intraperitoneally for 14 days
- Low-dose lycopene group (LLG); After the injury, 5 mg/kg lycopene was administered daily by direct intraperitoneal injection method. The same dose was continued intraperitoneally for 14 days
- High-dose lycopene group (HLG): After injury, only a single dose of 20 mg/kg lycopene was administered intraperitoneally.

Lycopene is a powder compound. It has been used in a liquid-based substance, corn oil, to make lycopene suitable for intraperitoneal injection. To determine the effect of corn oil alone, the CoG was created as a separate group. The dose of lycopene was chosen based on a previous study.[16]

After a 4 cm abdominal incision, the uterine horns were exposed and a lesion was created on the antimesenteric surface of each uterine horn (free part of the bicornual rat uterus in the pelvic area) surface with the help of a 10-volt bipolar cautery as previously described.[17] At the same time, extra adhesion was created by scraping operations on the visceral surface until serosal bleeding occurred. After the procedure was completed, the abdomen was closed continuously using 4.0 Vicryl. The rats were then allowed to recover for 2 weeks. A total of 4 animals died of lung infection before starting the experiment. Animals that died were excluded from the study. After the recovery period, the animals were sacrificed and evaluated for adhesion formations. The researchers who evaluated the adhesions had no prior knowledge of which group the rat belonged to. Adhesion scoring based on extent, severity, and resistance to applied force is summarized in table 1.[18,19]

The sum of the three parameters was used as the total score for each group. Tissue samples taken from the peritoneum and adhesion area were sent for histopathological examination. Adhesion examples are shown in figure 1.

Table 1. Macroscopic adhesion scoring method

Score	Extend	Severity	Degree
0	No	No	No
1	< 25%	Filmy avascular	Detached with gentle traction
2	Between 25 and 50%	Opaque, translucent, avascular	Detached with moderate traction
3	Between 50 and 75%	Vascular or opaque	Detached with sharp traction
4	More than 75%	Opaque, thick veins available	-

The adhesion score is equal to the sum of the scores from each part of the adhesion. The highest possible score is 11

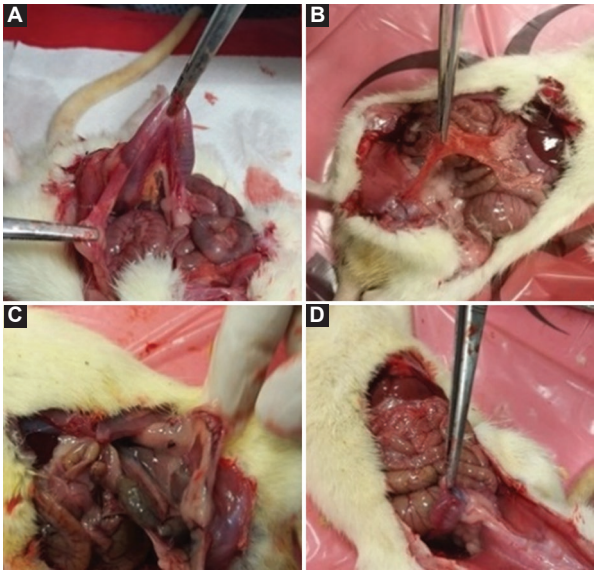

Figure 1. *Adhesion examples.* **A:** *adhesions between bowel and uterine horn.* **B:** *fibrous adhesion between bowel and uterine horn.* **C** *and* **D:** *complete adhesion to the anterior abdominal wall and bowel.*

Histopathological examination

Tissues were fixed with formaldehyde for 48 h and washed with phosphate-buffered saline at pH 7.4. Dehydration was achieved by passing the tissues through increasing concentrations of ethyl alcohol (from 80%, 90%, 90%, 96% and to 96%) for 45 min in each ethanol series. After dehydration, specimens were cleared in xylene and embedded in paraffin wax.[20] Paraffin tissue blocks (5-μm thickness) were cut using a rotary microtome. Tissue sections were stained with hematoxylin and eosin staining for histomorphological analysis.[21] Tissue slides were visually assessing with a Nikon Eclipse 80i image analysis system. A total of 100 fields were scored per tissue in 10 random slide of view taken with a ×10 objective for evaluation of tissue inflammation and edema.

Anti-vascular endothelial growth factor (VEGF) ımmunohistochemical staining

For immunohistochemistry (IHC), sections were incubated with H_2O_2 (3%) for 30 min to eliminate endogenous standard activity and blocked with protein block for 20 min at room temperature. Later, sections were incubated with primary antibody (anti-VEGF, Santa Cruz Biotechnology, Inc.; dilution 1/100) overnight at 4°C. Antibody detection was performed with the UltraTek HRP Anti-Polyvalent Staining System (ScyTec Inc., USA), and 3,30-diaminobenzidine was used to visualize the final product.[22]

Immunostaining was evaluated semiquantitatively using H-score analysis. Immunostaining intensity was categorized under the following scores: 0 (no staining), 1 (weak staining), 2 (moderate staining), and 3 (intense staining). H-score value was derived for each specimen by calculating the sum of the percentage of cells for the cytoplasmic and nuclear immunoreaction

of the sections that were stained at each intensity category multiplied by its respective score, by means of the formula H-score = ΣPi (i + 1), where i = intensity of staining with a value of 1, 2, or 3 (weak, moderate, or strong, respectively) and Pi is the percentage of stained cells for each intensity, varying from 0% to 100%. For each slide, 10 different fields were microscopically evaluated at ×20 magnification. H-score evaluations were independently performed by at least two investigators blinded to the source of the samples as well as to each other's results.

Biochemical analysis

Measurement of lipid peroxide level

Measurement of lipid peroxides in tissue samples was made by the Uchiyama and Mihara methods.[23] Malondialdehyde (MDA) levels in the samples were calculated from the calibration curve prepared from standard solutions. Results are given as nmoL/mg protein.

Measurement of VEGF level

Measurement of VEGF levels in tissue samples was carried out with an enzyme-linked ımmunosorbent assay (ELISA) kit (Sun Red, Shanghai Sunred Biological Technology Co. Ltd.). First of all, standard samples were prepared. Standard prefixes of 50, 100, 200, 400, 800, and 1600 ng/L were prepared from the stock solution. 0.05 mL standard and 0.05 mL HRP-streptavidin were added to the wells determined in the ELISA plate. Samples were pipetted. The plate was covered and incubated at 37°C for 90 min. For tissue samples, 0.04 mL of sample, 0.01 mL VEGF antibody, and 0.05 mL of the HRP-streptavidin were added. The ELISA plate was incubated at 37°C for 60 min. At the end of the period, all samples were removed from the ELISA plate with a pipette and washed 3 times with washing buffer. At the end of the washing process, chromogen A (0.05 mL) and B solutions (0.05 mL) were added to the wells, and the plate was incubated at 37°C for 15-30 min. At the end of the period, the reaction was stopped by adding 0.05 mL of stop solution to the wells. The optical density of the resulting yellow color was read in a microplate reader (Thermo Scientific® Multiskan Go) at 450 nm wavelength. Results were evaluated according to the standard calibration curve.

Measurement of total antioxidant capacity (TAC)

Measurement of TAC in tissue samples was performed spectrophotometrically with a commercial kit (Rel Assay Diagnostics). According to the principle of this method, the antioxidant molecules in the studied sample cause the formation of a lighter colored compound by reducing the dark blue-green colored ABTS radical. The absorbance of the resulting color is read in the spectrophotometer at a wavelength of 660 nm.[24] The level of antioxidant molecules in the sample is calibrated with the stable antioxidant compound Trolox Equivalent (a vitamin E analog) present in the kit.

Statistical analysis

The Statistical Package for the Social Sciences 25 (SPSS 25) (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. The statistical package program was used to evaluate the data. Histopathological changes between experimental groups were analyzed comparatively. Experiments were done independently in 6 replicates. Variables are expressed using mean ± standard deviation, percentage, and frequency values. Variables were evaluated after checking the preconditions for normality and homogeneity of variances (Shapiro Wilk and Levene test). For comparison of three or more groups, the one-way ANOVA test and the Tukey Honestly Significant Difference test, one of the multiple comparison tests, were used. For the significance level of the tests, $p < 0.05$ and $p < 0.01$ values were accepted.

Results

The results obtained from the present study are shown in table 2. The total adhesion scores were 5.86 ± 1.21 for the CG, 6.29 ± 1.49 for the CoG, 2.6 ± 1.14 for the LLG, and 2 ± 1.41 for the HLG. There were statistically significant differences between macroscopic adhesion scores between groups. A statistically significant decrease was found in all adhesion scores in rats given lycopene compared to groups not given lycopene, regardless of dose. There were significantly higher extent ($p < 0.05$), severity ($p < 0.05$), degree ($p < 0.05$), and total adhesion ($p < 0.05$) scores in the CG and CoG than in the LLG

Table 2. Macroscopic adhesion score, biochemical, histopathological findings, and VEGF H-score results

Variable	Mean ± standard deviation				p*	p**
	CG	CoG	LLG	HLG		
VEGF (ng/L)	283.75 ± 69.88	351.42 ± 96.47	313 ± 45.4	295 ± 86.44	p = 0.427	
TAC (mmoL trolox Eq/L)	0.77 ± 0.32	0.58 ± 0.13	0.68 ± 0.37	0.74 ± 0.32	p = 0.636	
MDA (nmoL/mL)	13 ± 3.82[a]	20.48 ± 5.29[a, b]	16.08 ± 4.27	11.47 ± 1.47[b]	p = 0.005***	p^a = 0.014*** p^b = 0.007***
Adhesion score						
Extend	2.71 ± 0.48[b,c]	2.85 ± 0.37[d,e]	1.4 ± 0.54[c,d]	1.4 ± 0.54[b,e]	p = 0.000***	p^b = 0.001*** p^c = 0.001*** p^d = 0.001*** p^e = 0.001***
Severity	1.71 ± 0.48[b]	2 ± 0.81[d,e]	0.8 ± 0.44[d]	0.4 ± 0.54[b, e]	p = 0.001***	p^b = 0.007*** p^d = 0.015*** p^e = 0.001***
Degree	1.42 ± 0.78[b]	1.42 ± 0.78[e]	0.4 ± 0.54	0.2 ± 0.44[b,e]	p = 0.007***	p^b = 0.029*** p^e = 0.029***
Total	5.85 ± 1.21[b,c]	6.28 ± 1.49[d,e]	2.6 ± 1.14[c,d]	2 ± 1.41[b,e]	p = 0.000***	p^c = 0.002*** p^b = 0.000*** p^d = 0.001*** p^e = 0.000***
Histopathological findings and VEGF H-score						
Inflammation	4.21 ± 1.3	4.01 ± 2.30	3.9 ± 1.36	1.10 ± 2.1[f]		p^f = 0.005***
Edema	2.42.0 ± 2.2	2.33 ± 0.26	2.212 ± 0.72	0.11 ± 0.64[f]		p^f = 0.002***
VEGF H-Score	271.30 ± 2.41	265.12 ± 0.96	152.23 ± 1.10[g]	132.56 ± 1.12[g]		p^g = 0.01***

*Data were analyzed using one-way ANOVA test.
**Data were analyzed using the Tukey HSD test.
***p-value was considered statistically significant.
p^a: comparison between CG and CoG.
p^b: comparison between CG and HLG.
p^c: comparison between CG and LLG.
p^d: comparison between CoG and LLG.
p^e: comparison between CoG and HLG.
p^f: comparison between CG, CoG, and LLG.
p^g: comparison between CG and CoG.
CG: control group; CoG: corn oil group; LLG: low lycopene group; HLG: high lycopene group; VEGF: vascular endothelial growth factor; TAC: total antioxidant capacity; MDA: malondialdehyde.

and HLG. Although some adhesion scores (severity, degree, and total adhesion score) were lower in the HLG compared to the LLG, these differences were not statistically significant. P-values were 0.73, 0.97, and 0.89, respectively. There was no significant difference between the CG and CoG in terms of all scoring. The line charts of the groups according to the adhesion score are shown in figure 2.

When histopathological findings are evaluated, a high level of inflammation was observed between the perimetrium and smooth muscles in the CG and CoG groups. Hyperemia and intense inflammatory cells have been detected in vascular structures. Moderate edema and thickening were also detected in the perimetrium. Similar to CG and CoG groups, high-level inflammation, hyperemia, and moderate edema were observed in the

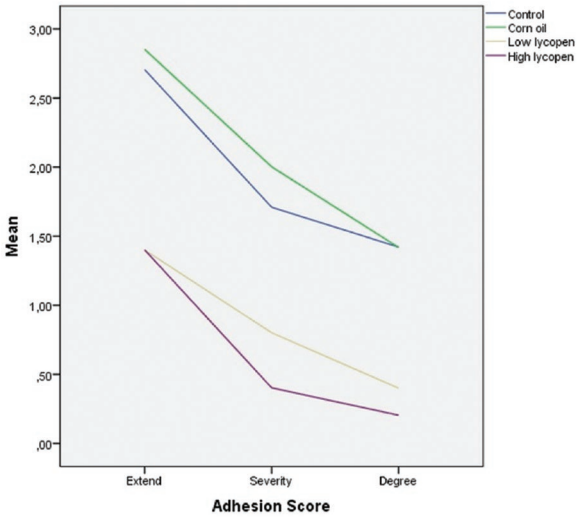

Figure 2. *Line charts according to the adhesion score of the groups.*

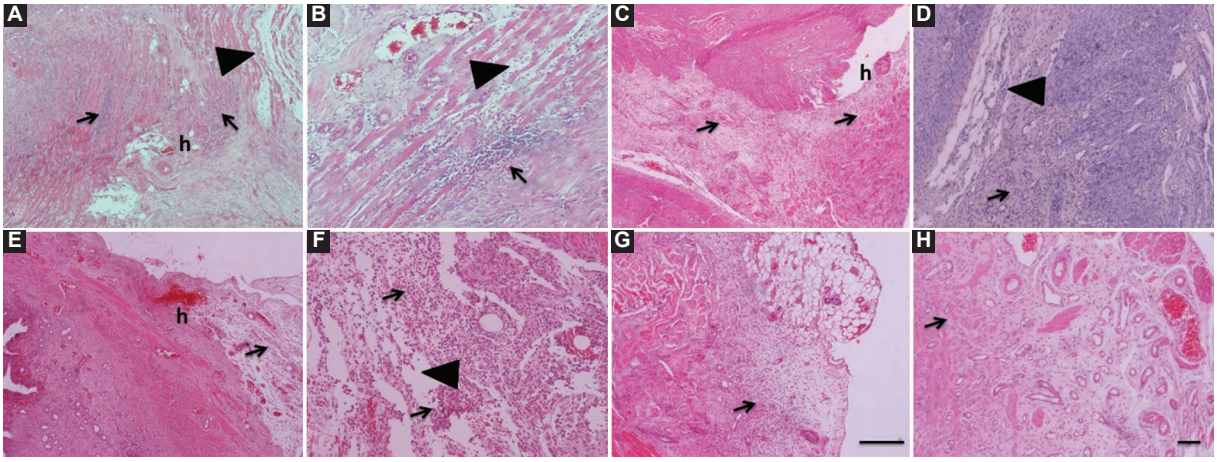

Figure 3. A: *control group (CG), black arrow; high level of inflammation in the perimetrium and between smooth muscles, arrowhead; moderate edema, h; hyperemia magnification ×4.* **B***: CG black arrow; high level of inflammation in the perimetrium and between smooth muscles, arrowhead; moderate edema, magnification ×10.* **C***: corn oil group (CoG), black arrow; high level of inflammation in the perimetrium and between smooth muscles, h; hyperemia magnification ×4.* **D:** *CoG arrowhead; moderate edema, magnification ×10.* **E***: low-dose lycopene group (LLG), black arrow; high level of inflammation in the perimetrium, h; hyperemia magnification ×4.* **F***: LLG black arrow; high level of inflammation in the perimetrium, arrowhead; medium edema magnification ×10,* **G***: high-dose lycopene group (HLG) black arrow; low level inflammation in the perimetrium ×4.* **H***: HLG black arrow; low-level inflammation in perimetrium, magnification ×10, hematoxylin and eosin staining.*

perimetrium in the LLG. Inflammation ($p = 0.005$) and edema ($p = 0.002$) decreased statistically significantly ($p < 0.05$) in the HLG group compared to the other groups, including the LLG group. Symptoms of hyperemia almost disappeared (Table 2 and Fig. 3).

Anti-VEGF involvement was observed around the vascular structures and perimetrium in the anti-VEGF IHC staining of the uterine sections of the experimental groups. It was observed that VEGF H-score values of the CG and CoG groups were statistically significantly different from LLG ($p = 0.01$) and HLG ($p = 0.01$) groups ($p < 0.05$). VEGF H-scores were significantly lower in lycopene-given groups, regardless of dose. When LLG and HLG were compared in terms of anti-VEGF H-score, no significant difference was observed (Table 2 and Fig. 4). There was no significant difference between the groups in terms of VEGF and TAC in biochemical parameters except for MDA (Table 2). Compared to the CoG group, MDA levels were statistically significantly lower in the CG and HLG ($p < 0.05$). Line charts of the results of biochemical TAG, MDA, and VEGF markers according to the groups are shown in figure 5.

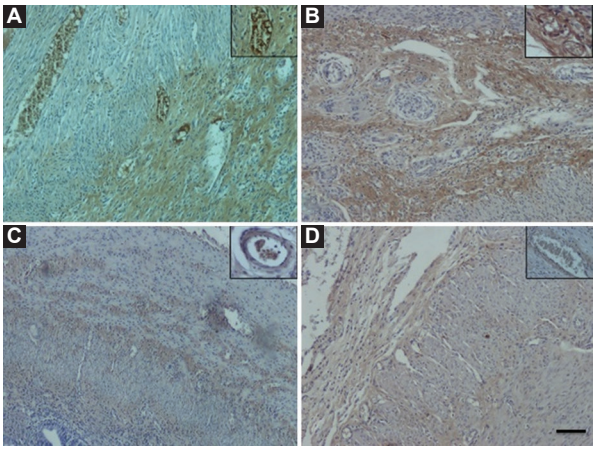

Figure 4. *Anti-vascular endothelial growth factor immunohistochemical staining.* **A***: control group.* **B:** *corn oil group.* **C:** *low-dose lycopene group.* **D:** *high-dose lycopene group, magnification of large pictures is ×10, thumbnails represent vascular structures belonging to groups.*

Discussion

Post-operative adhesions are a result of the cellular and biochemical response that occurs after peritoneal trauma while attempting to repair the peritoneum. Many methods have been used to reduce adhesion formation, such as reducing the initial inflammatory response, preventing fibrin formation, increasing fibrinolysis, preventing collagen deposition, and using a barrier against adhesion formation, and many studies have been conducted on them[25] but today there is still no drug or method that can be used alone that can prevent adhesion formation satisfactorily. Many studies have shown that inflammatory cells and reactive oxygen species play a role in the formation of adhesion. The anti-adhesion effects of antioxidants have been tested in various animal models.[26] Heparin application before and after the operation has been shown

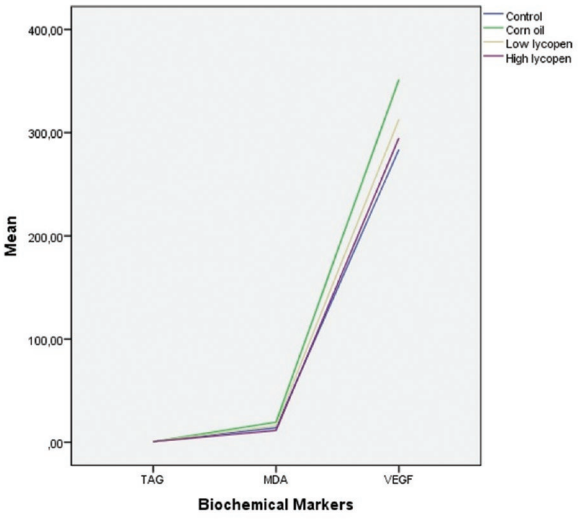

Figure 5. *Line charts of the results of biochemical TAG, MDA, and VEGF markers according to groups. MDA: malondialdehyde; TAC: total antioxidant capacity and VEGF: vascular endothelial growth factor.*

to have anti-adhesive efficacy in a rat adhesion model made by Başbuğ et al.[27] In another anti-adhesion model with quercetin, the adhesion scores of the Quercetin + Surgicel group were reported to be lower than the quercetin group.[17] In this study, we tried to examine the potential effect of lycopene, a potent antioxidant, antiproliferative, anticarcinogenic, and anti-inflammatory, on adhesion formation in rats with traumatized uterine serosa.[15] To our knowledge, the present study is the first study that used lycopene as an adhesion inhibitor in an animal model.

MDA is produced by cells involved in the inflammatory response. It is a by-product formed by oxygen radicals breaking down lipid-containing structures such as plasma and cell membranes. It is a parameter used in evaluating both tissue damage and inflammation severity.[28] In our study, a significant difference was observed between the HLG and CG in terms of MDA levels ($p = 0.007$). Although MDA levels were found to be lower in the HLG than in the LLG, this difference was not statistically significant.

VEGF is an angiogenic cytokine that participates in the process of adhesion formation through the formation of new vessels.[29] In this study, although there was no statistical difference between the groups in terms of VEGF release, numerically, more VEGF-positive cells were encountered in the treatment groups compared to the CG. We think that the biochemical and histopathological VEGF analysis differences between the experimental groups are due to the difference in the number of samples evaluated statistically.

Substances that prevent oxidation caused by free radicals and have the ability to capture and stabilize free radicals are called “antioxidants.” The total effect of all antioxidants in body fluids is called total TAC.[30] In this study, there was no significant difference between the groups in terms of TAC. Higher TAC levels were detected in the HLG but it was statistically insignificant.

Various methods have been used for grading intra-abdominal adhesions. The systems that are made according to the percentage of traumatized adherent area used by Linsky et al.[31] and Leach et al.[18] systems, consisting of three different parameters, are the most commonly used methods.[31] We used the system of Leach et al.[18] In this system, adhesions are scored in three separate categories according to type, prevalence, and easy or difficult separation. In our study, adhesion scores were significantly lower in the lycopene groups compared to the CG, which indicates the effectiveness of lycopene alone in reducing adhesion formation, in line with other studies.[32] In *in vitro* studies, it was found that vitamin E has antioxidant, anti-inflammatory, anticoagulant, and antifibroblastic effects to a similar effect of Lycopene. Yetkin et al. demonstrated that intraperitoneal vitamin E injection and human amniotic membrane separately reduced post-operative adhesion in rats; however, a synergistic increase in their effects could not be demonstrated with their co-administration.[33] The results of our study are consistent with these studies.

Our study had some limitations. First, it was the route of application of the anti-adhesion agent. We chose this method in our study because the intraperitoneal route is generally used in the literature. Another limitation is that the dose of intraperitoneal lycopene required to prevent adhesion is unknown. In this study, we used the doses used in animal models of oxidative stress.

Conclusions

Histological and mechanical parameters obtained in our study suggest that lycopene, which we use as an anti-adhesion agent, is effective in preventing intra-abdominal adhesions and does not negatively affect wound healing.

Funding

The authors declare that they have not received funding.

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 study does not involve patient personal data. The SAGER guidelines were followed according to the nature of the study. This study was approved by our University Animal Experiments Local Ethics Committee (April 26, 2017, Protocol No: 2017/011).

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

Machine learning for COVID-19 mortality prediction: enhancing cart models with node-specific odds ratios

Aprendizaje automático para la predicción de mortalidad por COVID-19: mejora de los modelos CART con razones de probabilidad específicas por nodo

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Abstract

Objective: *The objective of the study is to evaluate a classification and regression tree (CART) model combined with odds ratio (OR) to identify key predictors of COVID-19 mortality. Data from 1,432 patients hospitalized at Hospital General de México during the pandemic's 1st year were analyzed.* **Methods:** *A CART model was constructed using demographic, clinical, and laboratory data collected at admission. The model's performance was evaluated using multiple criteria, and ORs were calculated for each node to measure mortality.* **Results:** *Mechanical ventilation emerged as the strongest predictor of mortality. Patients intubated at admission with hospital stays under 17.5 days had the highest mortality rate (99%, OR = 80). Conversely, non-intubated patients hospitalized over 5.5 days with glomerular filtration rates above 66.5 had the lowest mortality (5%, OR = 0.26). The model showed excellent performance, with an F1 score of 0.918, accuracy of 0.903, and area under the curve of 0.955.* **Conclusions:** *The CART model, combined with OR calculations, offers a reliable and comprehensible tool for predicting COVID-19 mortality risk. This model provides practical utility in various healthcare settings, including resource-limited contexts, by focusing on readily available clinical parameters. The results emphasize the significant influence of mechanical ventilation on patient outcomes and the need for timely interventions in high-risk patients.*

Keywords: *COVID-19. Mortality prediction. Classification and regression tree model. Mechanical ventilation. Machine learning. Odds ratio.*

Resumen

Objetivo: *Evaluar un modelo CART con razones de probabilidad para identificar predictores de mortalidad por COVID-19 en 1432 pacientes hospitalizados.* **Métodos:** *Se construyó un modelo CART con datos demográficos, clínicos y de laboratorio al ingreso. Se evaluó el rendimiento y se calcularon las razones de probabilidad para medir el riesgo de mortalidad.* **Resultados:** *La ventilación mecánica fue el predictor más fuerte. Los pacientes intubados al ingreso con estancias de 5.5 días con filtración glomerular > 66.5 tuvieron la menor mortalidad (5%; OR: 0.26). El modelo mostró un excelente rendimiento (F1 = 0.918, precisión de 0.903, AUC = 0.955).* **Conclusiones:** *El modelo CART con razones de probabilidad ofrece una herramienta confiable para predecir la mortalidad por COVID-19, útil en diversos entornos, incluso con recursos limitados. Enfatiza la influencia de la ventilación mecánica y la necesidad de intervenciones oportunas en pacientes de alto riesgo.*

Palabras clave: *COVID-19. Predicción de mortalidad. Modelo CART. Ventilación mecánica. Aprendizaje automático. Razones de probabilidad.*

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Introduction

In December 2019, Wuhan, China, became the epicenter of a global health crisis because of the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. This novel virus, which causes coronavirus disease 2019 (COVID-19), belongs to the coronavirus family – a group of viruses capable of infecting both humans and animals. Coronaviruses are associated with several illnesses, from common colds to severe respiratory conditions, such as severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome.[1] A frequent and severe complication of these infections is acute hypoxemic respiratory failure or acute respiratory distress syndrome (ARDS).[2] ARDS is a diffuse inflammatory lung injury causing low blood oxygen levels; it is defined as a PaO_2 under 60 mmHg or a SaO_2 under 88%.[3] Pulmonary inflammation cytokines and other proinflammatory molecules damage the capillary endothelium and alveolar epithelium, disrupting the barrier between the capillaries and air spaces. As a result, patients with ADRS suffer severe respiratory distress that requires oxygenation therapy and respiratory support.[4,5]

On September 25, 2022, 612 million confirmed cases and 6.5 million deaths were recorded due to COVID-19 worldwide. In Mexico alone, the global report included 7,702,809 confirmed cases and 334,958 deaths.[6] Between 2020 and 2021, mortality in Mexico secondary to COVID-19 accounted for 47% of all deaths registered in the country, according to data from the National Institute of Statistics and Geography.

Globally, the most important risk factors influencing the progression and severity of infection include advanced age and comorbidities, such as diabetes, hypertension, cardiovascular disease, chronic lung disease, and chronic kidney disease.[7,8] The global prevalence of overweight and obesity remains alarmingly high, affecting 62.5% of adults, with 64.1% of men and 60.9% of women falling into this category.[9,10]

During the COVID-19 pandemic, a body mass index (BMI) > 35 kg/m^2 was strongly associated with an increased risk of intensive care unit (ICU) admission. Studies have noted that this BMI threshold not only heightened the likelihood of ICU admission but also increased the need for mechanical ventilation and prolonged hospital stays. Furthermore, overweight and obese individuals were found to have a greater likelihood of developing ARDS, accompanied by higher mortality rates.[11-13]

At the peak of the pandemic, most patients hospitalized for COVID-19 and/or ARDS required ventilatory support because of advanced disease progression. Ventilatory support is a critical intervention for managing respiratory failure by ensuring adequate oxygen delivery and gas exchange.[14] Various ventilatory support methods exist, including non-invasive ventilation and invasive mechanical ventilation, each with distinct benefits and risks.[15]

The decision between non-invasive and invasive ventilation strategies is influenced by several factors, such as the severity of respiratory failure, patient response to initial treatment, and the presence of comorbidities. Although intubation and invasive mechanical ventilation remain contentious due to their association with high morbidity and mortality rates (reported between 81% and 97%), they often play a pivotal role in managing severe cases.[5,16-19]

Another critical predictor of COVID-19 mortality was the duration of hospitalization. Prolonged hospital stay was found to triple the risk of mortality compared with shorter stays.[20] However, Sousa Neto et al.[21] observed that longer ICU stays paradoxically served as a protective factor for certain patients. This finding suggests that extended ICU care may benefit those admitted with extreme disease severity, improving outcomes despite the high initial risk.

The rapid spread of the virus, its capacity for mutation, patient-specific factors, and the natural history of the disease have led to a severe shortage of medical resources and trained personnel. This crisis underscores the urgent need for risk stratification models to optimize healthcare delivery.

Predictive models provide a means to identify patients at higher risk of mortality, enabling timely and targeted interventions. Machine learning (ML) classifiers have proven to be valuable tools for supporting clinical decision-making. As a branch of artificial intelligence, ML leverages large raw datasets to develop high-quality predictive models. Among these, Classification and Regression Trees (CART) are ML-based AI tools that utilize statistical, probabilistic, and optimization techniques to integrate risk factors and generate profiles of patients at high risk of mortality.[22,23] CART models have been applied in various medical domains, including survival analysis,[24] dyslipidemia classification,[25] and prognosis of heart failure.[26] CART can handle non-linear relationships through recursive

partitioning, creating splits based on different thresholds of the predictor variables.[27] Importantly, CART can manage both categorical and continuous variables without requiring extensive preprocessing, which enhances its usability in diverse contexts.[28]

This study aimed to identify the key predictors of mortality in patients admitted to the Hospital General de México "Dr. Eduardo Liceaga" (HGMEL) during the 1st year of the COVID-19 pandemic. Using available clinical and laboratory data, the research employs an easy-to-use and interpretable model developed with accessible software capable of presenting results in a user-friendly, visual format. This approach ensures its applicability in real-world healthcare settings. Identifying predictors of mortality in hospitalized patients with COVID-19 is crucial for improving patient survival and optimizing healthcare resources. By focusing on actionable insights, this study seeks to improve healthcare service delivery and patient outcomes.

Methods

This retrospective study was conducted at the HGMEL. A total of 1432 patients of both sexes, older than 18 years, positive for SARS-CoV-2 by polymerase chain reaction, hospitalized from the second quarter of 2020 to the fourth quarter of 2021, were included. Data were collected upon admission. Demographical data and laboratory test results were registered; the latter consisted of complete blood counts, blood gases, and chemical blood analyses.

The subjects were divided into two groups according to the main outcome: survivors and non-survivors. For the comparison of the variables between groups, the appropriate statistical test was used according to the normality of the data, taking a significant difference $p > 0.05$.

Research involving human subjects complied with all relevant national regulations and institutional policies, which are in accordance with the tenets of the Helsinki Declaration (as revised in 2013), and was approved by the Research Ethics Committee of the HGMEL (Reg. No. DMC-3369-20-20-1).

CART model

The variables to introduce in the model were selected following a literature survey and consensus among experts regarding the most pertinent patient characteristics that could predict mortality. The variables introduced were sex, age, days of hospital stay, BMI, type 2 diabetes mellitus, systemic arterial hypertension, glucose (mg/dL), cardiac rate in beats per minute (CR), respiratory rate in breaths per minute (RR), oxygen saturation in percentage (SpO_2), lactate dehydrogenase (LDH) in IU/L, glomerular filtration rate (GFR), hemoglobin (g/dL), leukocytes ($\times 10^3$), neutrophil/leukocyte ratio (NLR), invasive ventilatory support, and rejection of invasive ventilatory support. Subsequently, the variables underwent an analysis for multicollinearity employing the variance inflation factor approach, with all scoring between 1 and 5. Three variables, specifically BMI, HR, and RR rate, exhibited more than 10% of missing values (10.2, 12.9, and 12.8, respectively). These missing values amounts were considered acceptable on the one hand because even with some missing values, the sample size maintains sufficient statistical power for analysis, and on the other hand because CART models can handle missing data through surrogate splits, a mechanism that uses alternative splitting rules when the primary splitting variable is missing, and maintains all observations in the analysis, even those with missing values,[29] therefore identifying important relationships between variables that could be obscured by imputation.[30] The tree was built considering *deceased* as the dependent variable. The growth method selected was CART with a 10-fold cross-validation as the training method. The maximum tree depth was three levels, with 100 minimal subjects in parent nodes and 50 minimal subjects in child nodes. The Gini impurity measure was used as the splitting criterion, with 0.0001 as the minimum improvement required for a split. The prognostic value for mortality was recorded as a new variable to build a receiver operating characteristic curve. Tetrachoric tables with true/false positives and negatives were used to calculate the Odds Ratio (OR) of each node and the overall sensitivity, specificity, F1 score, positive and negative predictive values (PPV and NPV), positive and negative likelihood ratios (LR+ and LR−), area under the curve (AUC), and accuracy of the model.

All statistical data were analyzed using IBM Statistical Package for the Social Sciences (SPSS)® version 27.

Data availability statement

The data that support the findings of this study are openly available in Figshare at DOI: 10.6084/m9.figshare.28256057.[31] The dataset consists of a csv file. The data can be accessed without restrictions

 Any additional information required to reanalyze the data reported in this paper is available from the corresponding author upon request.

Results

A total of 1432 data from confirmed patients of COVID-19 were evaluated, among whom 583 (41%) survived and 849 (59%) died. The sex ratio differed significantly between sexes, with 936 males (66%) and 496 females (34%), $p < 0.001$. The mean age ± standard deviation of patients who died was higher than that of survivors. SpO_2 on admission was significantly lower among patients who died compared to survivors ($p < 0.001$). Among the biochemical findings, elevated LDH levels were observed in patients who died compared with those who survived ($p \leq 0.001$). The NLR was significantly higher in patients who died than in survivors ($p \leq 0.001$). Regarding the number of days of hospital stay, there was no significant difference between the groups. Interestingly, BMI showed no difference between survivors and non-survivors ($p = 0.167$). Demographic data are presented in table 1.

Figure 1 shows the obtained classification tree, which identified patients with a high-risk profile for mortality based on the risk factors present upon admission.

Patients intubated on admission who spent < 17.5 days (Node 9) had the highest mortality (466/470; 99%), with an OR of 80 (confidence interval [CI] 95% = 12.84-32.82, $p < 0.001$). Contrastingly, non-intubated patients who stayed more than 5.5 days and had a GFR > 66.5 (Node 14) had the lowest mortality (5/95; 5%). Moreover, this profile served as a protective factor (OR = 0.26, CI 95% = 0.22-0.32, $p < 0.001$).

The overall performance achieved by the tree was F1 score = 0.918, ACC (accuracy) = 0.903, AUC = 0.955, CI 95% = 0.944-0.965, $p < 0.001$ (Fig. 2). The other performance metrics were PPV = 0.917, NPV = 0.883, LR+ = 7.686, and LR− = 0.091.

Discussion

CART models provide a means of identifying high-risk subgroups to whom prevention and intervention efforts can be targeted, making them useful tools for addressing research questions that cannot be answered by traditional regression methods.[32]

Our model effectively captures the complex, non-linear relationship between length of stay and survival, particularly when considering ventilation status and subsequent physiological parameters.

Similar studies

Previous studies have compared ML algorithms to predict mortality in COVID-19 patients. Zakariaee et al.[33] used Weka 3.9.2 to compare various algorithms for mortality prediction in an 815-subject database, finding that random forest performed best with 97.2% accuracy, 100% sensitivity, 94.8% precision, 94.5% specificity, 97.3% F-score, and 99.9% AUC. Other ML algorithms with an AUC from 81.2% to 93.9% also showed good performance.

Mohammadi-Pirouz et al.[34] developed three classification tree algorithms (Chi-squared Automatic Interaction Detector [CHAID], C5.0, and CART) for 5080 COVID-19-positive subjects using R 4.2.1 and SPSS 26. All models indicated that factors such as ICU hospitalization, intubation, age, kidney disease, BUN, CRP, WBC, NLR, SpO_2, and hemoglobin influenced mortality rates. CART performed best, achieving 0.75 sensitivity, 0.91 specificity, 0.36 precision, 0.90 accuracy, 0.41 F-score, and 0.92 AUC.

A Mexican study[35] evaluated four ML algorithms in 580,570 COVID-19 patients, namely logistic regression, Naive Bayes, decision tree, and random forest, obtaining accuracy values of 0.91, 0.89, 0.91, and 0.91, respectively. An AUC of 0.92 was reported without specifying the algorithm.

These studies undoubtedly provide valuable insights into the application of ML models for COVID-19 prognosis. However, many are limited by small sample sizes and lack comprehensively report of all performance metrics.

Huyut and Üstündağ studied 686 patients in Turkey focused on COVID-19 diagnosis and prognosis using blood-gas data and the CHAID tree algorithm.[36] They achieved a total accuracy of 65.0% in predicting the prognosis of the disease and 68.2% in diagnosing the disease. Other performance metrics were not reported. In this work, the model was developed in SPSS version 25.

ORs

Previous studies using CART trees have used ORs for single features.[37] However, no similar study

Table 1. Demographics all figures represent means ± SD compared by Mann-Whitney's U except where indicated

Variable	Overall (n = 1347)	Survivors (n = 583)	Non-survivors (n = 764)	p
*Sex (Female n, %)	458 (34)	211 (36)	247 (32)	< 0.001
AGE	55.31 ± 14.51	50.72 ± 13.54	58.82 ± 14.25	< 0.001
**Days of hospital stay	11 (6-17)	11 (7-15)	11 (5-18)	0.865
BMI	28.22 ± 5.42	28.26 ± 5.14	28.18 ± 5.62	0.436
*DM n, (%)	505 (40)	176 (39)	329 (61)	0.003
*SAH n, (%)	778 (60)	336 (43)	442 (57)	< 0.001
Glucose	173.41 ± 135.53	146.02 ± 128.99	194.40 ± 136.75	< 0.001
CR	94.01 ± 19.31	89.17 ± 16.3	96.69 ± 20.3	< 0.001
RR	26.07 ± 7.37	23.14 ± 4.87	27.7 ± 8.0	< 0.001
SpO_2	75.52 ± 15.82	81.94 ± 10.30	70.75 ± 17.44	< 0.001
Serum LDH IU/L	506.74 ± 390.26	415.80 ± 170.44	577.74 ± 487.04	< 0.001
GFR	86.63 ± 53.19	101.68 ± 47.41	75.54 ± 54.51	< 0.001
HB	14.03 ± 3.1	14.42 ± 3.04	13.74 ± 3.11	0.021
Leukocytes	11.02 ± 6.67	9.02 ± 5.55	12.51 ± 7.04	< 0.001
NLR	14.36 ± 16.34	8.84 ± 7.84	18.58 ± 19.57	< 0.001
*Invasive ventilatory support n, (%)	708 (52)	59 (8)	649 (92)	< 0.001

*Chi-squared.
**Medians (Interquartile range) compared by the median test.
BMI: body mass index; DM: diabetes mellitus; SAH: systemic arterial hypertension; CR: cardiac rate; RR: respiratory rate; SpO_2: oxygen saturation; LDH: lactate dehydrogenase; GFR: glomerular filtration rate; HB: hemoglobin; NLR: neutrophil-to lymphocyte ratio; SD: standard deviation.

(supervised ML for COVID-19 mortality) combines the calculation of the OR of each profile. This combination significantly enhances the model's utility by:

- Risk quantification, as each patient profile has a precise OR with CIs
- Terminal nodes with specific risk profiles: For non-ventilated patients hospitalized for 5.5 days or less, OR was 0.56, thus acting as a protective factor (Node 7), while for those with 80.5 or less SpO_2 (Node 11), the OR for mortality was 3.36 (77% probability of dying).

While the standard statistical comparison of days of hospital stay found no differences between survivors and non-survivors, the tree and OR calculation showed this variable's importance. For intubated subjects with hospital stays ≤ 25.5 days, the OR was 20.53 (CI 95% = 12.84-32.82, p < 0.001), whereas for those with longer stays, the OR reduced significantly (1.36, CI 95% = 0.92-2.00, p < 0.001). This represents a 58% difference in the probability of dying.

This OR-enhanced analysis strengthens the model's value as a clinical decision support tool, providing clinicians with precise risk estimates for different patient subgroups.

Variables

While other studies found laboratory values, comorbidities, or demographic factors as primary predictors, this model identified mechanical ventilation as the strongest discriminator, even when glucose, hemoglobin, LDH, neutrophils, and lymphocytes were introduced. Prior research has also recognized mechanical ventilation as a critical factor in predicting mortality among patients with COVID-19.[21,38,39] Our study quantifies the dramatic impact of mechanical ventilation, with an OR of 7.55 for ventilated patients compared to 0.26 for non-ventilated patients.

The model's reliance on easily available parameters (mechanical ventilation, days of stay, GFR, SpO_2)

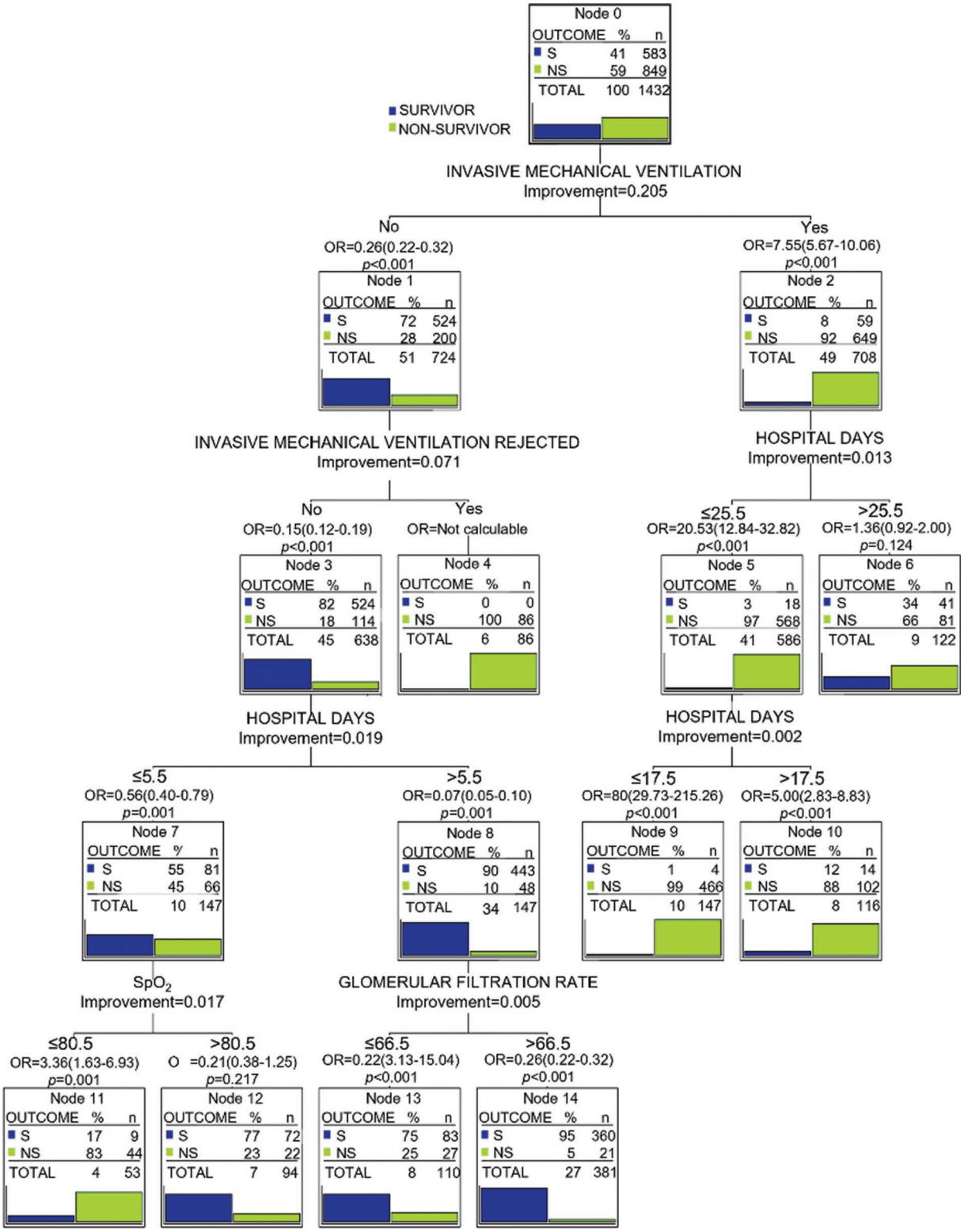

Figure 1. *Classification and regression tree obtained. Improvement is represented as the Gini index. OR is shown for each profile.*

represents a significant practical advantage, as all variables are routinely monitored during standard care without requiring highly specialized tests or extensive patient histories. This emphasis on easily obtainable clinical data, combined with the model's strong performance metrics, makes it valuable for real-world

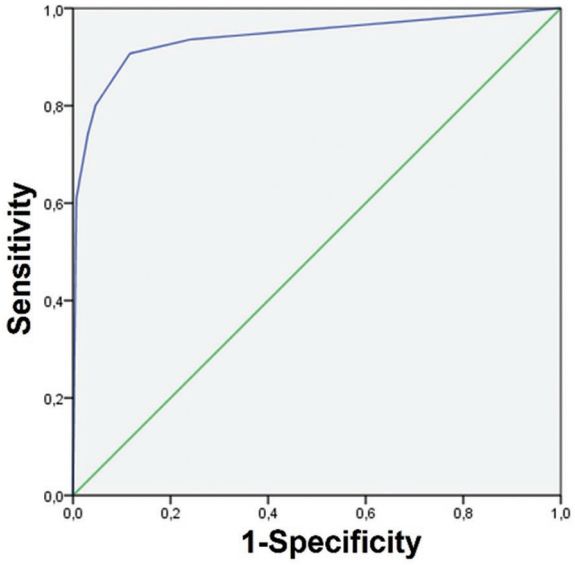

Figure 2. *Receiver operating characteristic curve obtained. Area under curve = 0.955, confidence interval 95% (0.944-0.965), p < 0.001. Sensitivity = 0.91. Specificity = 0.88.*

implementation across various healthcare settings, including resource-limited environments.

Voluntarily rejected mechanical ventilation

We observed that during the period of study, certain patients (or their responsible relatives on their behalf) rejected mechanical ventilation, mainly because of beliefs about COVID-19 and its treatments, shaped by misinformation or distrust in healthcare systems. Research has shown that health misinformation negatively affects individuals' decisions, leading to poor health outcomes and continued viral spread.[40] These beliefs may be influenced by fear and uncertainty in the context of the pandemic and the impact of social media, where even physicians posted misleading information.[41] In our study, a small number of patients rejected mechanical ventilation (86/1432; 6%); however, this decision had a striking impact on their outcome, given that none of them survived (Node 4, 0/86; OR not calculable). Recognizing this finding is crucial for evaluating the impact of misinformation and its outcomes within the context of pandemic outbreaks and could facilitate better-informed discussions on shared decision-making with patients and their families.

Metrics

The model exhibited strong discriminative performance, with balanced accuracy in both positive and negative predictions. It achieved a high sensitivity of 91.97% and specificity of 88.03%, reflecting its excellent capability to accurately identify both mortality and survival cases. Furthermore, the model's PPV of 91.76% and NPV of 88.34% demonstrate its reliability in predicting outcomes. Overall, the model's predictions are accurate approximately 90% of the time, regardless of the outcome.

The LR+ value of 7.686 indicates that a positive prediction is nearly 8 times more likely in true positive cases, whereas the very low LR– value of 0.0912 suggests that false negatives are rare. These values demonstrate strong diagnostic performance.

The F1 score (91.86%) and overall accuracy (90.36%) were fairly high, indicating that the model performed consistently well across all prediction aspects.

Although most published models limit their reporting to basic metrics such as accuracy, sensitivity, and specificity, our model provides a complete performance assessment through nine distinct metrics. Furthermore, the combination of node-specific ORs with these metrics (PPV, NPV, AUC) provides a thorough validation framework that surpasses the partial reporting common in published studies.

Compared with other clinical prediction models, these metrics indicate superior performance, suggesting that the CART model, which also accounts for intubation refusal, could be a highly reliable tool for COVID-19 mortality prediction, risk stratification, and resource allocation planning.

Limitations

This model needs to be tested using data from different centers with lower mortality rates. Potential temporal variations in COVID-19 treatment should be considered. Decisions on ventilation are not exempt from bias. Ultimately, the potential for selection bias must be acknowledged, as the study aimed to identify high-risk profiles during the initial phase of the pandemic; however, the selected participants may not accurately reflect the wider population due to the specific criteria set for inclusion. Finally, there exist confounding variables that may not have been considered in this investigation, including socioeconomic factors or discrepancies in healthcare practices.

Conclusions

The early identification of patients at high risk of mortality poses a significant challenge in medical

practice, especially in the context of SARS-CoV-2 infection, where timely intervention is critical.

By combining the CART model with the OR calculation of the profiles, our approach offers simple performance and interpretation, quickness, accessibility, and reliability, rendering it particularly suitable for implementation in resource-constrained healthcare settings, where the usage of perhaps more precise but indeed more complex tools for AI models (e.g. Python or R) represent a substantial complication, as they require much more specialized knowledge for installation, programming, and interpretation. By promptly identifying high-risk individuals, healthcare professionals can prioritize interventions and allocate resources more effectively, ultimately improving patient outcomes in the face of SARS-CoV-2 infection. Furthermore, insight into patients who voluntarily rejected mechanical ventilation provides real-world evidence of the impact of misinformation and supports clinical teams in counseling patients and families about prognosis.

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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 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 artificial intelligence was used in the writing of this manuscript. Paperpal was used throughout the manuscript to correct and improve English writing.

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ORIGINAL ARTICLE

The importance of neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio to prediction severity of esophageal injury after corrosive substance ingestion

La importancia del INL y el IML para predecir la gravedad de la lesión esofágica tras la ingestión de sustancias corrosivas

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Abstract

Objectives: *The ability to predict the severity of corrosive injury in patients remains challenging. This study aims to explore the potential of the neutrophil-to-lymphocyte ratio (NLR) and the monocyte-to-lymphocyte ratio (MLR) as novel diagnostic markers to predict the severity of esophageal injury following corrosive substance ingestion (CSI).* **Methods:** *We conducted a retrospective cohort analysis on patients with CSI. Demographic data, complete blood counts, and endoscopic findings were collected and analyzed. Esophageal injuries were graded using Zargar's classification. The NLR and MLR were calculated and evaluated as potential predictors of injury severity.* **Results:** *The mean age, NLR, MLR, red distribution width (RDW), and platelet count were increased in the hospitalized patients. Patients with severe esophageal injury also had higher mean age, NLR, MLR, and RDW. In receiver operating characteristic analyses for patients with severe esophageal injury, the area under the curve for NLR and MLR in predicting injury severity and hospitalization was statistically significant.* **Conclusions:** *NLR, MLR, and RDW hold promise as easily accessible and cost-effective inflammatory markers for predicting esophageal injury severity in patients with CSI. These markers could assist healthcare providers in assessing injury extent, avoiding unnecessary esophagogastroduodenoscopy, and guiding treatment decisions.*

Keywords: *Caustic injury. Neutrophil-to-lymphocyte ratio. Monocyte-to-lymphocyte ratio. Red cell distribution. Esophagogastroduodenoscopy.*

Resumen

Objetivo: *Explorar el potencial del índice neutrófilos-linfocitos (INL) y del índice monocitos-linfocitos (IML) como nuevos marcadores diagnósticos para predecir la gravedad de la lesión esofágica tras la ingestión de sustancias corrosivas.* **Métodos:** *Se realizó un estudio de cohortes retrospectivo de pacientes con ingestión de sustancias corrosivas. Se recopilaron y analizaron datos demográficos, hemogramas completos y hallazgos endoscópicos. Las lesiones esofágicas se calificaron utilizando la clasificación de Zargar. El INL y el IML se calcularon y evaluaron como predictores potenciales de la gravedad de la lesión.* **Resultados:** *La edad media, el INL, el IML, la amplitud de distribución eritrocitaria y el recuento de plaquetas aumentaron en los pacientes hospitalizados. La edad media, el INL, el IML y la amplitud de distribución eritrocitaria aumentaron en los pacientes con lesión esofágica grave. En los análisis ROC realizados en pacientes con lesiones graves en el esófago, el AUC del INL y del IML para predecir la gravedad de la lesión y la hospitalización fue estadísticamente significativo.* **Conclusiones:** *El INL, el IML y la amplitud de distribución eritrocitaria se muestran prometedores como marcadores inflamatorios de fácil acceso y rentables para predecir la gravedad de la lesión esofágica en pacientes con ingestión de sustancias corrosivas. Estos mar-*

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cadores podrían ayudar a los proveedores de atención médica a evaluar la extensión de la lesión, evitar una esofagogastroduodenoscopia innecesaria y guiar las decisiones de tratamiento.

Palabras clave: *Lesión cáustica. Índice linfocitos-neutrófilos. Índice monocitos-linfocitos. Distribución eritrocitaria. Esofagogastroduodenoscopia.*

Introduction

Corrosive substance ingestions (CSIs) constitute a significant portion of emergency cases and pose a major health challenge, especially in developing countries, but also in developed ones. CSIs can occur either intentionally, as suicide attempts (often in adolescents and adults), or accidentally (mainly in children). The consequences can be devastating, resulting in individual suffering, disability, resource utilization, and costs. Common complications include the formation of gastrointestinal tract strictures, perforation, and hemorrhage. In addition, systemic effects such as disseminated intravascular coagulation, multi-organ system failure, and sepsis may occur. However, predicting which patients will develop such complications is a challenging task. Patient history and clinical findings are insufficient to reliably predict the severity of corrosive injury. Several studies have shown that clinical signs are not always reliable indicators of the degree of injury and the potential outcome of stricture formation.[1] Given that patient follow-up and treatment strategies depend on the severity of the injury, accurately determining the extent of damage is crucial. While esophagogastroduodenoscopy (EGD) is considered the gold standard for assessing the severity of caustic injury, it is invasive, expensive, and yields negative results in 60-82% of cases.[2,3] Therefore, there is a pressing need for a quantifiable, rapid, inexpensive, and reproducible indicator to predict the severity of corrosive injury.

The neutrophil-to-lymphocyte ratio (NLR) and the monocyte-to-lymphocyte ratio (MLR) are inexpensive and easily accessible inflammatory indicators that can be calculated using a simple blood count. These ratios, especially MLR, reflect the balance between innate and adaptive immunity, offering a straightforward measure of immune status and inflammation level. Numerous studies in the literature have demonstrated associations between NLR and MLR with various inflammatory diseases, several types of cancer, and various liver conditions.[4-7]

However, the predictive value of NLR and MLR in assessing the severity of esophageal injury in patients with CSIs has not yet been explored. In this study, we introduce novel diagnostic markers, NLR and MLR, for predicting the severity of CSIs.

Methods

This retrospective cohort analysis consecutively enrolled a series of patients with CSIs who were admitted to the emergency department and underwent EGD between May 2016 and December 2022. Data from medical records included patients' age, sex, duration between corrosive ingestion and hospital presentation, treatment modality, and complications. A complete blood count (CBC) was obtained upon admission, and EGD was performed within 48 h of the initial injury by experienced endoscopists. Esophageal injuries were graded using the method of Zargar et al. as follows: grade 0: normal; grade 1: mucosal edema and hyperemia; grade 2a: hemorrhagic, bullous mucosa, exudates, fibrinous membranes, or superficial ulceration; grade 2b: circumferential ulceration in addition to grade 2a; grade 3: scattered small necrotic areas, multiple and deep ulcerations; grade 3b: extensive necrosis; and grade 4: perforations.[8] Grades 1 and 2a were defined as mild-moderate lesions, while grades 2b and 3 were defined as severe lesions. Subsequently, patients were divided into two groups: mild-moderate injury and severe injury.

General information was collected, including gender, age, and comorbidity. Laboratory blood results were obtained, including hemoglobin, platelet count (PLT), neutrophil count, lymphocyte count, monocyte count, mean platelet volume (MPV), and red distribution width (RDW). The MLR was calculated as the ratio between the absolute monocyte and lymphocyte counts, and the NLR was calculated as the ratio between the absolute neutrophil and lymphocyte counts.

Exclusion criteria included the presence of other conditions such as malignancy, hematologic disease, use of immunosuppressants, active infection within 1 month before admission, severe hepatic or renal dysfunction, major trauma, or surgery; and missing blood parameter data at admission.

All patients were categorized into two groups: mild-moderate injury and severe injury. In addition, they were further divided into two groups: hospitalized patients and discharged patients. These groups were then compared in terms of demographic and laboratory parameters.

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences for Windows, Version 25.0, Armonk, NY, USA: IBM Corp. Qualitative data were expressed as frequency and percentage (n [%]), while quantitative data were expressed as mean and standard deviation (SD). The Chi-square test was used for qualitative variables, one-way analysis of variance (F test) for quantitative variables, and *post hoc* Tukey honestly significant difference test for pairwise comparisons. Receiver operating characteristic (ROC) curves were generated, and the area under the curve (AUC) and 95% confidence intervals were calculated for the studied hemogram parameters. Sensitivity and specificity values were determined based on cut-off points identified as the value closest to 1 in the ROC curves. A $p < 0.05$ was considered significant.

Results

EGD was performed on 168 patients due to CSI. Among them, 123 patients exhibited corrosive damage during endoscopy. Thirty-three patients were excluded due to comorbid diseases and missing data.

Of the 90 patients included in the study, 43 were male, and 47 were female. The youngest patient was 21 years old, and the oldest was 85 years old. The mean age was 52.5 ± 14 years. The distribution of patients according to Zargar's classification and the severity of internalization are presented in table 1.

A summary of the comparison of demographic and laboratory parameters is provided in table 2. Mean age, NLR, MLR, RDW, and PLT were increased in hospitalized patients with severe injuries. Mean age, NLR, MLR, and RDW were also increased in patients with severe esophageal injuries (Table 2).

The ROC curve analysis for NLR and MLR demonstrated statistically significant predictive value for both the severity of injury and hospitalization (Tables 3 and 4, Figs. 1 and 2).

In the ROC analyses conducted for hospitalized patients, the AUC was found to be 0.821 (95% confidence interval: 0.72-0.91) for the selected cut-off value of 2.1 for NLR, with a sensitivity of 77.7% and specificity of 77.1%. For MLR, the AUC was found to be 0.784 (95% confidence interval: 0.68-0.88), with a sensitivity of 77.3% and specificity of 77.1% for the selected cut-off value of 0.26 (Fig. 1).

In the ROC analyses conducted for patients with severe esophageal injuries, the AUC was found to be 0.841 (95% confidence interval: 0.75-0.93) for the selected cut-off value of 2.3, with a sensitivity of 76.2% and specificity of 80.0% for NLR. For MLR, the AUC was found to be 0.796 (95% confidence interval: 0.69-0.88), with a sensitivity of 76.2% and specificity of 78.3% for the selected cut-off value of 0.27 (Fig. 2).

Table 1. Endoscopic findings and the distribution of the patients according to the Zargars' classification

Grade	Outpatient	Inpatient	Total	p
Zargar Grade				0.000
Grade 1	25	0	25	
Grade 2a	19	4	23	
Grade 2b	1	18	19	
Grade 3a	0	12	12	
Grade 3b	0	11	11	
Total	45	45	90	
Severity				0.000
Mild-moderate	45	22	67	
Severe	1	22	23	
Total	46	44	90	

Discussion

Esophageal corrosive injuries are common clinical problems, often requiring immediate attention. It is essential to identify the severity of injury accurately to determine appropriate treatment and predict the prognosis of patients. However, endoscopy, the gold standard for evaluating corrosive injuries, is an invasive procedure that may not always be feasible or safe in certain clinical scenarios, such as unstable patients or those with contraindications. Therefore, the search for non-invasive markers to predict the severity of corrosive injuries is of great importance. In this study, we investigated the utility of two easily accessible and cost-effective markers, NLR and MLR, in predicting the severity of esophageal injuries in patients with CSIs. Our results indicate that both NLR and MLR are significantly associated with the severity of corrosive injuries and hospitalization.

Table 2. Comparison of the demographic and laboratory parameters of all patients

Variables	Outpatient (n = 45)	Inpatient (n = 45)	p	Mild-moderate (n = 46)	Severe (n = 46)	p
Sex (m)	19	24	0.55	32	11	0.23
Age (y)	45.2 ± 12.7	55.5 ± 10.6	0.013	46.1 ± 13.1	55.05 ± 10.7	0.015
NLR	1.81 ± 0.6	5.06 ± 3.5	0.000	2.0 ± 1.8	4.9 ± 3.3	0.000
MLR	0.24 ± 0.1	0.53 ± 0.40	0.000	0.27 ± 0.2	0.51 ± 0.34	0.007
RDW	12.8 ± 1.1	13.7 ± 2.3	0.000	12.8 ± 1	13.8 ± 2.38	0.000
PLT	231.4 ± 55.8	268.89 ± 96.2	0.000	241.8 ± 71.3	258.7 ± 89	0.12
MPV	10.3 ± 1.9	10.6 ± 1.1	0.051	9.9 ± 1.9	10.8 ± 162	0.058

NLR: neutrophil-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio; RDW: red cell distribution width; Plt: platelet; MPV: mean platelet volume.

Table 3. ROC curve was used to evaluate the predictive value of neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio for hospitalization

Test variable (s)	AUC	Asymptotic significant	CI	Cut off	sens	1-spes
NLR	0.821	0.000	0.72-0.91	2.1	77.7	77.1
MLR	0.784	0.001	0.68-0.88	0.26	77.3	77.1

AUC: area under curve; Sig: significance; CI: confidence interval; Sens: sensitivity; Spes: specificity; NLR: neutrophil-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio.

Table 4. ROC curve was used to evaluate the predictive value of neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio for the severity of esophageal injury

Test variable (s)	AUC	Asymptotic significant	CI	Cut-off	Sens	Spes
NLR	0.841	0.000	0.75-0.93	2.3	76.2	85.4
MLR	0.794	0.000	0.70-0.89	0.26	81.2	69.4

AUC: area under curve; Sig: significance; CI: confidence interval; Sens: sensitivity; Spes: specificity; NLR: neutrophil-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio.

Looking at the studies on CSI, most of them have been conducted in children, while the incidence of caustic substance ingestion in adults is not low. Each year, a total of 5,000-15,000 CSI cases are reported.[9] CSI poses a significant health challenge, particularly in developing countries. The severity of injury and subsequent complications can vary greatly among individuals, making it crucial to identify patients at risk. Clinical signs alone are often insufficient for accurately predicting the extent of corrosive injury, and endoscopy, while considered the gold standard, has its limitations, including invasiveness and false-negative results.[10] Upper gastrointestinal endoscopy is necessary to assess the severity of the injury. However, EGD is not always easily accessible, and it is invasive, expensive, and yields false-negative results in 70% of cases.[11] In addition, some researchers are cautious about early EGD in cases of suspected esophageal injury due to the risk of perforation. The supine position during esophagoscopy under general anesthesia can cause reflux of the corrosive agent from the stomach to the esophagus, increasing the risk of damage. Furthermore, EGD does not always provide an accurate assessment of the degree of esophageal injury.[12,13] Therefore, there is a need for a more easily accessible, inexpensive, and safe test to determine the severity of esophageal damage. Identifying such a test that can at least predict which patients should undergo endoscopy would be valuable.

In this study, the gender distribution between the groups was equal. Patients with severe injury and/or hospitalized patients were older than the other groups. The NLR, MLR, RDW, and PLT count showed significant differences when evaluating endoscopic severity and CBC parameters in hospitalized patients. The mean PLT count was higher in patients with mild-moderate injury and discharged patients, although it was only statistically significant for hospitalization.

RDW, NLR, MLR, and PLT count are quantitative measurements of variability that is routinely reported in CBC, widely available, inexpensive, and highly reproducible tests. RDW, calculated by dividing the MPV by the SD of erythrocytes and then multiplying by 100 to express the data as a percentage, has long been used for the differential diagnosis of anemias and has emerged as a new risk marker for many different diseases associated with acute and chronic

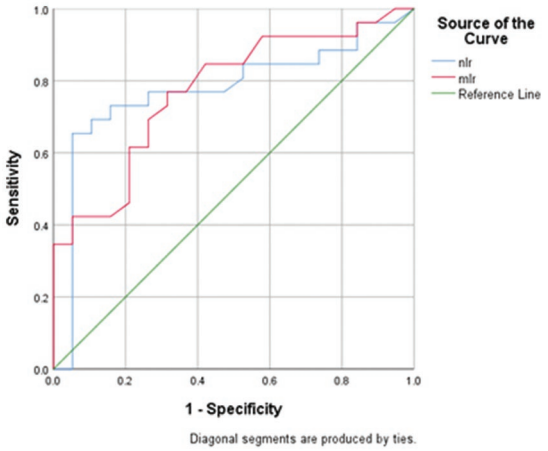

Figure 1. *Receiver operating characteristic curve analysis for hospitalization in patient with caustic substance intake.*

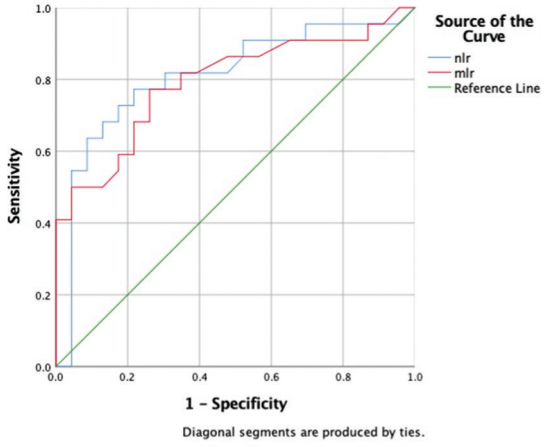

Figure 2. *Receiver operating characteristic curve analysis for the severity of esophageal injury in patient with caustic substance intake.*

inflammation.[14,15] In our study, we found some important results. RDW was higher in hospitalized patients and patients with severe esophageal injury compared to others. We speculate that the inflammation caused by the caustic substance may shorten the half-life of erythrocytes, alter membrane characteristics, and increase RDW values.

NLR is an inexpensive inflammatory indicator that can be calculated by dividing the absolute neutrophil count by the absolute lymphocyte count from a CBC. Numerous publications in the literature have shown that NLR is associated with various inflammatory diseases, and it has become widely accepted as a useful tool for evaluating inflammatory activity.[16] Azab et al. determined the normal range of NLR to be between 1.7 and 2.28 in their study with 9427 individuals, while Aydın et al. from Turkey determined the normal range to be between 1.0 and 2.3.[17,18] In our study, we found that NLR was significantly higher in patients with severe esophageal injury and hospitalized patients compared to the others. Furthermore, we demonstrated that an NLR over 2.1 could be used to predict hospitalization with 77.7% sensitivity and 77.7% specificity, and an NLR of 2.3 could be used to predict severe esophageal injury with 76.2% sensitivity and 85.4% specificity.

MLR has gained interest as a biomarker. As a new, inexpensive, and readily available inflammatory and infectious biomarker, MLR has been shown to be applicable in predicting and prognosticating various inflammatory diseases. MLR reflects the balance of change between innate and adaptive immunity and provides a simple indicator of immune status and inflammation level.[19-21] To the best of our knowledge, no studies have reported on the predictive value of MLR for the severity of esophageal injury in patients with CSI. In our study, we found that MLR was significantly higher in patients with severe esophageal injury and hospitalized patients compared to the others. In addition, we demonstrated that MLR values above 0.26, as determined by the ROC curve, can predict hospitalization with 77.3% sensitivity and 77.1% specificity, and predict severe esophageal injury with 81.2% sensitivity and 69.4% specificity.

PLT, which can be easily and promptly evaluated upon admission in most clinical settings, was significantly decreased in hospitalized patients, although there was no thrombocytopenia in our study. There is now a large body of evidence showing that platelets play a central role in inflammatory reactions. Moreover, in some studies, thrombocytopenia has been associated with increased mortality, highlighting the beneficial roles of platelets in inflammation.[22] The measurement of platelets upon admission to the emergency room may be one of the most accurate and convenient parameters for precisely assessing the prognosis of patients with caustic injury.

Regarding the relationship between age and the severity of esophageal injury, the literature presents conflicting results. In our study, we found that patients with severe esophageal injury and hospitalized patients were older than the others.[10,23] Based on this finding, we can predict that older patients may develop more severe esophageal injury.

It is important to acknowledge certain limitations of our study, including its retrospective design and

relatively limited sample size. We could not analyze some contributing factors such as the specific caustic substances ingested. However, this study is the first one in the literature to demonstrate the correlation between NLR and MLR values and the severity of esophageal injury.

Conclusions

Although EGD is considered the gold standard for determining the severity of esophageal injury, it has several disadvantages as previously mentioned. Therefore, the necessity of endoscopy in patients with caustic substance ingestion is still controversial, and there is no definitive recommendation. Our study highlights the potential of NLR and MLR as valuable and easily accessible diagnostic markers for predicting the severity of esophageal injury in patients with CSI. By incorporating these markers into clinical practice, healthcare providers may be able to better assess the extent of injury, guide treatment decisions, and improve patient outcomes. Further research is needed to fully elucidate the mechanisms underlying the associations observed in this study and to validate our findings in larger, prospective cohorts.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely collected and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed. The Research Ethics Board of the Research Institute of the Tokat Gaziosmanpasa University Faculty of Medicine approved the study (study code 23-KAEK-276), which was conducted 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 or creation of the content of this manuscript.

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ARTÍCULO ORIGINAL

Retraso en la referencia y el tratamiento por cáncer de mama en un hospital oncológico de tercer nivel del IMSS, 2019-2020

Referral and treatment delay for breast cancer treated at a third level oncology hospital of IMSS, 2019-2020

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Resumen

Objetivo: *Comparar el retraso en la referencia (Rref) y el retraso en el tratamiento (Rtx) de las trabajadoras con cáncer de mama (CaMa) tratadas en un hospital oncológico de tercer nivel (HOnco) en 2019 y 2020.* **Métodos:** *Se realizó un estudio de cohorte retrospectivo en trabajadoras con diagnóstico de CaMa que acudieron al HOnco en 2019 y 2020. El Rref y el Rtx se definieron como los días transcurridos desde la consulta de sospecha hasta el envío al HOnco y de este al inicio del tratamiento. Para comparar las variables se usaron χ^2 y U de Mann-Whitney, con $p \leq 0.05$.* **Resultados:** *En un total de 542 casos, el Rref fue de 21 días y el Rtx de 35 días. Al comparar 2019 y 2020 se encontraron diferencias significativas en Rref (17 vs. 24 días), estadio avanzado (32.2% vs. 51%) y atención privada previa (14.5% vs. 38.8%).* **Conclusiones:** *El Rref por CaMa fue significativamente mayor en el año 2020.*

Palabras clave: *Cáncer de mama. Retraso de referencia. Retraso de tratamiento. Incapacidad temporal para el trabajo.*

Abstract

Objective: *To compare the referral delay (Dref) and the treatment delay (Dtx) of workers with breast cancer (BrCa) treated at a third level oncology hospital (HOnco) in 2019 and 2020.* **Methods:** *A retrospective cohort study was carried out in workers who attended the HOnco in 2019 and 2020 diagnosed with BrCa. Both, the Dref and the Dtx were defined as the elapsed days from suspicion consultation until the referral to HOnco and from this to the beginning of treatment. The data was gathered from the clinical file. In order to compare the variables, χ^2 and U Mann y Whitney were used with $p \leq 0.05$.* **Results***: With a total of 542 cases, the Dref was 21 days and the Dtx was 35 days. When comparing 2019 and 2020, significant differences were found in the Dref (17 vs. 24 days) advanced stage (32.2% vs. 51%) and primary private care (14.5% vs. 38.8%).* **Conclusions***: Dref for BrCa was significantly higher for 2020.*

Keywords: *Breast cancer. Referral delay. Treatment delay. Temporary disability.*

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Introducción

El cáncer es uno de los mayores retos de salud pública. El cáncer de mama (CaMa) tiene una incidencia mundial de 47.8 por 100,000 habitantes y una mortalidad de 13.6 por 100,000 habitantes.[1] La supervivencia en las poblaciones altamente desarrolladas llega a ser del 75-90%, y en los países con un menor desarrollo es del 47-76%.[2] En América Latina es más frecuente en las mujeres de 40 a 75 años.[3] El Instituto Mexicano del Seguro Social (IMSS) reporta que las pacientes con CaMa se encuentran en estadios III y IV en el 57.5% de los casos.[4]

Atención medica en el IMSS

El IMSS se divide en tres niveles la atención médica: el primero con atención médica integral y continua al paciente, el segundo para recibir atención diagnóstica, terapéutica o de rehabilitación según su padecimiento, y el tercero con unidades médicas de alta especialidad, con capacidad de tecnología y máxima resolución diagnóstica y terapéutica.[5] El sistema de referencia-contrarreferencia se creó para facilitar la canalización de los pacientes entre los niveles de atención, disminuyendo el periodo de espera y los trámites administrativos.[6]

Cerca del 40% de las mujeres diagnosticadas con CaMa se encuentran en edad laboral productiva; de ellas, cerca del 80% son asalariadas[7] y la prescripción de la incapacidad temporal para el trabajo (ITT) forma parte del tratamiento de las aseguradas. En 2016, Campos Raymundo[8] reportó hasta 504 días de ITT por CaMa en el HOnco.

Tipos de retraso para la atención de los padecimientos oncológicos

Diversos artículos publicados describen el problema del retraso en la atención por cáncer, diferenciando según el lugar donde se origina el retraso:

- Retraso por el paciente: periodo durante el cual el paciente presenta síntomas, pero no acude a revisión médica.
- Retraso de referencia (Rref): periodo durante el cual el médico de primer contacto realiza el envío con el médico especialista.
- Retraso médico: periodo durante el cual el personal de salud no tiene un diagnóstico certero de la enfermedad del paciente.
- Retraso de tratamiento (Rtx): periodo durante el cual el paciente espera desde su consulta con el médico especialista hasta iniciar su tratamiento definitivo oncológico.
- Retraso por el sistema de salud: periodo durante el cual los procesos y procedimientos del sistema causan un retraso para que el paciente tenga un tratamiento oncológico.[9]

El objetivo del estudio fue comparar el Rref y el Rtx de las trabajadoras con CaMa tratadas en un HOnco en 2019 y 2020.

Métodos

Se realizó un estudio cohorte retrospectivo analítico, durante el periodo de enero de 2019 a diciembre de 2020, en mujeres con diagnóstico de CaMa en el HOnco. Se efectúo una revisión de registros en ese periodo de estudio de pacientes con dicho diagnóstico y que además tuvieran en el número de seguridad social el agregado 1F, que generalmente son mujeres que se encuentran en la categoría de trabajadoras, excluyendo aquellas estudiantes o que al verificarlo no fueran trabajadoras. Se procedió a la búsqueda de los formatos de envío de las unidades al HOnco, conocidos como «hojas de referencias», y se eliminaron aquellas con atención en otra unidad de tercer nivel y que solo acudían para tratamiento complementario al HOnco. Se realizó el cálculo de días de Rref desde la fecha de envío hasta la fecha de primera consulta en el HOnco, y para el Rtx desde esta última fecha hasta la fecha del primer día que se recibió el tratamiento. Durante estos periodos de espera de las pacientes se buscó información sobre la ITT en un sistema único de subsidios y ayudas. En el expediente clínico se buscaron otros datos, como edad, estadio clínico, diagnóstico histopatológico, atención médica en medio privado y tipos de tratamiento recibidos. Para las variables cuantitativas se aplicó Kolmogórov-Smirnov como prueba de normalidad, con resultado de una distribución no normal, y estos datos se reportaron como mediana y rango intercuartilar 25 a 75 (RIC_{25-75}). Las variables cualitativas se expresaron como frecuencia y porcentaje. Se realizaron pruebas de hipótesis para dos variables cuantitativas con U de Mann-Whitney y pruebas de hipótesis para dos

variables cualitativas con χ^2. Se consideró un resultado significativo contar con valor $p < 0.05$.

Resultados

Se incluyeron 542 mujeres trabajadoras con CaMa, con una mediana de edad de 47 años (RIC_{25-75}: 41-54). El diagnóstico histológico más frecuente fue carcinoma ductal en 465 (86.2%). El estadio clínico IIA se reportó en 154 (28.4%) como el más frecuente, seguido por el IIB en 103 (19%). Se identificó que el 72.8% de las pacientes recibieron atención por CaMa en alguna otra unidad del IMSS antes de llegar al HOnco, y el 25.5% recibieron alguna atención en un medio privado. Dentro de los datos de ITT, 264 (48.7%) de las aseguradas contaban con una incapacidad previa a su primera consulta en el HOnco, y el rango de días otorgados fue hasta por 18 días; cuando la paciente inicia tratamiento aumenta el número de casos de ITT a 508 (93.7%), con una mediana de 9 días (RIC_{25-75}: 2-28). El tratamiento que recibieron al llegar a HOnco fue en 228 (42%) radioterapia, en 170 (31.4%) tratamiento médico y en 144 (26.6%) tratamiento quirúrgico.

La medida de días desde la referencia hasta la primera consulta en el HOnco fue de 21 días (RIC_{25-75}: 12-34). La mediana de días transcurridos desde la primera consulta en el HOnco hasta el inicio de alguno de los tratamientos fue de 35 días (RIC_{25-75}: 18.7-65.7) (Tabla 1).

Al comparar los años 2019 y 2020, este último en plena pandemia de COVID-19, se identificó que en 2019 la mediana de días de Rref fue de 17 días (RIC_{25-75}: 9-31) y en 2020 fue de 24 días (RIC_{25-75}: 16-37; $p = 0.000$). Las trabajadoras con ITT en el año 2019 fueron 147 (43.5%) y en el año 2020 fueron 117 (47.8%; $p = 0.687$). Los días de ITT otorgados durante el periodo de Rref fueron similares en los dos años (RIC_{25-75}: 0-18 días para 2019 y 0-17 días para 2020; $p = 0.626$) (Tabla 2).

La mediana de días transcurridos desde la primera consulta en el HOnco hasta el inicio del tratamiento fue de 37 días (RIC_{25-75}: 19-67) en 2019 y 35 días (RIC_{25-75}: 19-64; $p = 0.570$) en 2020. Los días de ITT otorgados a las trabajadoras durante el periodo de Rtx fue de 7 días (RIC_{25-75}: 2-28) en 2019 y 11 días (RIC_{25-75}: 3-28; $p = 0.011$) en 2020.

En cuanto a los días de Rtx por tipo de tratamiento, se observa que la diferencia más marcada estuvo en las pacientes que recibieron quimioterapia, ya que en 2020 casi se duplicó el tiempo de espera (20 vs. 32 días); no así para radioterapia, pues el tiempo fue mayor en 2019 (60 vs. 49 días; $p < 0.000$) (Tabla 3).

Los casos se agruparon en estadios tempranos (I, IIA y IIB,) y avanzados (IIIA, IIIB, IIIC y IV). En 2019, los estadios avanzados fueron 96 (32.3%), y en 2020 fueron 125 (51%; $p = 0.000$). Para los días de ITT en estadios tempranos se encontró un RIC_{25-75} de 0-12

Tabla 1. Datos sociodemográficos, clínicos y de referencia de las pacientes con cáncer de mama

Variables	n (% o RIC)
Total	542
Edad, años	47 (41-54)
Año del diagnóstico de cáncer de mama	2019 = 297 (54.8)
	2020 = 245 (45.2)
Diagnóstico histológico	
Carcinoma ductal	467 (86.2)
Carcinoma lobulillar *in situ*	29 (5.4)
Carcinoma lobulillar	28 (5.2)
Carcinoma mucinoso	6 (1.1)
Carcinoma papilar	5 (0.9)
Carcinoma medular	3 (0.6)
Carcinoma metaplásico	2 (0.4)
Carcinoma intraductal *in situ*	1 (0.2)
Carcinoma tubular	1 (0.2)
Estadio clínico	
I	64 (11.8)
IIA	154 (28.4)
IIB	103 (19.0)
IIIA	94 (17.3)
IIIB	61 (11.3)
IIIC	24 (4.4)
IV	42 (7.7)
Tratamiento que recibió en HOnco	
Tratamiento quirúrgico	144 (26.6)
Tratamiento médico	170 (31.4)
Radioterapia	228 (42)
Atención previa a su referencia	
IMSS	395 (72.8)
Servicio privado	138 (25.5)
Secretaría de salud	6 (1.1)
Otro	3 (0.6)
Retraso de referencia, días	21 (12-34)
Retraso de tratamiento, días	35 (18.7-65.2)
ITT durante el retraso de referencia	
Sí	264 (48.7)
No	278 (51.3)
ITT durante el retraso de tratamiento	
Sí	508 (93.7)
No	34 (6.3)

HOnco: hospital oncológico de tercer nivel; IMSS: Instituto Mexicano del Seguro Social; ITT: incapacidad temporal para el trabajo; RIC: rango intercuartilar.

Tabla 2. Retraso de referencia y antecedente de incapacidad temporal para el trabajo en 2019 y 2020

Variables	2019	2020	p
Retraso de referencia, días	17 (RIC_{25-75}: 9-31)	24 (RIC_{25-75}: 16-37)	0.000
ITT durante el retraso de referencia			
Sí	147 (43.5%)	117 (47.8%)	0.687
No	150 (56.5%)	128 (52.2%)	
Tiempo de ITT durante el retraso de referencia, días	0 (RIC_{25-75}: 0-18.5)	0 (RIC_{25-75}: 0-17)	0.626

ITT: incapacidad temporal para el trabajo; RIC: rango intercuartilar.

Tabla 3. Retraso de tratamiento y antecedente de incapacidad temporal para el trabajo en 2019 y 2020

Variables	2019	2020	p
Retraso de tratamiento, días	37 (RIC_{25-75}: 19-67)	35 (RIC_{25-75}: 19-64)	0.570
ITT durante el retraso de tratamiento			0.045
Sí	284 (95.6%)	224 (91.4%)	
No	13 (4.4%)	21 (8.6%)	
Tiempo de ITT durante el retraso de tratamiento, días	7 (RIC_{25-75}: 2-28)	11 (RIC_{25-75}: 3-28)	0.011
Tiempo de tratamiento, días			0.00
Quirúrgico	49 (RIC_{25-75}: 30-70)	60 (RIC_{25-75}: 14-46)	
Médico	20 (RIC_{25-75}: 23-88)	32 (RIC_{25-75}: 20-87)	
Radioterapia	49 (RIC_{25-75}: 10-37)	33 (RIC_{25-75}: 20-51)	

ITT: incapacidad temporal para el trabajo; RIC: rango intercuartilar.

Tabla 4. Comparación de la atención por cáncer de mama en 2019 y 2020

Variables	2019	2020	p
Estadios clínicos, n (%)			0.000
Temprano	201 (67.7)	120 (49)	
Avanzado	96 (32.3)	125 (51)	
Atención previa, n (%)			0.00
Servicio médico privado	43 (14.5)	95 (38.8)	
IMSS e instituciones públicas	254 (85.5)	150 (61.2)	

IMSS: Instituto Mexicano del Seguro Social.

días y en un estadio tardío de 0-24 días (p = 0.000). Se categorizó según la atención medica que se recibió previo a su referencia en dos grupos; en el servicio privado, en el año 2019 fueron 43 (14.5%) casos y en el año 2020 fueron 95 (38.8%) casos (p = 0.000) (Tabla 4).

Discusión

Las características generales del cáncer son concordantes con la literatura mundial. El principal diagnóstico histológico, según Barraga-Ruiz et al.[3], es el carcinoma ductal, del cual encontramos una frecuencia del 86.2%. La etapa clínica más frecuente es IIA en los dos años, con el 28.4%, considerando que el hospital es de tercer nivel.

La edad reportada en la literatura nacional es de 40 a 75 años. El rango de edad de las trabajadoras de este análisis se encuentra en 41 a 54 años, con un mínimo de 18 y máximo de 77 años.[3]

El tiempo de Rref fue de 21 días, lo cual sobrepasa los días de oportunidad de referencia para el tratamiento mencionados en la NOM-041-SSA1-2011,[10] que indica que debe ser de 10 días. Encontramos que fue mayor en el año 2020, lo que podría deberse a la diferencia de atención medica durante ese año por la contingencia sanitaria de la COVID-19, ya que la atención medica recibida por las pacientes en alguna unidad del IMSS fue de hasta un 72.8%; sin embargo, en el año 2019 la atención médica en el servicio médico privado fue del 14.5% y en el año 2020 fue de hasta el 38.8%. Al realizar la prueba de Spearman encontramos una correlación positiva y significativa entre el Rref y la etapa clínica, pero no así para el tipo de atención con la etapa clínica o el Rref. Los factores que influyeron para identificar etapas clínicas más avanzadas entre los dos años no fueron un objetivo planteado en el estudio, pero podría abordarse en otras investigaciones. Al comparar el Rref con lo reportado por Allgar y Neal[9], quienes realizaron un cuestionario en Inglaterra a pacientes con diversos tipos de cáncer, entre ellos CaMa, encontrando 13.2 días, aún este valor está por arriba de lo establecido en la NOM-041-SSA1-2011, por lo que sería importante reconsiderar estos puntos de cohorte para establecer la oportunidad de la referencia por esta enfermedad, generando indicadores reales que guíen los esfuerzos de las instituciones a reducirlos al mínimo en beneficio de la salud de las pacientes con CaMa.

En los estadios clínicos de CaMa recibidos en el HOnco, en el año 2019 se observó un mayor porcentaje de pacientes en estadios tempranos, con un 83.5%, y un 16.5% en estadios avanzados, y en el año 2020 fueron un 68.2% y un 31.8%, respectivamente. Tal como mencionan Vanni et al.[11] en un

estudio transversal en el que aplicaron un cuestionario a pacientes de Roma con CaMa, las pacientes en aislamiento presentaron ganglio centinela con más frecuencia que las del año previo, y esto tendrá repercusiones a largo plazo. También Maringe et al.[12], quienes recolectaron información de expedientes médicos y compararon los datos prepandémicos con los datos durante la pandemia, refieren que habrá un incremento de muertes por año por diagnóstico de cáncer. El estadio clínico de la enfermedad también desempeñó un papel importante para la incapacidad, pues se reportó un mayor número de días de ITT en las pacientes con estadios avanzados.

La atención medica recibida por las pacientes fue en alguna unidad del IMSS hasta en un 72.8%; sin embargo, en el año 2019 la atención médica en el servicio médico fue del 14.5% y en el año 2020 fue hasta del 38.8% de las aseguradas, teniendo un importante papel en el diagnóstico.

El Rtx tuvo una mediana de 35 días, y la NOM-041-SSA1-2011 menciona que deben ser menos de 15 días para iniciar el tratamiento en un centro oncológico[10]. El tiempo de ITT durante la espera de recibir algún tratamiento fue de 8 días en el año 2019 y de 16 días en el año 2020, una diferencia con significancia estadística. El número de días que exceden a la Norma tiene repercusión en la prescripción de la incapacidad y, por ende, en el costo. Un estudio realizado por el Instituto Nacional de Cancerología en el año 2012 por medio de un cuestionario aplicado a las pacientes reportó un Rtx de 141 días; no así en este estudio, ya que los datos fueron obtenidos de las fuentes primarias, evitando el riesgo de sesgo de memoria y de medición.[13]

El tiempo de Rtx varió según el tipo de tratamiento. Para el tratamiento médico (quimioterapia) fue de 28 días de mediana; se encontró en las diversas notas médicas una demora en la realización de la interconsulta por el servicio de tumores de mama. El servicio de radioterapia tuvo una mediana de 33 días, y en la revisión del expediente clínico se encontró que aquellas pacientes referenciadas del segundo nivel aún tenían algún ciclo de quimioterapia pendiente, retrasando su inicio de radioterapia, así como que la gran cantidad de pacientes que acuden a esta unidad solo a radioterapia hacía más larga la espera para el inicio del tratamiento. El Rtx quirúrgico tuvo una mediana de 51 días; los procedimientos se veían afectados por la realización de estudios como revisión de laminillas, expresión de genotipo y estudios de laboratorio y gabinete. La comparación entre 2019 y 2020 evidenció un incremento en los días para el tratamiento médico y para el tratamiento quirúrgico. Papautsky y Hamlish[14] realizaron un cuestionario a pacientes y encontraron que el 30% percibieron un retraso en la atención terapéutica.

El tiempo de ITT tuvo una mediana de 9 días para tratamiento médico y de 14 días para radioterapia, esto por efectos del tratamiento más que por la etapa clínica.

Entre las limitaciones del estudio cabe señalar el tipo de población incluida, pues al ser pacientes consideradas como trabajadoras activas es probable que haya diferencias importantes con el resto de las pacientes con CaMa, principalmente en la variable analizada sobre la atención previa en un medio privado, por ser un grupo que pudo solventar esta necesidad por sus propios medios, sobre todo en el año 2020, cuando podemos considerar que el temor a ser contagiadas de COVID-19 las condujo a dirigirse a lugares privados y poco concurridos. De igual manera, al ser un hospital de tercer nivel se limita la validez externa.

Conclusiones

El CaMa es una enfermedad en la que el diagnóstico oportuno es la mejor manera para disminuir la mortalidad, y por ello la realización de un mayor número de estudios de tamizaje debe priorizarse en el primer nivel de atención. El Rref y el Rtx son mayores que los reportados en otros países y sobrepasan los días referidos en la normatividad. Para el año 2020 se encontró el mayor rezago, dejando para los siguientes años una gran carga de trabajo en los diversos servicios oncológicos, tanto para este cáncer como probablemente para el resto de los cánceres. Los resultados apuntan a que se deben reforzar las estrategias para mejorar la atención de las pacientes con CaMa, acortando el tiempo de espera para la consulta con el especialista en oncología y el tiempo para la realización de estudios complementarios del diagnóstico necesarios para la toma de decisiones terapéuticas. Esto también tendrá un efecto en la disminución de los días de ITT, otorgando a las trabajadoras una mayor oportunidad de reincorporación laboral.

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Conflicto de intereses

Los autores declaran no tener conflicto de intereses con respecto a la investigación ni la publicación de este artículo.

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, de acuerdo con la Asociación Médica Mundial y la Declaración de Helsinki. Los procedimientos fueron autorizados por el Comité de Ética de la institución.

Confidencialidad, consentimiento informado y aprobación ética. Los autores han obtenido la aprobación del Comité de Ética para el análisis de datos clínicos obtenidos de forma rutinaria y anonimizados. Debido a la naturaleza del estudio, no fue necesario el consentimiento informado individual. Se han seguido las recomendaciones éticas pertinentes.

Declaración sobre el uso de inteligencia artificial. Los autores declaran que no se utilizó ningún tipo de inteligencia artificial generativa para la redacción ni la creación de contenido de este manuscrito.

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ORIGINAL ARTICLE

Liver transplant program outcomes at a Colombian center: 14 years of experience

Resultados del programa de trasplante de hígado en un centro colombiano: 14 años de experiencia

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Abstract

Objectives: *The objective of the study was to analyze outcomes of a liver transplant program over 14 years and evaluate associations between patient characteristics, surgical factors, complications, and mortality.* **Methods:** *A retrospective cohort study was conducted at a transplant center, including patients from 2011 to 2025. Descriptive statistics, X^2, Mann–Whitney U tests, and multivariate logistic regression were used to identify mortality predictors. Kaplan-Meier survival analysis was also performed.* **Results:** *The study included 109 liver transplant recipients. Rejection rates were higher among deceased patients (30.3% vs. 13.2%, p = 0.034). One-year survival improved from 63.3% (2011-2014) to 89.1% (2023-2025), with 100% rejection-free survival in the most recent cohort. Complications like multi-organ failure, bronchopneumonia, acute renal failure, ventilatory failure with coma, and leukoencephalopathy significantly increased mortality risk (odds ratio 4.27, p = 0.002).* **Conclusions:** *One-year survival has improved, with reduced rejection rates reflecting better post-transplant care. However, complications remain a major mortality risk. Shorter ischemia times indicate optimized surgical and logistical procedures.*

Keywords: *Liver transplantation. Mortality. Survival. Complications. Graft rejection. Tissue donors.*

Resumen

Objetivos: *Analizar los resultados de un programa de trasplante hepático durante 14 años y evaluar la relación entre las características del paciente, los factores quirúrgicos, las complicaciones y la mortalidad.* **Métodos:** *Estudio de cohorte retrospectivo en un centro de trasplantes, incluyendo pacientes entre 2011 y 2025. Se usaron estadísticas descriptivas con pruebas χ^2 y U de Mann-Whitney para identificar predictores de mortalidad. Se aplicó análisis de supervivencia de Kaplan-Meier.* **Resultados:** *Se incluyeron 109 receptores. El rechazo fue mayor en los fallecidos (30.3% vs. 13.2%; p = 0.034). La supervivencia al año mejoró del 63.3% (2011-2014) al 89.1% (2023-2025), con un 100% de supervivencia libre de rechazo en la cohorte más reciente. Las complicaciones como falla multiorgánica, bronconeumonía, insuficiencia renal aguda y falla*

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ventilatoria con coma aumentaron el riesgo de mortalidad (OR: 4.27; p = 0.002). **Conclusiones:** *La supervivencia al año ha mejorado y la reducción del rechazo refleja un mejor cuidado postrasplante. Sin embargo, las complicaciones siguen siendo clave en la mortalidad. Los tiempos de isquemia más cortos indican optimización quirúrgica y logística.*

Palabras clave: *Trasplante hepático. Mortalidad. Supervivencia. Complicaciones. Rechazo del injerto. Donantes.*

Introduction

Liver transplantation has become a crucial therapeutic intervention for patients with end-stage liver disease, significantly improving survival rates and quality of life.[1] Worldwide, it is estimated that more than 41,000 people received a liver transplant in 2023, with the American region being the location with the highest number of procedures (around 35%).[2] Since the first transplant in 1963, the procedure has evolved considerably in both surgical techniques and post-operative management.[3] However, it remains a complex intervention with a high risk of complications. At present, patient survival rates at 1, 3, and 5 years are approximately 91.8%, 83.8%, and 76.1%, respectively.[4,5] In Colombia, despite the implementation of this intervention more than four decades ago,[6] challenges persist, including donor availability, access to immunosuppressive therapies, and the management of post-operative complications.[7]

In Colombia, organ donation and transplantation are regulated by a legal framework aimed at ensuring organ availability and improving access to transplants. The legislation follows the principle of presumed consent, meaning individuals are considered donors unless they explicitly choose otherwise. To optimize the donation process, strategies such as awareness campaigns, strengthening the transplant network, and enhancing organ procurement logistics have been implemented.[8] However, liver donation remains a significant challenge due to multiple barriers faced by medical personnel, including insufficient training in brain death certification, difficulties in communicating with families, and limitations in hospital infrastructure. These factors negatively impact donation rates, making it essential to address them from the healthcare team's perspective to enhance access to liver transplantation and improve care for patients on the waiting list.[9]

The long-term success of this intervention largely depends on the appropriate use of immunosuppressive therapies, which prevent graft rejection and improve patient survival. Various immunosuppression protocols combine drugs such as calcineurin inhibitors, antimetabolites, and corticosteroids, each with specific mechanisms of action aimed at modulating the immune response. The selection of an immunosuppressive regimen should be based on multiple factors, including recipient characteristics, rejection risk, and the presence of comorbidities, highlighting the importance of an individualized approach to post-transplant management.[10]

Common complications after liver transplantation include infections, acute graft rejection, renal dysfunction, biliary stenosis, and pulmonary or neurological disorders.[11] Bacterial infections, particularly in the immediate post-operative period, are a major cause of morbidity. Acute rejection usually occurs within the 1st few weeks and requires prompt treatment to preserve graft function. Renal dysfunction is often linked to nephrotoxic immunosuppressants and intraoperative hemodynamic fluctuations. Biliary stenosis, affecting around 13% of recipients, is one of the most significant complications.[12,13] Neurological complications, though less common, range from mild manifestations to potentially life-threatening conditions, reflecting their multifactorial etiology. Given these challenges, this study aims to analyze the key outcomes of a liver transplant program over 14 years in Colombia, identifying the association between patient characteristics, surgical factors, post-operative complications, and mortality after transplantation.

Methods

A retrospective cohort study was conducted at a high-complexity institution, including patients who underwent liver transplantation between May 2011 and March 2025. The study was carried out at a liver transplant center of excellence, supported by a multidisciplinary team of hepatologists, internists, hepatobiliary surgeons, nurses, nutritionists, psychologists, social workers, psychiatrists, anesthesiologists, and nephrologists. Post-transplant follow-up was structured to ensure close monitoring and timely interventions. During the 1st month, patients were evaluated weekly, followed by biweekly assessments if recovery progressed favorably. Subsequently, follow-up visits

were scheduled monthly, then every 3 months, and eventually every 5 months as the post-transplant period lengthened. In cases of liver function abnormalities or immunosuppression imbalances, weekly assessments continued until stabilization was achieved.

Participants

The liver transplantation program includes patients who meet the Milan criteria, which specify that candidates must have either a single liver tumor measuring < 5 cm in diameter or 2-3 tumors, each measuring < 3 cm at the time of diagnosis.[14,15] For this study, all patients enrolled in the liver transplantation program were included in the study. In addition to liver cancer cases that meet these criteria, the program also accommodates patients with other liver diseases requiring transplantation, such as cirrhosis of various etiologies (including viral hepatitis B and C, alcoholic liver disease, metabolic disorders, primary and secondary biliary cirrhosis, and autoimmune hepatitis), polycystic liver disease with associated symptoms and deterioration of quality of life, acute or fulminant hepatitis, and primary biliary cirrhosis in non-cirrhotic patients who experience significant quality of life impairment. Patients < 13 years and those with liver cancer who did not meet Milan criteria were excluded. Participant selection was based on a registry from the liver transplantation center of excellence, following a consecutive selection process to verify eligibility.

Variables

Sociodemographic variables included age (years); sex (male or female); type of social security (contributory, subsidized, particular and other); educational level (primary, secondary, technical, professional, postgraduate and no information); marital status (single, married, separated, widowed, common law union, not disclosed); area of residence (rural or urban); and occupation (homemaker, unemployed, Business person, employee, Independient, others, Disability pensioner).

Clinical variables as personal history, including alcohol consumption (daily consumption: more than seven drinks per week; occasional consumption: less than once per week; weekly consumption: 1-7 drinks per week; does not consume), smoking history (former smoker: quit more than 6 months ago; never smoked; current smoker), diabetes (including whether insulin-dependent), dyslipidemia, obesity, history of hepatitis (A, B, C, or unspecified), heart failure, acute myocardial infarction, and cirrhosis. Family history, including liver cancer, pancreatic cancer, and other types of cancer were also measured.

Variables related to the procedure's characteristics were collected, such as ischemia times (cold and warm), transplant classification (adult or pediatric), donor type (living or deceased), and transplant outcomes such as the need for re-transplantation. Regarding complications, rejection occurrence was assessed and classified as acute, chronic, along with its potential causes, including treatment adherence, administrative factors related to insurance, subtherapeutic drug levels, or other causes. Biliary complications were also analyzed, specifically strictures, bile leaks, and other related issues.

In addition, complications were considered, including the necessity for surgical reintervention. These were categorized based on temporal occurrence, distinguishing between reintervention due to hemorrhage within the initial 48 h and reintervention within the 1st month. Furthermore, other observed complications encompassed multi-organ failure, unspecified bronchopneumonia, acute renal failure, ventilatory failure with coma, leukoencephalopathy, and acute myocardial infarction. Post-operative complications were additionally classified using the Clavien-Dindo classification, which standardizes the assessment of surgical adverse event severity.[16] The primary outcome measure was all-cause mortality following liver transplantation, assessed both during hospitalization and throughout the follow-up period. Mortality was ascertained through institutional medical records and follow-up telephone communications, conducted as part of the liver transplant program's ongoing surveillance. To determine mortality, hospital records and updated medical histories were reviewed at each follow-up visit.

Data sources

The information was obtained from medical records, including surgical notes, progress notes, and outpatient consultations documented by healthcare personnel. These data are stored in the transplant center of excellence's database, maintained on the research electronic data capture platform under project PID 690.[17,18] To minimize information bias and ensure data quality, strategies such as double data entry, cross-validation of records, and training of personnel responsible for data extraction were implemented.

Statistical analysis

The descriptive analysis was performed first, assessing normality using the Kolmogorov-Smirnov test. The median was calculated, along with the interquartile ranges. Categorical variables were presented as frequencies and percentages. A bivariate analysis was conducted using mortality as the outcome variable, applying the X^2 test for categorical variables, and the Mann-Whitney U test for those continuous without a normal distribution. A multivariate logistic regression model was developed to identify independent predictors of mortality. Variable selection followed a backward elimination approach, initially including factors with a $p < 0.25$. Only variables with a $p < 0.05$ were retained in the final analysis. Model fit was assessed using the Hosmer-Lemeshow test and the pseudo R^2 statistic.

Furthermore, a survival analysis was performed using the Kaplan-Meier estimator to evaluate the probability of developing complications over time (mortality, graft rejection, biliary and vascular complications). Survival data of liver transplant patients were analyzed across four different periods: 2011-2014, 2015-2018, 2019-2022, and 2023-2025. Comparisons between these periods were performed using the log-rank test to assess differences in survival distributions. All analyses were conducted using RStudio software and Stata version 16 (StataCorp, College Station, TX, USA).

Results

A total of 109 patients who underwent liver transplantation were analyzed, of whom 76 (67%) survived, and 33 (33%) died, mostly of men (63.3%) with a global median of age of 53 years (range: 42-63). Most patients are affiliated with the contributory health insurance system (60.6%), followed by the subsidized system (33.9%). Regarding education, the majority completed primary or secondary school (31.2% each), while 21.1% have professional, technical (9.17%), or postgraduate education (0.91%), 41.3% were married, and 89.9% live in urban areas (Table 1).

In the bivariate analysis, the mean age was significantly higher in patients who died during the follow-up after liver transplantation compared to those who survived (59 vs. 51.5; $p = 0.031$). A higher proportion of surviving patients were affiliated with the subsidized healthcare regime (36.8%) compared to those who died (27.7%; $p = 0.031$). In addition, a greater proportion of surviving patients had secondary or technical education compared to those who died (51.2% vs. 15.1%, respectively; $p < 0.001$) (Table 1).

When evaluating the personal and family history of patients with liver transplant, alcohol consumption was reported by 49.54%, while 78.89% had never smoked. Diabetes (22.94%), obesity (11.01%), and

Table 1. Sociodemographic characteristics of patients with liver transplant

Variable	Alive	Deceased	Total	p
	n = 76 (%)	n = 33 (%)	n = 109 (%)	
Sex				
Female	29 (38.1)	11 (33.3)	40 (36.7)	0.631
Male	47 (61.8)	22 (66.6)	69 (63.3)	
Age*	51.5 (40.5-60.0)	59 (47-63)	53 (42-63)	0.031
Type of security and social				
Contributory	45 (59.2)	21 (63.6)	66 (60.6)	0.031
Subsidized insurance	28 (36.8)	9 (27.7)	37 (33.9)	
Particular	3 (3.95)	0 (0.00)	3 (2.75)	
Other	0 (0.00)	3 (9.09)	3 (2.75)	
Level of education				
Primary	22 (28.9)	12 (31.1)	34 (31.2)	< 0.001
Secondary	30 (39.4)	4 (12.1)	34 (31.2)	
Technical	9 (11.8)	1 (3.03)	10 (9.17)	
Professional	15 (19.7)	8 (24.2)	23 (21.1)	
Postgraduate	0 (0.00)	1 (3.03)	1 (0.91)	
No information	0 (0.00)	7 (6.42)	7 (6.42)	
Marital status				
Single	22 (28.5)	5 (15.1)	27 (24.8)	0.386
Married	27 (35.3)	18 (54.5)	45 (41.3)	
Separated	4 (5.26)	1 (3.03)	5 (4.59)	
Widowed	2 (2.63)	2 (6.06)	4 (3.67)	
Common law union	19 (25.0)	6 (18.1)	25 (22.9)	
Not disclosed	2 (2.63)	1 (3.03)	3 (2.75)	
Area of residence				
Rural	9 (11.8)	2 (6.06)	11 (10.1)	0.357
Urban	67 (88.1)	31 (93.4)	98 (89.9)	
Occupation				
Home	21 (27.6)	10 (30.3)	31 (28.4)	0.535
Unemployed	6 (7.89)	1 (3.03)	7 (6.42)	
Business person	8 (10.53)	2 (6.06)	10 (9.17)	
Employee	12 (15.7)	3 (9.09)	15 (13.8)	
Independient	14 (18.4)	8 (24.4)	22 (20.2)	
Others	15 (19.7)	8 (24.4)	23 (21.1)	
Disability pensioner	0 (0.00)	1 (3.03)	1 (0.91)	

*Median. IQR: interquartile range.

cirrhosis (49.54%) were common, with no significant differences between groups. Notably, Hepatitis B was more frequent in survivors (15.79% vs. 3.03%; p = 0.050). Other comorbidities, including heart failure and dyslipidemia, were only present in patients who did not survive (Table 2).

In the analysis of clinical outcomes and post-transplant complications, the median total ischemia time was 393 min (321-515), with cold ischemia at 343 min (280-440) and warm ischemia at 60 min (50-67), showing no significant differences between groups. All transplants were from deceased donors, and 8.26% of patients required re-transplantation. A significantly higher occurrence of rejection was observed in deceased patients (30.30%) compared to survivors (13.15%) (p = 0.034). Other post-transplant complications were significantly more common in deceased patients (45.45%) compared to survivors (17.10%) (p < 0.001). Reintervention percentages due to bleeding (11.92%), post-operative bleeding at 48 h (11.01%), and re-intervention within the 1st month (27.78%) were higher in deceased patients (33.33%), but without significant differences between groups (Table 3). Similarly, according to the Clavien-Dindo, the majority were classified as grade IIIb (52.14%), followed by IIIa (25.64%) and IVa (11.11%). Grade II complications accounted for 5.98%, while the most severe events – grades IVb and V – each represented 2.56% of the total (Table 4).

Table 2. Personal and family history of patients with liver transplant

Variable	Alive n = 76 (%)	Deceased n = 33 (%)	Total n = 109 (%)	p
Personal history				
Alcohol consumption				
Daily consumption	18 (23.68)	10 (30.30)	28 (25.69)	0.807
Occasional consumption	7 (9.21)	4 (12.12)	11 (10.09	
Weekly consumption	11 (14.47)	4 (12.12)	15 (13.76)	
Does not consume	40 (52.63)	15 (45.45)	55 (50.46)	
Smoking history				
Former smoker	13 (17.11)	8 (24.24)	21 (19.27)	0.484
Never smoked	61 (80.26)	25 (75.76)	86 (78.89)	
Currently smokes	2 (2.63)	0	2 (1.83)	
Diabetes	15 (19.74)	10 (30.30)	25 (22.94)	0.228
Dyslipidemia	4 (5.26)	0	4 (3.67)	0.231
Obesity	7 (9.21)	5 (15.15)	12 (11.01)	0.275
Hepatitis A	1 (1.32)	0 (0.00)	1 (0.92)	0.697
Hepatitis B	12 (15.79)	1 (3.03)	13 (11.93)	0.050
Hepatitis C	4 (5.26)	1 (3.03)	5 (4.59)	0.521
Unspecified hepatitis	9 (11.84)	4 (12.12)	13 (11.93)	0.598
Heart failure	2 (2.63)	0	2 (1.83)	0.484
Myocardial infarction	1 (1.32)	1 (3.03)	2 (1.83)	0.516
Cirrhosis	39 (51.32)	15 (45.45)	54 (49.54)	0.574
Family history				
Liver cancer	1 (1.32)	0	1 (0.92)	0.697
Pancreatic cancer	1 (1.32)	0	1 (0.92)	0.697
Other cancer	1 (1.32)	0	1 (0.92)	0.697

Daily consumption: more than 7 drinks per week; Occasional consumption (less than once a week); Weekly consumption (1-7 drinks per week); Former smoker (quit more than 6 months ago).

During the 2011-2014 period, the 1-year survival percent was 63.3% (95% confidence interval [CI]: 43.6-77.7%), with a progressive decline in the first 6 months post-transplant. For the 2015-2018 period, the 1-year survival percentage improved to 84.2% (95% CI: 58.6-94.6%). In the 2019-2022 period, the 1-year survival percentage was 74.1% (95% CI: 48.5-88.3%), showing a slight decrease compared to the 2015-2018 period. Finally, during the 2023-2025 period, the 1-year survival percentage reached 89.1% (95% CI: 73.4-95.7%) (p = 0.093) (Fig. 1).

Kaplan-Meier survival analysis assessed the cumulative incidence of graft rejection across four periods: 2011-2014, 2015-2018, 2019-2022, and 2023-2025, with a 365-day follow-up. The probability of remaining rejection-free at 1 year was 70.4% (95% CI: 49.4-84.0) in the 2011-2014 cohort (n = 29), with a decline within the first 100 days (100-74.3%). In 2015-2018 (n = 19), rejection-free survival improved to 1 year at 78.6% (95% CI: 52.5-91.4), stabilizing after the first 100 days. The 2019-2022 cohort (n = 20) exhibited a further increase to 88.2% (95% CI: 59.8-96.9), with fewer early rejection events. Notably, in 2023-2025 (n = 40), rejection-free survival reached 100%, with no recorded rejection events, suggesting significant advancements in graft survival outcomes, p = 0.009 (Fig. 2).

Biliary and vascular complication-free survival varied across periods. For biliary complications, survival declined to 70.0% at 365 days (95% CI: 48.7-83.8%) in 2011-2014, 67.1% (95% CI: 40.9-83.7%) in 2015-2018, 70.3% (95% CI: 41.9-86.7%) in 2019-2022, and improved to 91.4% (95% CI: 75.7-97.2%) in 2023-2025 (p = 0.076) (Fig. 3A). Vascular complication-free survival followed a similar pattern: 89.4% at 31 days (95% CI: 70.6-96.5%) in 2011-2014, 89.16% (95% CI: 63.2-97.2%) in 2015-2018, 90.0% (95% CI: 65.6-97.4%) in 2019-2022, and 92.4% (95% CI: 78.1-97.5%) in 2023-2025, p = 0.975 (Fig. 3B).

The cold ischemia time (in blue) shows a gradual reduction over the periods, with medians of 461.50 min in 2011-2014, 398.00 min in 2015-2018, 395.50 min in 2019-2022, and 319.00 min in 2023-2025, indicating a decreasing trend in this parameter (p < 0.001). On the other hand, the warm ischemia time (in brown) remains relatively stable across the different periods, with

Table 3. Clinical outcomes and post-transplant complications in liver transplant patients

Variable	Alive n = 76 (%)	Deceased n = 33 (%)	Total n = 109 (%)	p
Ischemia times (min)	385 (320-504.5)	440 (330-515)	393 (321-515)	0.856
Cold*	330.5 (271-435)	405 (307.5-456)	343 (280-440)	0.166
Warm*	60 (50-67)	59 (52.5-65)	60 (50-67)	0.856
Transplant outcomes				
Re-transplantation	6 (7.89)	3 (9.09)	9 (8.26)	0.550
Transplant classification				
Adult	72 (94.74)	31 (93.94)	103 (94.50)	0.591
Pediatric	4 (5.26)	2 (6.06)	6 (5.50)	
Donor type				
Living	0	0	0	
Deceased	76 (100)	33 (100)	109 (100)	0.034
Rejection occurrence	10 (13.15)	10 (30.30)	20 (18.35)	
Rejection type				
Acute	5 (6.57)	7 (21.21)	12 (11.01)	0.325
Chronic	5 (6.57)	3 (9.09)	8 (7.34)	
Rejection cause				
Treatment adherence	2 (2.63)	0	2 (1.83)	0.306
Administrative (insurance- related)	1 (1.31)	0	1 (0.92)	
Subtherapeutic drug levels	1 (1.31)	0	1 (0.92)	
Other	1 (1.31)	2 (6.06)	3 (2.75)	
Biliary complications				
Stricture	9 (11.84)	9 (27.27)	18 (16.51)	0.645
Bile leaks	0 (0.00)	2 (6.06)	2 (1.83)	
Other	3 (3.94)	2 (6.06)	5 (4.59)	
Other complications	13 (17.10)	15 (45.45)	28 (25.69)	< 0.001
Post-transplant re interventions				
Reintervention due to bleeding	8 (10.52)	5 (15.15)	13 (11.92)	0.528
Reintervention due to bleeding at 48 h	8 (10.52)	4 (12.12)	12 (11.01)	0.521
Reintervention within the 1st month	19 (25.00)	11 (33.33)	30 (27.78)	0.321

*Median. IQR: interquartile range.

Table 4. Complications according to the Clavien-Dindo classification

Classification	Number of complications	%
II	7	5.98
IIIa	30	25.64
IIIb	61	52.14
IVa	13	11.11
IVb	3	2.56
V	3	2.56
Total	117	100

values close to 35 min, suggesting that there have been no significant changes in this variable (p = 0.028). Regarding the total ischemia time (in green), a progressive reduction is observed, decreasing from 605.00 min in 2011-2014 to 579.00 min in 2023-2025 (p = 0.038) (Fig. 4).

In the logistic regression analysis, the presence of other complications was identified as an independent predictor of mortality in patients undergoing liver transplantation (Odds ratio = 4.28, p = 0.002) (95% CI: 1.71-10.68). Besides, patients who experienced post-transplant complications were 4.28 times more likely to die compared to those without complications. The overall model was statistically significant (Likelihood-ratio X^2 [1] = 9.83, p = 0.0017), although it explained a relatively small proportion of the variance in mortality (Pseudo R^2 = 0.0749) p < 0.001.

Discussion

The evolution of liver transplant outcomes reflects a significant improvement in the transplant team's

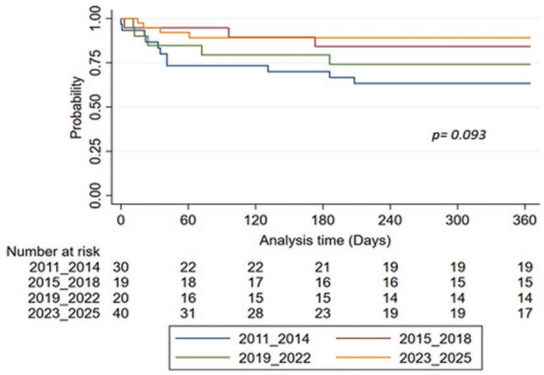

Figure 1. *Kaplan-Meier survival curves for mortality within 1 year after liver transplant. Cumulative survival probability within 1-year post-liver transplantation, comparing different time periods. The number of patients at risk is shown at time intervals.*

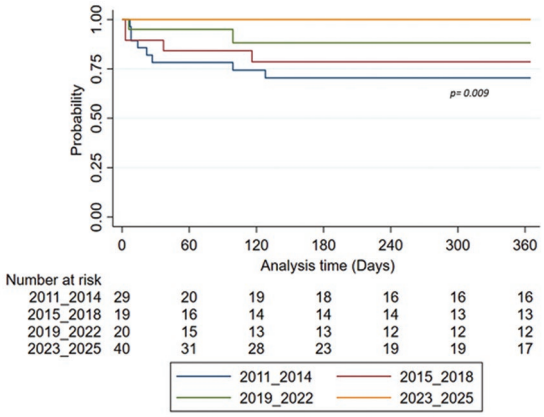

Figure 2. *Kaplan-Meier Survival curves for graft rejection within 1 year after liver transplant. Cumulative probability of freedom from graft rejection within 1-year post-liver transplantation, comparing different time periods. The number of patients at risk is presented at time intervals.*

experience, leading to better clinical results and increased survival probabilities. In our study, the median age was 7.5 years higher in patients who died compared to those who survived, with a statistically significant difference, similar to findings reported by Su et al.[19] One-year survival consistently improved, rising from 63.3% in 2011-2014 to 89.1% in 2023-2025. Comparable results were observed in a meta-analysis by Barbetta et al., showing the same trend over time.[20] This increase indicates advancements in patient selection, optimization of surgical procedures, and greater efficacy in post-operative management. Likewise, Colombian transplant centers have reported improved perioperative protocols and early detection of complications, contributing to better outcomes.[21] The findings from other Latin American transplant centers further support the regional advancement of transplantation practices. For instance, a recent publication by Varón-Vega et al. presents the experience of a high-altitude lung transplant center in Bogotá, Colombia, offering valuable insights into the development and consolidation of complex transplant programs in resource-constrained settings across Latin America.[22] These institutional reports highlight the importance of local expertise, multidisciplinary care, and adaptability in improving outcomes and building sustainable transplant programs in the region.

A notable finding in this study is the progressive reduction in cold ischemia time, with the median duration decreasing from 461.5 min in the 2011-2014 period to 319.0 min in 2023-2025. This trend reflects advancements in organ preservation protocols and logistical efficiencies in transplantation. In contrast, warm ischemia time remained relatively stable, and its variation did not show a significant association with patient mortality. This result is consistent with previous reports, suggesting that while minimizing cold ischemia time is essential for graft viability and long-term outcomes, variations in warm ischemia time within clinically acceptable limits may not have a substantial impact on post-transplant survival.[23,24]

An improvement in rejection prevention was evident, with a lower incidence observed among surviving patients compared to those who did not survive during the studied periods. The absence of rejection episodes within the 1st year post-transplant, observed in the most recent evaluation period, reflects advancements in immunosuppressive management and post-transplant care. Optimized immunosuppressive protocols, tailored treatment strategies, and strict adherence to follow-up regimens have likely contributed to these findings. Research in Latin America has demonstrated that personalized immunosuppressive approaches play a crucial role in reducing rejection rates and prolonging graft survival. These results emphasize the need for ongoing refinement of immunosuppressive therapies and patient monitoring to enhance long-term transplant success.[25,26]

Besides, patients who experienced post-transplant complications were 4.28 times more likely to die compared to those without complications, highlighting the need to further strengthen strategies for the prevention and management of these complications.[27] This finding underscores the importance of close monitoring during the 1st post-operative month, particularly given that vascular and biliary complications primarily

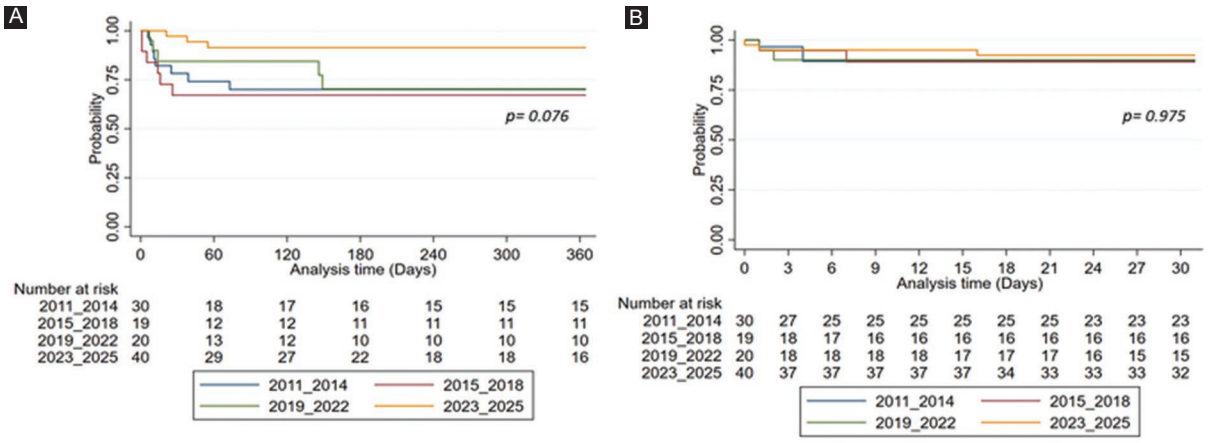

Figure 3. A *and* **B:** *Kaplan-Meier survival curves for biliary and vascular complication. Kaplan-Meier survival analysis for the absence of complications at 1 year (biliary) and 1 month (vascular) following liver transplantation.*

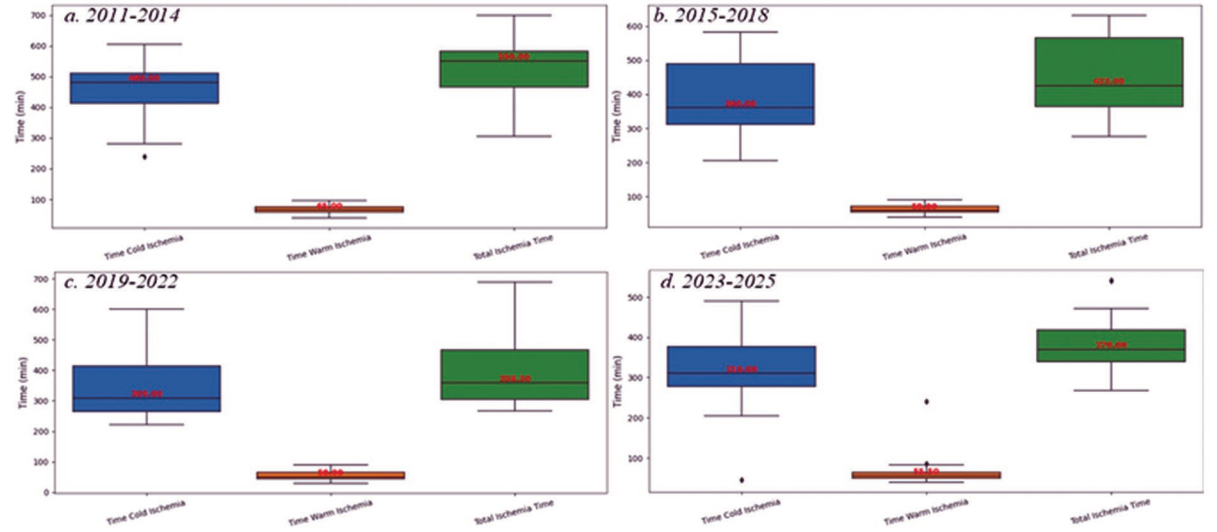

Figure 4. *Cold, warm, and total ischemia times in liver transplantation. The boxplots show the evolution of cold, warm, and total ischemia times over four distinct periods; they show a general trend of improvement in ischemia times, with notable consistency in warm ischemia time.*

occurred during this period.[7] Period-based analysis also reveals a decrease in the incidence of rejection and an improvement in survival, which may be attributed to the accumulated clinical experience of the treating team, the adoption of new technologies, and enhancements in perioperative management protocols.[28] In Colombia, hospitals implementing multidisciplinary post-transplant follow-up programs have reported a significant reduction in early post-operative complications and better long-term patient outcomes.[29]

It is also important to consider the potential influence of the COVID-19 pandemic on post-transplant outcomes, particularly in the earlier years of the 2020s. Several studies have reported that patients with underlying liver disease, including cirrhosis or metabolic-associated fatty liver disease, faced increased risks of severe COVID-19 and mortality, which may have indirectly affected transplant survival rates during that period. In addition, drug-induced liver injury and systemic inflammatory responses related to SARS-CoV-2 have been implicated in liver dysfunction, complicating the clinical course of transplant recipients. The heightened vulnerability of these patients to infections, immune dysregulation, and liver injury during the pandemic years could have contributed to increased post-transplant morbidity and mortality, warranting further investigation in future studies.[30]

These findings reaffirm that the accumulated experience over the years has been a key factor in improving liver transplant outcomes.[31] It is recommended to continue optimizing ischemia times, strengthening measures to prevent acute rejection, and refining strategies to reduce post-operative complications. Future research should focus on identifying prognostic factors that enhance the accuracy of rejection and post-operative complication risk prediction, as well as evaluating the impact of novel immunosuppressive therapies and surgical techniques on long-term outcomes. In addition, comparative studies between different transplant centers in Latin America could provide valuable insights into best practices and opportunities for standardizing care protocols across the region.[32]

This study has some limitations inherent to its retrospective design, as well as the fact that the data come from a single institution, which may restrict the generalizability of the findings to other settings. Nevertheless, it has several strengths. It provides a detailed analysis of long-term outcomes in liver transplant patients, supported by a rigorous follow-up protocol and a multidisciplinary approach.

Conclusions

The results of this study demonstrate a progressive improvement in 1-year survival, along with a reduction in rejection incidence, suggesting advances in post-transplant management. However, post-transplant complications, excluding biliary and vascular complications, remain a significant risk factor for mortality. Finally, the progressive reduction in cold and total ischemia times reflects an optimization of surgical and logistical procedures in liver transplantation.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the World Medical Association and the Declaration of Helsinki. The procedures were authorized by the Institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The study was approved by the Research Ethics Committee (REC) of the Fundación Cardiovascular de Colombia under the approval code CEI-2024-016-8. All patient data were anonymized to ensure confidentiality, and the study was conducted in accordance with the principles outlined in the Declaration of Helsinki. This article complies with the provisions set forth in Resolution 008430 of 1993 by the Ministry of Health of Colombia, which establishes guidelines for the protection of the rights of research subjects in scientific studies. Informed consent was obtained from all participants before their inclusion in the study, and no identifiable information was disclosed in this publication. The datasets generated and analyzed during the study are available on reasonable request from the corresponding author.

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

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ORIGINAL ARTICLE

Identifying the best cutoff value of the fecal occult blood immunochemical test in the detection of advanced and neoplastic colorectal lesions

Identificación del mejor punto de corte de la prueba inmunoquímica de sangre oculta en heces en la detección de lesiones colorrectales avanzadas y neoplásicas

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Abstract

Objective: *Screening is an effective tool for detecting colorectal lesions in asymptomatic subjects. There is a positive correlation between fecal immunochemical test (FIT) values and the size of tumors. Despite the efficacy of screening, the detection of colorectal cancer (CRC) remains low. The primary objective was to evaluate the best FIT cutoff value for detecting advanced adenomas and CRC among individuals at average risk in a country with a high incidence and morbidity from CRC.* **Methods:** *This observational and prospective study analyzed consecutive cases in 1461 asymptomatic subjects with a positive FIT (≥ 100 ng hemoglobin [Hb]/mL) referred for colonoscopy (2012-2015) at a tertiary center in Uruguay.* **Results:** *Colorectal lesions were detected in 35.3% (516/1461) of cases, with a mean age of 62.8 ± 8.3 years. About 53.2% were men and 65.1% of the tumors were located in the left side of the colon. The size of the lesion and FIT values (p = 0.001) were positively correlated. Laterally spreading tumors predominated in the right colon (586 ng Hb/mL; 95% Confidence interval [CI] 443.4-760). One hundred and thirty-five (26%) lesions were advanced adenomas (15 ± 6.7 mm); 694.6 ng/mL; 95% CI 632.4-756.9). The highest diagnostic yield (0.5112) for advanced adenomas was at a FIT level of 400 ng Hb/mL (accuracy 88.6%). There were significant differences in FIT values early and advanced CRC (927 ng/mL; [95% CI: 637-1082] vs. 1453 [95% CI: 1352-1594; p = 0.001]).* **Conclusions:** *A FIT value of 400 ng Hb/mL was the best diagnostic yield to detect advanced adenomas and CRC. This value is useful during the COVID-19 pandemic as it allows prioritization of colonoscopy to those most at risk of significant disease, thus reducing risks to both patients and healthcare workers.*

Keywords: *FIT. Fecal occult blood immunochemical test. Advanced adenomas. Colorectal cancer.*

Resumen

Objetivo: *El cribado es una herramienta eficaz para detectar lesiones colorrectales en sujetos asintomáticos. Existe una correlación positiva entre los valores de la prueba inmunoquímica fecal (FIT) y el tamaño de los tumores. A pesar de la eficacia del cribado, la detección del cáncer colorrectal (CCR) sigue siendo baja. El objetivo principal fue evaluar el mejor valor de corte FIT para detectar adenomas avanzados y CCR entre personas con riesgo promedio en un país con alta incidencia y morbilidad por CCR.* **Métodos:** *Este estudio observacional y prospectivo analizó 1461 sujetos asintomáticos con FIT positivo (≥ 100 ng de hemoglobina [Hb]/mL) remitidos para colonoscopia (2012-2015) en un centro terciario en Uruguay.* **Resultados:** *Se detec-*

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taron lesiones colorrectales en el 35.3% (516/1461) de los casos, con una edad media de 62.8 ± 8.3 años. Alrededor del 53.2% eran hombres y el 65.1% de los tumores estaban ubicados en el lado izquierdo del colon. El tamaño de la lesión y los valores FIT (p = 0.001) se correlacionaron positivamente. Los tumores con extensión lateral predominaron en el colon derecho (586 ng Hb/mL; intervalo de confianza [IC] del 95%: 443.4-760). Ciento treinta y cinco (26%) lesiones fueron adenomas avanzados (15 ± 6.7 mm); 694.6 ng/ml; IC 95% 632.4-756.9). El rendimiento diagnóstico más alto (0.5112) para los adenomas avanzados se obtuvo con un nivel FIT de 400 ng Hb/ml (precisión del 88.6%). Hubo diferencias significativas en los valores de FIT de CCR temprano y avanzado (927 ng/mL; [IC 95%: 637-1082] vs. 1453 [IC 95%: 1352-1594; p = 0.001]). **Conclusiones:** *Un valor FIT de 400 ng Hb/mL fue el mejor rendimiento diagnóstico para detectar adenomas avanzados y CCR. Este valor es útil durante la pandemia de COVID-19, ya que permite priorizar la colonoscopia a aquellos con mayor riesgo de padecer una enfermedad importante, reduciendo así los riesgos tanto para los pacientes como para los trabajadores de la salud.*

Palabras clave**:** *Prueba inmunoquímica de sangre oculta en heces. Adenomas avanzados. Cáncer colorrectal.*

Introduction

The incidence and mortality of cancer have increased in lower-income countries. This is likely due to epidemiological and demographic transition (aging and population growth) as well as exposure to risk factors such (alcohol and smoking).[1] In 2018, the number of new cases detected was 18.1 million with, 9.6 million cancer-related deaths. The incidence in the United States of America (USA) was 21% with a mortality of 14.4%.[2-4] The organs most commonly involved in Central and South America were as follows: prostate, lung, colon, and rectum colorectal cancer (CRC) and stomach in men, and breast, cervix/uterus, CRC, and lung in women. In 2018, the overall incidence and mortality reported were 10.2% and 9.2%, respectively, for both men and women.[2]

Cancer incidence has increased in Central/South America and Eastern Europe but is decreasing in developed countries such as the USA, Canada, Australia, New Zealand, and the rest of Europe).[2] The incidence rates among men and women in Latin America were 10.3 and 16.8, respectively. Incidence in the countries with the highest rates was as follows: Uruguay (34.2 men and 24.7 women), Brazil (27.7 and 21.5), and Argentina (25.2 in men).

Mortality is extremely high in Central (8-9 fold) and South America (3-5 fold) when compared to Europe and USA[5]. Although it has generally been reported as being < 10, mortality is high in Uruguay (17.7 among men and 12.0 among women), Cuba (11.3 women), and Argentina (14.6 men).[6,7]

Uruguay and Argentina have implemented national programs for the early detection of CRC.[7-10] Detailed knowledge of the natural history of cancer development (the adenoma-carcinoma sequence) allows for early detection at the subclinical stage and appropriate therapeutic intervention.[11]

In sporadic CRC, the tiered non-linear accumulation of genetic and chromosomal alterations occurs in approximately 7-10 years;[11,12], but this time period is shorter for hereditary CRC.

CRC is a common public health problem (5% incidence). Screening is effective when the appropriate population is targeted. Endoscopic removal of adenomas reduces the incidence of CRC (76%) and its mortality (53%).[13-15] Although colonoscopy is the most commonly used method for detecting adenomas and CRC, it is not the most cost-effective tool.[16,17] Screening programs have been implemented in the WHO population programs.[18,19]

The fecal occult blood (FOB) or fecal immunochemical test (FIT) is currently the best screening method[20]. FIT accurately detects globin component of hemoglobin (Hb) to the nearest nanogram (ng) per milliliter (mL) of feces using immunoassay. Colonoscopy is indicated when the patients' FIT values are ≥ 100 ng Hb/mL, due to the high sensitivity of detecting disease.[16,21,22]

For adequate population screening, FIT positivity rates should range around 3-6%.[21-25] In the case of CRC, sensitivity (Sn), specificity (Sp), positive predictive values, and negative predictive values (NPV) of FIT were reported as 100%, 90%, 16%, and 100%, respectively; and 74%, 93%, 45%, and 98%, respectively, for all neoplasms. FIT detects virtually all CRCs and 74% of significant colorectal lesions.[26]

Screening should be started at the age of 50 and be suspended either at 75 years of age or when the patient is expected to live < 10 years. Between 75 and 85 years, the risk to benefit ratio should be individualized. There is no benefit beyond the age of 85.[11] In the US, screening is opportunistic, unlike other

countries where it is more systematic and organized to cover more of the population.

The primary objective was to evaluate the best FIT cutoff value for detecting advanced adenomas and malignancies among individuals at average risk in a country with a high incidence and morbidity from CRC.

Methods

Consecutive patients with an average risk of CRC and a positive FIT (> 100 ng Hb/mL) scheduled for a colonoscopy at the Centre for Digestive Cancer of the National Cancer Institute of Montevideo, Uruguay, were recruited. All individuals provided written consent and this study followed the standards for reporting diagnostic accuracy. This cross-sectional, prospective, observational, and single-center study was carried out between 2012 and 2015. The study is part of the systematic program for the prevention and early detection of CRC under the Ministry of Health of Uruguay.

Selection criteria

- Inclusion: asymptomatic individuals, over 50 years of age, positive FIT (> 100 ngHb/mL), and informed written consent.
- Exclusion: personal or family history of CRC, digestive bleeding, colorectal resective surgery, inflammatory bowel disease and/or red flag signs (weight loss, anemia, and abdominal masses), and incomplete examination due to poor bowel cleansing.

Mass media campaign (television, radio, and press) were used to invite the population to participate in the national CRC screening program. The process for collecting samples, storing at –10°C, and returning it within 5 days was explained to each patient. There were no restrictions on diet or medication.

Patients with positive FIT results were scheduled for a colonoscopy within 8 weeks, which was performed after informed consent and after bowel preparation. The quality of FIT measurements was ensured through daily calibration and external validation using samples supplied by the manufacturer every 6 months. The colonoscopies were performed by three experienced endoscopists with a minimal total experience of 3000 colonoscopies. The cold technique was typically used to remove lesions < 5 mm and endoscopic mucosal resection to remove larger ones.

Clinical and demographic data were recorded, including age, sex, FIT values (ng Hb/mL), presence of colorectal lesions (type – Paris classification –, size and location; in addition to laterally spreading tumors (LST) > 10 mm), and histological types (subtypes and degree of dysplasia/differentiation).

The adenomas were classified as advanced or not advanced. Early CRC did not extend beyond the submucosa (Tis-T1); for invasive, CRC malignant cells were observed in the *muscularis propria* or beyond. The size of the polyps was defined *ex vivo* after resection and before fixation with 10% formaldehyde.

Definition of variables

- Subjects at average risk of CRC: Asymptomatic adult individuals over 50 years of age, with no personal/family history of CRC and/or adenomas or inflammatory bowel disease[7].
- Advanced adenomas: Adenomas ≥ 10 mm and/or with villous component ≥ 25% and/or high-grade dysplasia. Non-advanced adenoma: 1-2 adenomas each < 10 mm in size[7].
- (FIT-OC-Eiken [Eiken Chemical Co., Eiken, Japan]) was used during this study. The reported sensitivity and specificity was 96-98% and 91-95%, respectively[27,28]. The detection range was between 0 and 2000 ng Hb/mL of buffer, which enabled the cutoff point to be set for a positive result. The cutoff point was 100 ng Hb/mL as recommended by the manufacturers[14].

Statistical analysis

The data were captured in a Lotus Approach v. 9.7 Windows database and included age, sex, topography, size, histopathological diagnosis, and FIT quantification. To evaluate the differences between independent samples, Chi-squared tests and the exact Fisher's test were used for categorical variables and Student's t-test was applied for quantitative variables, with a significance level of 0.05. One-way analyses of variance and covariance were used to adjust the contrast between lesions in terms of age, sex, and positive findings of colorectal lesions. A hyperbolic function was calculated for two parameters.

The Sn, Sp, PPV, NPV, and accuracy of different FIT cutoff points were calculated, and the ROC curve plotted ($y = 0.5 \text{ Ln } (x) + 1$ Area Under the Curve × 0.5112) for the best FIT cutoff point in the detection of advanced adenoma. SPSS v. 17.0 and Epi Info v. 3.3.2.0 as statistical software were used.

Table 1. Type of colorectal lesions detected through colonoscopy in asymptomatic individuals

Paris classification	Type of colorectal polyps detected in 516 colonoscopies				
	A Pedunculated Polyp (Ip)	B Semi-pedunculated polyp (Isp)	C Sessile Polyp (Is)	D Lateral spreading tumor	p
Number of lesions	142	114	248	12	-
Age (years)					
Average	62.1	62,8	62.4	65.5	0.5
SD	88	8.2	8.1	8.3	
95% CI	60.6-63.6	61.1-64.5	61.3-63.5	60.8-70.3	
Size (mm)					0.001
Average	12.9	8.6	5.6	14.8	
SD	6.2	5.4	4.3	9.5	
IC95%	11.9-13.1	7.4-9.7	5.0-6.3	12.1-17.5	
FIT (ng Hb/mL)					0.001
Average	631.3[a]	452.1[b]	401.4[c]	779.2[d]	
SD	484	407	368	525	
IC95%	537.6-705	366.2-558	348.7-454.5	544-1614	

The letters (a, b, c or d) show the statistically significant differences between the groups, where the letter a differs from the other groups (b, c or d). Example: a = a, but a ≠ b or c or d.
FIT: fecal occult blood immunochemical test; SD: standard deviation; 95% CI: confidence interval 95%.

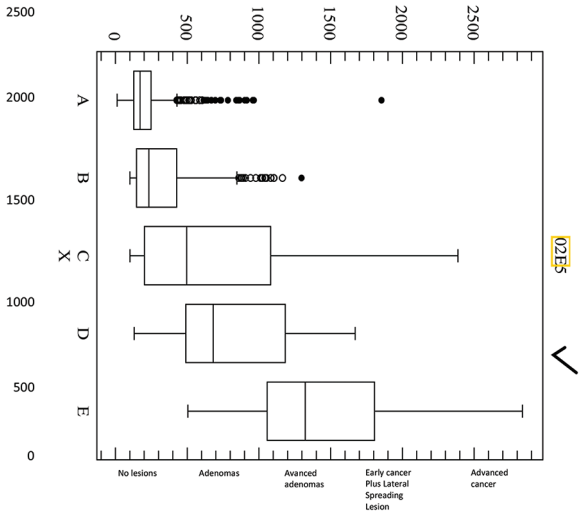

Figure 1. *Differences between FIT levels and the type of colorectal lesion.*

Results

The study included 1461 colonoscopies of subjects with average cancer risk and with FIT values ≥ 100 ng. Complete FIT and colonoscopy outcomes were available for 1461 patients who met the inclusion criteria for the final analysis.

No colorectal lesions (advanced adenomas/adenomas/early CRC or advanced CRC) were detected in 945 cases (64.6%). The average age of those subjects was 61 ± 9 years (55% men) and their average FIT was 317 ± 180 (95% CI 295.9-338.5). No visible lesions were found in 485 (237 ± 140 ng; 95% CI 21.3-270.7). Median FITs were 237, 370, 382, and 188 for diverticulitis (n = 396), angiodysplasias (n = 36), non-specific rectocolitis (n = 10), and colonic ulcers (n = 7), respectively. Other findings included three cases of pinworm (*Enterobius vermicularis*), two submucosal lesions, and two cases of chronic idiopathic ulcerative colitis.

Colorectal lesions were detected in 516 cases (35.3%). About 25.7% of the patients presented with > 2 lesions. For the purpose of FIT value analysis, the largest lesion was used. The average age was 62.8 ± 8.3 years and 53.2% were male. Majority of lesions were located in the left colon (336, 65.1%)) and with 180 (34.9%) in the right colon. The morphological Paris classification of lesions is described in table 1. There was a statistical difference between lesion types and FIT levels (p = 0.0001) and also size (p = 0.001). Figure 1 demonstrates differences between FIT levels and lesion type.

The most common lesions confirmed by histology were tubular adenoma (n = 167), tubulovillous adenoma (n = 104), hyperplastic (n = 63), advanced CRC (n = 54) villous adenoma (n = 38), early CRC (n = 17), and serrated adenomas.[12] Lesion size and FIT levels were positively correlated (p = 0.001), see table 2. Patient's age did not correlate with FIT levels. There was no significant difference between FIT value and LST or early CRC size.

Table 2. Colorectal lesions and FIT levels

Lesions	FIT Levels (ng Hb/mL)								
	100-200	201-300	301-400	401-500	501-600	601-700	701-800	> 801	p
Number	169	62	45	24	18	21	28	149	
Average size (mm) (SD)	6.37 (3.3)	7.1 (4.1)	7.5 (5.3)	10.8 (8.5)	12.6 (7.8)	12.6 (7.9)	14.2 (8)	22 (13.1)	0.001
95% CI	4.8-7.8	4.7-9.6	4.7-10.4	6.9-14.7	8-17.1	8.4-16.8	10.6-17.9	20.5.23.6	

FIT: fecal occult blood immunochemical test; SD: standard deviation; 95% CI: confidence interval 95%.

Table 3. Diagnostic accuracy to correctly diagnose colorectal lesions based on the 400 ng/mL FIT cutoff value

Tumor	ROC Curve (AUC)	IC 95%
Adenoma	0.691	0.656, 0.724
Advanced adenoma	0.831	0.798, 0.861
Laterally Spreading Tumors	0.907	0.878, 0.933
Early CRC	0.996	0.985, 0.999
Advanced CRC	1.0	0.993, 1.0
Laterally Spreading Tumors + early CRC	1.0	0.992, 1.0
All the lesions	0.777	0.749, 0.802

AUC: area under the curve; 95% CI: 95% confidence interval; CRC: colorectal cancer.

LST lesions predominated in the right colon (n = 12; 66.6%) and early CRC in the left (n = 17; 88%). There were no significant differences between size (17.5 vs. 15, p = 0.1) and FIT values (average 626 vs. 927 ng/mL, p = 0.1).

There were 135 cases of advanced adenomas, with an average size of 15 ± 6.7 mm (95% CI 13.6-16.3) and FIT levels of 694.6 ng (95% CI 632.4-756.9). There was no correlation between advanced adenoma size and FIT levels (R = 0.22). The best cutoff value for detecting significant pathology was 400 ng/mL (Sn 0.59, Sp 0.84) with false-negative rates of 0.16. The positive likelihood ratio (LR+) and negative likelihood ratio (LR-) were 3.81 and 0.48, respectively. Table 3 and figure 2 illustrate the diagnostic accuracy for a 400 ng/mL cutoff and ROC curves. Diagnostic accuracy for different FIT levels is demonstrated in table 4.

There were 71 cases of CRC (17 early and 54 advanced) with an average age of 65.8 ± 8 years (1:1 male-female ratio) predominating in the left colon (88% early and 80% advanced). There were significant differences between FIT values for early and advanced CRC (average 927 ng; [95% CI: 637-1082] vs. 1453 [95% CI: 1352-1594; p = 0.001]). The degree of tumor differentiation was well differentiated (n = 31), moderately differentiated (n = 34), and poorly differentiated (n = 6).

11/12 LST were treated endoscopically and one was surgically resected. 14/17 early CRC were treated by endoscopic resection and the remainder required surgery. All advanced CRCs were referred to the oncology team.

Discussion

A FIT cutoff value of 100 ng Hb/mL is highly sensitive for detecting CRC and advanced adenomas. The Sn, Sp, PPV, and NPV to detect CRC were 100%, 90%, 16%, and 100%, respectively, and for advanced neoplasms 74%, 93%, 45%, and 98%, respectively. A FIT detects 100% of CRC and 74% of colorectal lesions.[29]

Although the frequency of advanced adenomas and malignant lesions was higher in our studied population, there was not a correlation between the size (average 15 ± 6.7 mm) and the FIT level of 694.6 ng (R = 0.22). However, the most significant accuracy was seen with a value of 400 ng Hb/mL (Sn 0.59, Sp 0.84) with a 0.16 false-negative rate, a positive likelihood ratio (LR+) and negative likelihood ratio (LR-) of 3.81 and 0.48, respectively.

Nagorni et al.[30] reported a higher detection rate of advanced adenoma among individuals with a positive FIT than in symptomatic subjects undergoing colonoscopy (11.6% vs. 5.1%).[30] Similarly, our group reported a higher detection rate in colonoscopy in asymptomatic subjects (positive FIT) compared with symptomatic patients without FIT testing (8.9 vs. 4.35%) in 3234 consecutive cases at the Cancer Detection Center in Montevideo, Uruguay.[31] qFIT (quantitative)

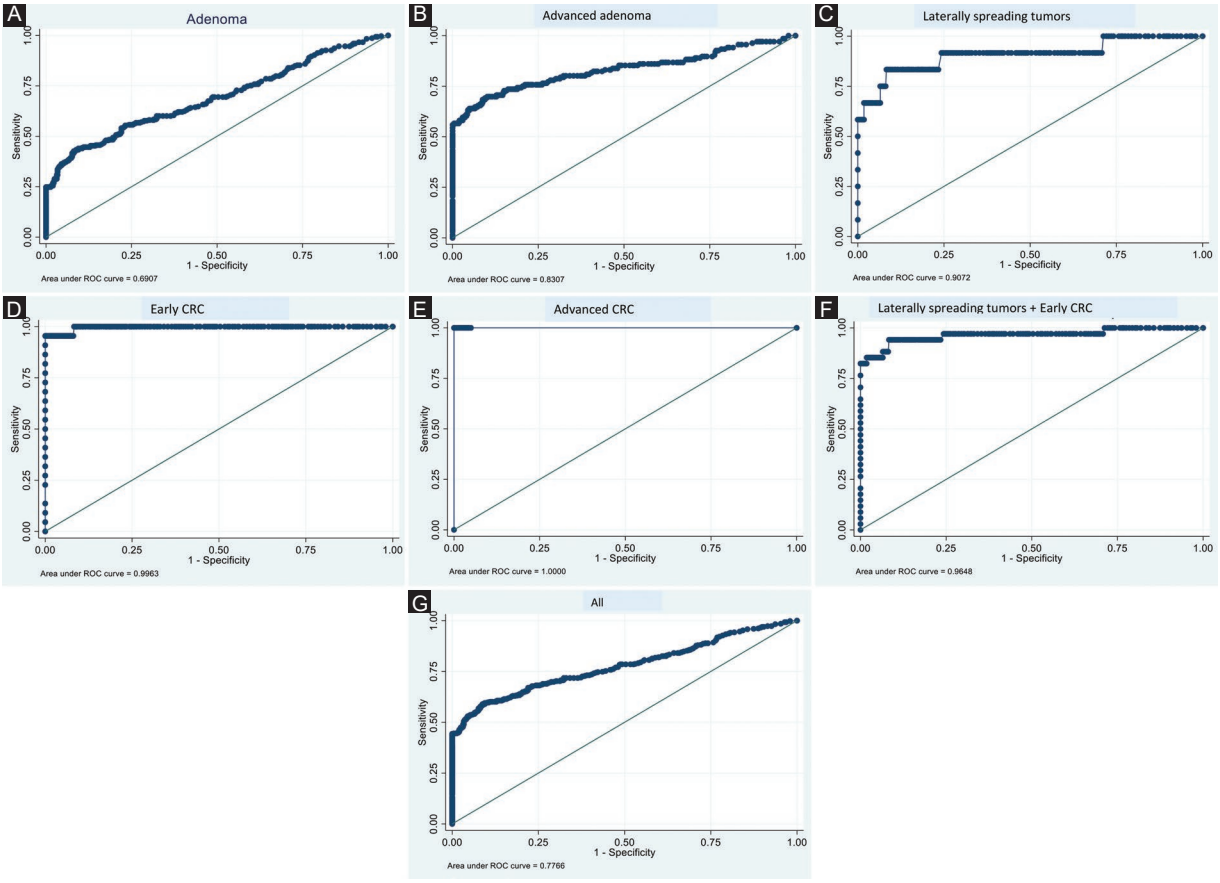

Figure 2. *ROC curve for the detection of colorectal lesions using FIT.* **A:** *simple adenomas,* **B:** *advanced adenomas,* **C:** *laterally spreading tumors,* **D:** *early CRC,* **E:** *advanced CCR,* **F:** *laterally spreading tumors plus early CRC, and* **G:** *all.*

showed a directly proportional relationship between the size of the lesion and the amount of bleeding. For each mm increase, the value of Hb in FIT increased by 35 ± 9 ng ($p < 0.001$) with the best diagnostic yield of 15 mm, where the values stabilized and the curve almost flattened between 1100 and 1900 ng/Hb.

The frequency of advanced adenomas/CRC was high (13.7%) in our study when compared to previous studies. Van Rossum et al.[29] reported a CRC detection rate of 0.45, 0.44, 0.39, 0.39, 0.39, 0.39, 0.39, and 0.37% using values of 50, 75, 100, 125, 150, 175, 200, and 225 ng Hb/mL, respectively. However, the number of colonoscopies required to detect one case was 15.3 (50 ng Hb/mL), 12.4 (75 ng Hb/mL), 11.7 (100 ng Hb/mL), 10.3 (125 ng Hb/mL), 9.8 (150 ng Hb/mL), 9.0 (175 ng Hb/mL), 8.3 (200 ng Hb/mL), and 8.1 (225 ng Hb/mL) with very wide 95% confidence intervals (95% CI). In this study, the Sp to detect advanced adenoma using a value of 400 ng Hb/ml was over 96% (96-98.7%).

Hernandez et al.[32] reported that the FIT cutoff points with the highest yield for advanced neoplasm and CRC were 272.57 ± 597.28 (ROC Curve 0.97) and 998.00 ± 1,075.44 (ROC Curve 0.72), respectively. In our study, the cutoff points with the highest yield (the highest true-positive rate together with the lowest false-positive rate) for predicting advanced adenoma were 395 ng Hb/mL, 927 Hb/mL ng for early CRC, and 1453 ng Hb/mL for advanced CRC.

The assessment of FIT cutoff values and advanced adenomas is often limited in studies due to the number of colonoscopies performed, type of FIT immunoassay used, and the inclusion of both the high-risk screening population and symptomatic patients. These cofounders limit the applicability of findings to screening populations.

Yuan et al. reported that different cutoff values were associated with the performance of qFIT (quantitative). The sensitivity and specificity of qFIT for advanced neoplasia (AN) was 51.3% and 86.4%, respectively, with the best cutoff level of 400 ng/mL. The sensitivity and specificity for CRC were 61.0% and 89.1%, with the best cutoff level of 500 ng/mL.[33]

Table 4. Diagnostic accuracy of FIT for lesions at different cutoff values

Diagnosis	200	300	400	500	600	700	800	900	1000
Adenoma									
Sensitivity	58.0	43.0	29.0	21.0	17.0	13.4	9.4	6.4	5.0
Specificity	70-0	91.2	97.0	100	100	100	100	100	100
Accuracy	65.1	71.8	69.7	68.2	66.6	65.2	63.6	62.5	62.0
Advanced adenoma									
Sensitivity	78.6	67.0	59.5	51.5	48.5	46.3	38.2	33.1	29.4
Specificity	70.0	91.2	100	100	100	100	100	100	100
Accuracy	72.0	85.5	88.3	88.6	88.0	87.4	85.5	84.3	83.5
Laterally spreading									
tumors	91.7	88.3	-	66.7	41.7	-	-	-	33.3
Sensitivity	70.0	91.2	-	97.0	100	-	-	-	100
Specificity	74.0	91.0	-	96.2	98.5	-	-	-	98.2
Accuracy									
Early CRC									
Sensitivity	100	100	95.4	-	81.8	60.0	50	-	31.8
Specificity	70.0	91.2	97.0	-	100	100	100	-	100
Accuracy	71.3	91.6	97	-	99.1	98.0	97.6	-	96.5
Advanced CRC									
Sensitivity	100	100	100	100	94.3	92.4	88.7	79.2	70.770.3
Specificity	70.3	91.2	97.0	100	100	100	100	100	100
Accuracy	73.3	92.1	97.4	100	95.4	99.2	98.8	97.8	97.0
CRC + Lateral Spreading									
Sensitivity	97.0	94.1	94.1	85.2	-	64.7	47.0	35.3	32.3
Specificity	70.7	91.2	92.0	97.0	-	100	100	100	100
Accuracy	72.0	91.4	91.8	96.2	-	97.5	96.2	95.4	95.2
All lesions									
Sensitivity	70.0	58.3	47.8	39.7	-	36.2	33.4	23.0	20.5
Specificity	70.2	91.2	97.0	100	-	100	100	100	100
Accuracy	70.0	73.5	70.0	67.5	65.3	63.5	61.0	48.5	57.1

Shahidi and Cheung[34] evaluated FIT performance in an average risk Canadian population; using cutoff values of > 100 ng Hb/mL, this increased the PPV for advanced adenoma by 6.5% and CRC by 1.5% but the main trade-off was the potential for missed lesions. A 50 ng Hb/mL cutoff value has been shown to be most cost-effective value.

These findings could be highly important in the decision-making process during the SARS-COV-2 (COVID-19) pandemic, helping clinicians to risk stratify which invasive aerosol generating procedures are need to be undertaken in timely manner and which can be safely postponed to a later date. During the most difficult times in the COVID-19, pandemic screening programs, elective colonoscopies in patients with positive FITS were postponed and only emergency procedures undertaken.[35]

Unfortunately, it is still too early to know the impact on the subsequent health, quality of life, and endoscopic lesion detection of the postponed individuals with positive FIT who were scheduled for colonoscopy.

In our study, the detection rate of colorectal lesions was 35% (post-test likelihood) using a non-invasive test (FIT) in subjects at average risk. We observed significant differences in location (left colon), FIT values (p = 0.0001), and lesion size (p = 0.001), but not for age or gender.

Nationwide policies have implemented CRC screening programs in many countries[11]. CRC along with breast cancer screening is the only malignancies where screening is effective in the prevention or progression of disease. In 90% of cases, colorectal lesions are in the pre-cancerous (adenomatous) phase when patients are usually asymptomatic; therefore, screening can be highly effective.[21]

Screening in asymptomatic subjects reduces the incidence and mortality of CRC. Colonoscopy is the most commonly used method following a positive FIT for lesion detection and removal.[13] However, it is not a cost-effective tool for screening as over 75% of the detected lesions are not CRC.[29]

Uruguay and Argentina have implemented screening programs for CRC. Uruguay initiated a study to promote screening and healthy behavior in the general population and those most at risk (14,000 people)[9] Uruguay has had a National Policy for the Detection of (CRC Program) since 1998. It includes the annual screening of asymptomatic individuals with ages ranging from 50 to 70 years using an immunochemical test (iFOBT). This recently changed to FIT as this more specific to the lower GI tract. Colonoscopy is then recommended for positive cases.[9,10] The widespread use of FIT is vitally important in countries where cancer poses a major health problem.[13]

The compliance rates for FIT and colonoscopy in a feasibility study involving 11,734 asymptomatic individuals over the age of 50 were 90.1% and 75.1%, respectively. FIT was positive in 1170 (11.1%) responders and colonoscopy was performed in 879 (75.1%), revealing 330 (38%) lesions, including 54 advanced cancers, 47 early cancers, 131 advanced adenomas, and 98 low-risk non-advanced adenomas. Predictive values for cancer were 0.95 and 8.6% and for advanced adenomas 1.24 and 11.2%.[14]

In one Dutch study, 8806 (3.3%) of 265 881 participants had a positive FIT. Three thousand two hundred and fifty-four (1.2%) AN and 557 (0.2%) CRC were reported in colonoscopy. Prognostic models for detecting AN and CRC in round 3 were performed. The predicted risk ranged from 0.4% to 36.7% for AN and from 0.0% to 5.5% for CRC. In external validation, the model retained similar discrimination accuracy for AN (C-statistic 0.77, 95% CI 0.66 to 0.87) and CRC (C-statistic 0.78, 95% CI 0.66 to 0.91). The models accurately predict the risk of subsequent AN and CRC, discriminate those outcomes with a high degree of concordance, and allow for clinically meaningful risk stratification.[36]

FIT and colonoscopy have been shown in randomized trials to reduce the incidence of CRC and its associated mortality. The incidence of advanced adenoma and CRC in preventive screening (Positive Fecal Tests) is depending on the number of people who undergo endoscopy. Even though, they have been showed to decrease CRC mortality but overestimate the rate of adenomas and cancer.[37]

Our study has also shown that the population most at risk of malignancies is an economically active population (> 60 years) who are also more likely to have comorbidity. Thus, we must consider this in addition to the patient's individual risk and the odds based on FIT values.

Future risk stratification will require evaluating the current cutoff point (FIT > 100 ng) to enhance the performance of the test, while not overwhelming the health-care system. The likelihood of detecting colorectal neoplasms was 25% before the test and 37.7% after the test (LR+ 5.7) in 63,393 subjects with average risk in Uruguay[10] suggesting that deferring the colonoscopy would not be the most appropriate strategy. It is important to consider that the age group in which colonoscopy is indicated matches the age group with a higher potential risk of complications from COVID-19.

There are, however, some limitations of this study, with the main one being that the short and long-term patient outcomes are unknown for those who did not proceed to colonoscopy with a positive FIT. Furthermore, the results from this tertiary center may not be generalizable to smaller hospitals with different patient demographics as other risks influence mortality such as associated diseases such as cardiovascular disease or infection, population pyramid, and the prevalence of overweight or obese individuals.[37-39]

The main findings of the study are well-timed to guide service delivery during the COVID-19 pandemic, with a diagnostic yield of 400 ng Hb/mL demonstrating likely advanced adenomas or CRC. The indirect benefit of implementing such a cutoff is that it would reduce the burden of care and the risk of transmission of the virus during the epidemic in subjects at higher risk of comorbidity. Although lower cutoff levels would increase the detection rate of lesions, this would be at the expense of a higher number of colonoscopies. Prioritization of patients based on this cut-off point (400 ngHb/mL) in the challenging new setting for endoscopy in the fight against CRC, appears to be a feasible strategy that can lower the risks to both patients and healthcare workers.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely

collected and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed.

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

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REVIEW ARTICLE

Risk factors associated with mortality from explosions in civilian and military populations

Factores de riesgo asociados a mortalidad por explosiones en poblaciones civil y militar

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Abstract

Trauma from explosions is among the most serious injuries faced by healthcare professionals. There are few studies that describe the risk factors for mortality, or the patterns of blast injuries in the civilian compared to the military population. Review of articles extracted from Medline, PubMed, and Scopus published (01/2014-03/2024). Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed. Data on mortality and injury patterns were extracted from the articles that met the inclusion criteria to describe the type of injuries and to identify risk factors for mortality. Sixteen articles were included. Average age of civilians was 40.0 years ± 3.7, with men representing 79.4% compared to a mean age of 24.5 ± 1.4 and 79.0% for the military patients. While there was no difference in the distribution of injuries by body regions, the civilian population was more likely to sustain severe cranial and thoracic injuries (31.9% and 20.4% vs. 18.1% and 9.9%, respectively). Civilian population had a non-statistically significant lower risk of death (odds ratio = 0.96; 95% confidence interval = 0.82, 1.13). The findings of this review indicate that clinical experience derived from explosions occurring in one setting may not be fully generalizable to explosions occurring in other contexts, as demographic, environmental, and contextual factors contribute to distinct injury patterns.

Keywords: *Explosions. Injury patterns. Injury severity. Blast injuries. Mass-casualty incidents. Mortality. Risk factors.*

Resumen

Los traumatismos por explosiones se encuentran entre las lesiones más graves a las que se enfrentan los profesionales sanitarios. Existen pocos estudios que comparen los factores de riesgo de mortalidad o los patrones de lesiones por explosión en la población civil en comparación con la población militar. Se realizó una revisión sistemática de artículos publicados en Medline, PubMed y Scopus, de enero de 2014 a marzo de 2024, siguiendo las directrices PRISMA. Se extrajeron datos sobre mortalidad y tipos de lesiones de los estudios que cumplieron los criterios de inclusión. Se incluyeron 16 artículos. La edad media de los civiles fue de 40.0 ± 3.7 años, con un 79.4% de varones, frente a 24.5 ± 1.4 años y un 79.0% de varones en los militares. No hubo diferencias en la distribución de las lesiones por regiones corporales, pero la población civil presentó una mayor probabilidad de sufrir lesiones craneales y torácicas graves (31.9% y 20.4% frente a 18.1% y 9.9%, respectivamente). La población civil tuvo un riesgo de muerte menor, aunque no estadísticamente significativo (OR: 0.96; IC 95%: 0.82-1.13). Esta revisión sugiere que la experiencia clínica derivada de las explosiones en un entorno específico podría no ser completamente extrapolable a otros contextos, debido a diferencias demográficas, ambientales y operativas que influyen en los patrones de lesión.

Palabras clave: *Explosiones. Patrones de lesiones. Gravedad de las lesiones. Lesiones por explosión. Incidentes con múltiples víctimas. Mortalidad. Factores de riesgo.*

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Introduction

Traumatic injuries remain one of the leading causes of morbidity and mortality in the world population.[1] Although trauma and acute care surgeons have experience with more common injury mechanisms, such as motor vehicle accidents and interpersonal violence, they are not as familiar with less frequent, but more lethal, blast-related injuries.[2,3] Blast or explosion-related injuries encompass a wide spectrum of trauma resulting from explosive events and are typically classified by their setting in military (war-related) defined as those occurring in the context of organized armed conflict involving military forces, and civilian (non-war-related) contexts, as those occurring outside active combat zones, including terrorism, industrial accidents, and unintentional explosions; by injury mechanism (primary to quinary); and by the nature of the explosion as accidental blast – such as gas line ruptures, boiler failures, or chemical plant accidents – usually occur in industrial or residential settings and often involve thermal burns, blunt force trauma, and inhalation injuries from structural collapse or fire. In contrast, intentional explosions – such as those from improvised explosive devices (IEDs), car bombs, or suicide attacks – are engineered for maximum lethality, combining multiple mechanisms including blast overpressure, penetrating trauma from shrapnel, and complex polytrauma. Distinguishing between these events is essential not only due to their intent but also due to differing injury patterns: accidental explosions tend to injure bystanders, whereas intentional blasts are often premeditated to affect densely populated or enclosed areas, amplifying casualty severity. Recognizing these distinctions is critical for anticipating injury profiles and guiding effective emergency response and trauma care.

Explosions result in multisystem injuries through a range of mechanisms, including both direct and indirect blast effects. These effects generate shearing and tearing forces that can lead to tissue penetration, organ perforation or rupture, and thermal burns.[4] In addition, blast waves may produce internal injuries that are often occult, difficult to detect due to their non-visible nature and the unique injury mechanisms involved.[5,6] Explosive involve also has the potential to cause mass casualty incidents (MCI) given their non-discriminatory and spreading impact across wide areas.[4] Victims located near the epicenter typically sustain immediate fatal or severe injuries, while those further from the blast radius are more likely to suffer minor to moderate trauma (Fig. 1).[7] As a general rule, for every fatality, at least two individuals sustain injuries.[8]

The global incidence of deaths due to armed conflict and terrorism has been rising, with an estimated 129,700 fatalities reported in 2017 alone.[9] As blast injuries increasingly occur in civilian settings,[10,11] there is a growing need for emergency personnel to be proficient in the assessment, management, and triage of blast-related trauma and potential MCIs.[12-17] Nonetheless, accidental explosions remain a more frequent source of blast injuries among civilians. A notable example is the 2020 Beirut harbor explosion, in which the detonation of stored ammonium nitrate – located adjacent to a fireworks warehouse – resulted in over 200 deaths and tens of thousands of injuries.[18]

The distribution of injuries to the different body regions varies and is often directly related to the mechanism of the explosion and the location of the explosive material.[19] The placement of IEDs at ground level as opposed to a higher level leads to a different distribution of body regions injuries. For example, in the 2013 Boston Marathon bombing, two IEDs were placed at ground level causing predominantly lower extremity injuries.[16] Lung injuries and tympanic membrane perforations were the most common following the 2004 Madrid train bombings from over-pressurization in confined space.[20] In contrast, the Beirut port shock wave occurred in an open-air space, but quickly spread to the densely populated capital, where it was amplified by reflecting off surfaces. The pressure of the blast wave caused extensive damage to buildings and glass windows, resulting in blunt head injuries from falling debris and masonry, and penetrating wounds to the face and extremities.[19]

To date, relatively few studies have systematically investigated the risk factors associated with adult mortality following blast trauma, particularly with respect to differences in injury patterns between civilian and military populations. These distinctions may be critical in anticipating injury severity and guiding appropriate medical response. Within this context, the present study aims to examine and compare the injury profiles and associated mortality risk factors from both accidental and intentional explosions across civilian and military settings.

Methods

Data sources and search strategy

A literature search was performed using Medline, PubMed, Scopus, and through searching citations of

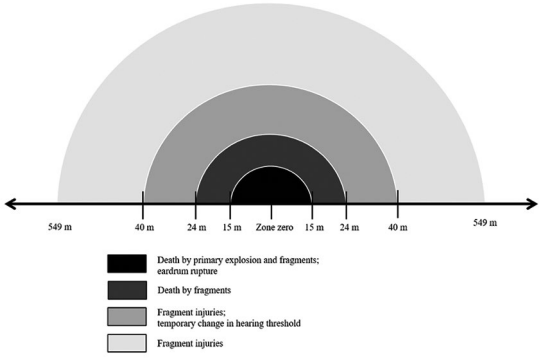

Figure 1. *Type of injuries according to distance from the explosion.*

other original articles. MeSH terms utilized were explosions, blast, blast waves, blast injuries, injury patterns, and mass-casualty incidents. Articles published in English and Spanish were selected from 1/1/2014-3/31/2024 (Fig. 2). The authors attempted to register this systematic literature review in PROSPERO, as it does not currently accept registrations for scoping reviews, literature reviews, or mapping reviews.

Study selection criteria

Only original and human subject research articles were included, encompassing both prospective and retrospective descriptive studies. Eligible studies were required to report injury profiles, defined as the distribution of injuries sustained from explosions stratified by injury severity score (ISS) and abbreviated injury score (AIS) body region. Exclusion criteria included studies involving non-human subjects, clinical case reports, literature reviews, pediatric populations, and publications in languages other than English or Spanish.

Data extraction

The first author (P. Petrone) supervised the entire process, from article selection to data extraction methodology. Data extraction was conducted in two phases: One international research fellow (Jordi Marin-García) independently extracted the first set of data, which was then verified by PP. In turn, PP extracted the second set of data, which was subsequently verified by JMG. For the articles published in Spanish, three of the first three authors are native Spanish speaker, ensuring accurate interpretation. Data were extracted using a standardized table that included the following variables: Author, year of publication, study type, number of patients, age, gender, injury types, and injury severity (as measured by ISS and AIS). To ensure consistency and accuracy, any disagreement between the authors was resolved through a structured consensus process. Initial differences were identified during independent data review and addressed through open discussion. When informal consensus could not be achieved, a third senior investigator was consulted to provide an impartial opinion. This stepwise approach ensured methodological rigor, minimized bias, and maintained alignment with the study's predefined criteria and objectives.

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses and Assessing the methodological quality of systematic reviews guidelines to ensure methodological rigor and transparency. A comprehensive literature search was performed to answer the following PICO-formulated research question (Population, Intervention, Comparison, and Outcome):

- Population: Victims of explosion-related injuries (civilian and military).
- Intervention/exposure: Blast exposure in different operational contexts (war-related vs. non-war-related).
- Comparison: Injury pattern differences between groups.
- Outcome: Distribution and severity of injury by anatomical region.

An assessment of risk of bias was performed per individual study, using the Newcastle - Ottawa Quality Assessment Scale for both case control studies and cohort studies as valid evaluation tool.

Given the heterogeneity in study designs, populations, and outcome measures, data from the included studies were synthesized using a narrative synthesis approach. The involved systematic categorization of key themes, patterns, and findings across studies, with specific attention to contextual variables, such as setting, intent of explosion, and injury mechanisms, enabled a comprehensive synthesis of the available evidence and facilitated the identification of recurring trends, knowledge gaps, and clinically relevant associations

To assess the certainty of the overall body of evidence, each outcome was evaluated using established domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Certainty ratings were assigned as high, moderate, low, or very low, and any decision to downgrade the certainty was explicitly documented and justified to ensure transparency.

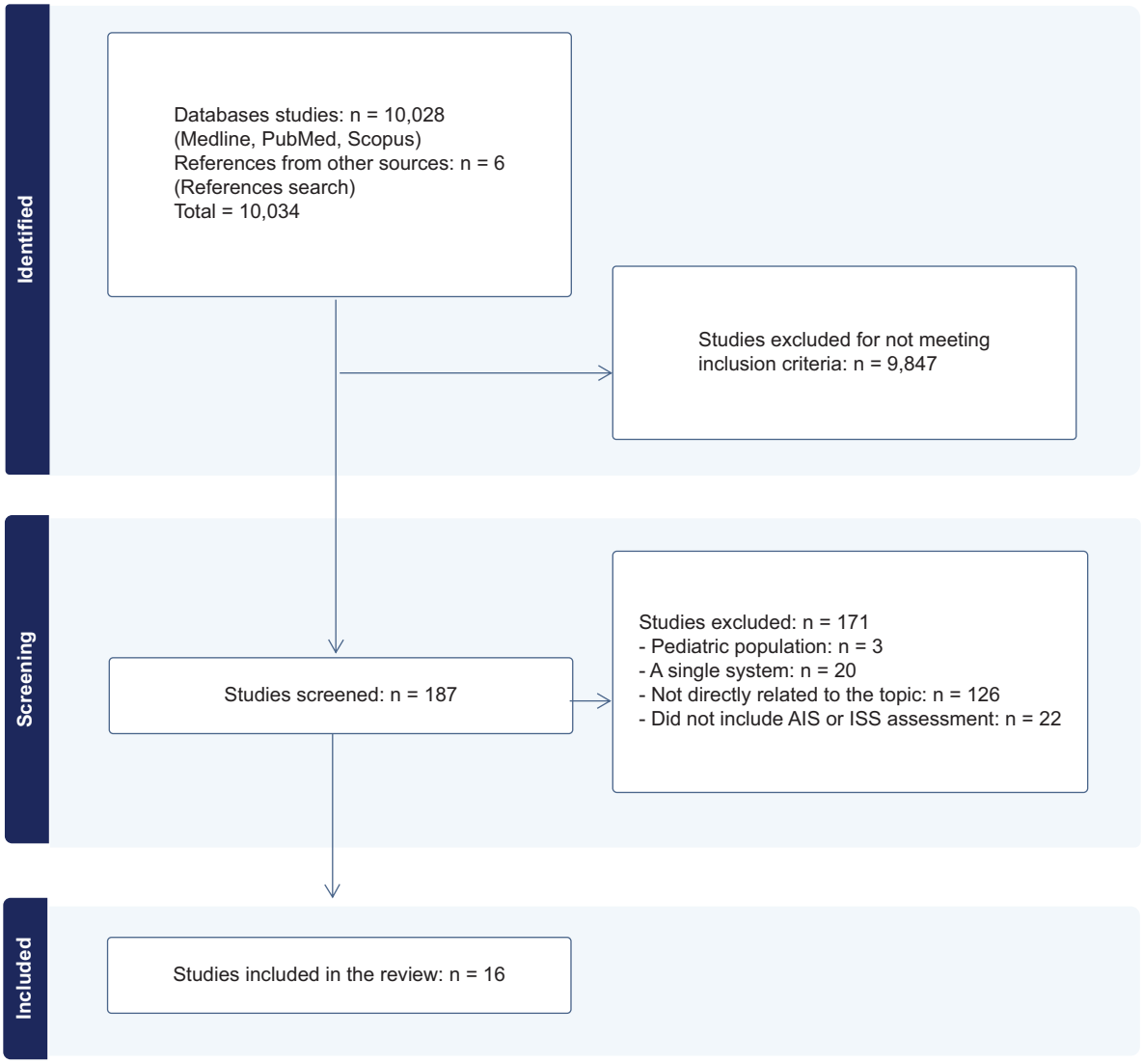

Figure 2. *Preferred reporting items for systematic reviews and meta-analyses flowchart.*

The AIS is an anatomically based injury severity scoring system that rates injury by body region on a six-point scale that provides data to calculate the ISS.[21,22] There are six regions of the body according to the ISS classification to which injuries can be assigned, although the AIS dictionary 2005 – Update 2008 is divided into nine anatomical chapters.[22,23]: head or neck injuries, facial injuries, thoracic injuries, abdominal injuries, pelvic, extremity, or pelvic girdle injuries, external injuries, and other traumatic injuries.

Statistical analysis

The data set was assessed for normality using the Shapiro-Wilk test, and continuous data were analyzed using Welch's t-test.[24,25] The Welch's t-test was selected instead of the Student's t-test because it provides better control for type I errors when homoscedasticity (the assumption that the variance of the data is homogeneous) is violated, while performing the Student's t-test when homoscedasticity is maintained.[26,27] Discrete variables were compiled into contingency tables to determine the odds ratio (OR). Fisher's exact test was used instead of the chi-square for greater reliability.[28] Continuous variables are reported as mean with standard deviation (SD). Statistical significance was conferred if $p < 0.05$.

Results

Of the 10,028 articles initially identified through searches of Medline, PubMed, and Scopus, ten met the predefined

inclusion criteria. An additional six eligible articles were identified through citation tracking of original studies, resulting in a total of 16 articles included in the final review (Fig. 2). Duplicate publications were identified and removed using automated software (Covidence; Melbourne VIC 3000, Australia). All reviewers independently evaluated these 16 studies and agreed on their inclusion following a detailed assessment. Notably, only one of the included articles directly compared outcomes between civilian and military populations (Table 1).[7,19,29-42]

Table 1. Studies included by author and by type of population

Author (year of publication)	Study period	Type of population	n = 14,942
Rozenfeld et al.[29]	2004-2011	Military	474
Rozenfeld et al.[2]	2012-2013	Military	19
Shakargy et al.[46]	2003-2014	Military	844
Heldenberg et al.[7]	2000-2005	Civilian	1261
Yu et al.[32]	2015	Civilian	75
Sharrock et al.[33]	2003-2014	Military	80
Ashkenazi et al.[34]	1994-2005	Civilian	66
Rozenfeld et al.[35]	1997-2016	Civilian	1025
Schweizer et al.[36]	2001-2018	Military	739
Maddry et al.[37]	2011-2014	Military	915
Nunziato et al.[38]	2015	Civilian	2682
Al-Hajj et al.[39]	2020	Civilian	791
Tapia et al.[40]	2007-2020	Military	1526
Gebran et al.[19]	2020	Civilian	315
Rozenfeld et al.[41]	1997-2018	Civilian-Military	3908
Shakargy et al.[46]	1982-2021	Military	222

Study demographics

Of the 16 studies included, 9 (56%) investigated the effects of explosions in the military populations, while the remaining seven focused on civilian populations. Across all studies, a total of 14,942 patients were affected by explosions – 9,240 civilians and 5,702 military personnel. Collectively, 27,270 injuries were reported: 17,620 in the civilian population resulting from both terrorist and accidental explosions, and 9,650 in the military population. Demographic characteristics of the study populations are summarized in table 2. The average age of victims in the civilian population was significantly higher than that of victims of military casualties (40 ± 3.7 vs. 24.5 ± 1.4; $p < 0.05$). However, there was no statistically significant difference in sex distribution, with a predominance of male victims in both groups (79.4% vs. 79.0%; $p > 0.05$). Mortality rates were also comparable between the two populations (4.6% vs. 4.7%; $p > 0.05$). No independent risk factors for mortality were identified that distinguished civilian from military outcomes (OR = 0.96, 95% confidence interval [CI] = 0.82, 1.13; $p = 0.659$), nor were there significant predictors for the occurrence of severe injuries, defined as ISS ≥ 15 (OR = 1, 95% CI = 0.82, 1.23; $p = 0.952$).

Table 2. Demographics of the study population

Variable	Civilian events	Military events
Age	40 years (SD ± 3.65)	24.5 years (SD ± 1.41)
Sex, n (%)		
Male	7366 (79.4)	4505 (79.0)
Female	1742 (20.6)	1197 (21.0)
Mortality, n (%)	421 (4.6)	267 (4.7)
ISS	8 (IQR = 2)	9 (IQR = 10.5)

SD: standard deviation; ISS: injury severity score; IQR: interquartile range.

Injury profile and severity of injuries

The overall distribution of injuries among civilians did not differ significantly from that observed in the military population. Injuries involving the head–face–neck, thoracic, and abdominal regions occurred in 29.8% vs. 34%, 8.8% vs. 7.7%, and 7.3% vs. 6.5% of cases, respectively. However, extremity injuries were significantly more frequent among military casualties than among civilians (39.8% vs. 30.8%; $p < 0.05$). Conversely, head and thoracic injuries were more prevalent in the civilian population (31.9% vs. 18.1% and 20.4% vs. 9.9%, respectively), while severe extremity injuries occurred more commonly in military personnel (51.8% vs. 30.9%). None of the included studies specified whether the explosive devices involved were high-order or low-order explosives.

Discussion

The objective of this review was to compare the risk factors associated with mortality among patients injured

by different types of explosions across civilian and military settings. Interestingly, the finding data suggests that, despite clear differences in the context and underlying causes of explosions between these populations, there are several similarities in injury patterns and outcomes. These commonalities may indicate the degree of transferability in treatment strategies and clinical management approaches across both settings.

As one would expect, the victims of war-related explosions were young adults with a mean age of 24.5 years, while civilian victims had a mean age of 40.0 years. The patterns of injuries in the civilian population showed a greater proportion of severe injuries to the head and thoracic body regions and a lower incidence of severe injuries to the pelvic and extremities compared to the military population. These differences can be ascribed to the types of explosive devices responsible for the explosions in the civilian and military environment and the universal use of protective equipment by the military personnel. IEDs and landmines, also known as antipersonnel mines, are among the most common causes of localized military explosions aimed at increasing the logistic burden for caring for the victims by causing either traumatic amputations of the lower extremities or massive lower extremities and pelvic injuries, as opposed to the civilian explosions that predispose the victims to head and thoracic injuries.[41,43] Some degree of similarity between intentional and terrorism explosions is observed when high explosives are placed in maximum proximity to potential victims; in this setting, a massive amount of the explosive energy is transferred to victims.[41,43]

The placement of an explosive device in enclosed environments, such as within a vehicle during assassination attempts, or in confined public spaces like buses, bars, or coffee shops during terrorist attacks, amplifies the impact of the blast by redirecting and concentrating the pressure wave toward victims inside the space.[44,45] In contrast, unintentional outdoor explosions, like the one mentioned in Beirut, tend to produce a more heterogenous injury pattern due to the dissipation of the blast wave in open air.[29]

Explosions typically occur in one of four primary contexts: Domestic settings (e.g., gas leaks or residential fires), industrial environments involving occupational hazards (e.g., mining, demolition, or the production of chemical products and fuels), armed conflict zones, and acts of terrorism. An additional critical factor influencing the resulting injury patterns is the physical environment in which the explosion takes place, as factors such as confinement, proximity, and structural surroundings significantly affect the blast's impact. Underwater blast waves cause greater damage due to the water's incompressibility.[30,31] These waves travel faster and farther than in the air, leading to more severe injuries over longer distances.[32] Personnel floating in water are more prone to abdominal than thoracic injuries, while fully submerged victims face equal risk of both, even at 3 times the blast distance.[46]

Explosion-related injuries are classified into four categories based on the mechanism of injury (Table 3 and Fig. 3) and by distance from the blast epicenter (Fig. 1):

- Primary blast injuries result from the direct interaction of the blast shock wave with the body. Gas-containing organs, such as the middle ear, lungs, and gastrointestinal tract, are at particular risk. In contrast, solid organs, including the skin, are more resistant to the blast wave. Notably, patients with isolated primary blast injury may present with minimal signs of trauma despite significant internal damage.
- Secondary blast injuries are caused by energized fragments propelled by the blast. These include both *primary fragments* (components of the explosive device itself) and *secondary fragments* (environmental debris such as glass, metal, or building materials). These injuries often result in penetrating trauma, lacerations, traumatic amputations, and traumatic brain injury, and can affect any part of the body.
- Tertiary blast injuries occur when the victim is physically displaced by the blast wind and thrown against a hard surface or when heavy objects are propelled into the body. These injuries are commonly associated with blunt trauma, crush injuries, and structural collapse. The combination of primary and tertiary forces may lead to complex injuries such as limb avulsion, crush syndrome, and compartment syndrome.
- Quaternary blast injuries result from the thermal effects of the blast, combustion gases, and chemical or environmental contaminants. Victims may present with thermal burns, asphyxiation, and toxic syndromes secondary to fuel, metal exposure, or environmental contamination.

Limitations of the evidence and review process

Several limitations were identified in the available body of evidence. First, there was substantial heterogeneity

Table 3. Classification of trauma explosion

Mechanism	Cause	Organs affected	Typical injuries
Primary	Increased pressure	Predominates in organs with air: lungs, middle ear, gastrointestinal tract	Tympanic rupture
			Lung injuries
			Intestinal perforation
			TBI
			Eye injury
Secondary	Splinters/shrapnel	Whole body	Penetrating injuries
			Lacerations
			Compartment syndrome
Tertiary	The victim is thrown against a stationary object, or objects are thrown towards people	Whole body	Blunt trauma (contusions, fractures, crush injuries)
			Polytrauma
			Amputations
			Compartment syndrome
			Crush syndrome
			TBI
Quaternary	Other explosion-related injuries (e.g., heat)	Whole body Burns: unprotected skin (face, neck, hands)	Burns
			Inhalation
			Smoke poisoning
			Infections
Quinary	Bacteria, chemicals, radiologic materials	Hyperinflammatory or hypermetabolic responses	Shock, fever, coagulopathy without clear trauma mechanisms

TBI: traumatic brain injury.

across studies in terms of study design, populations examined, injury classification systems, and outcome measures, which limited direct comparability and precluded pooled analysis. Many of the included studies were retrospective or descriptive, often with small sample sizes and limited external validity. In addition, methodological details were frequently underreported, reducing the ability to assess study quality and risk of bias comprehensively.

Contextual factors – such as the type of explosive device used, the environmental setting of the incident (e.g., open vs. confined spaces), and the use of personal protective equipment – were inconsistently reported, further complicating interpretation of findings. Notably, within the civilian population, most studies did not differentiate between injuries resulting from accidental explosions and those related to acts of terrorism, limiting the specificity of conclusions drawn for this subgroup.

Regarding the review process itself, several limitations must also be acknowledged. Although a comprehensive and systematic search strategy was employed, it is possible that relevant studies published in non-English languages or non-Spanish languages, as well as those in the grey literature, were inadvertently excluded. Screening and data extraction were conducted independently by the authors, with discrepancies resolved through consensus or third-party adjudication. Nonetheless, the potential for subjectivity in data interpretation remains and may have influenced the synthesis of findings. The authors emphasize that this review provides a descriptive synthesis rather than a meta-analytic comparison.

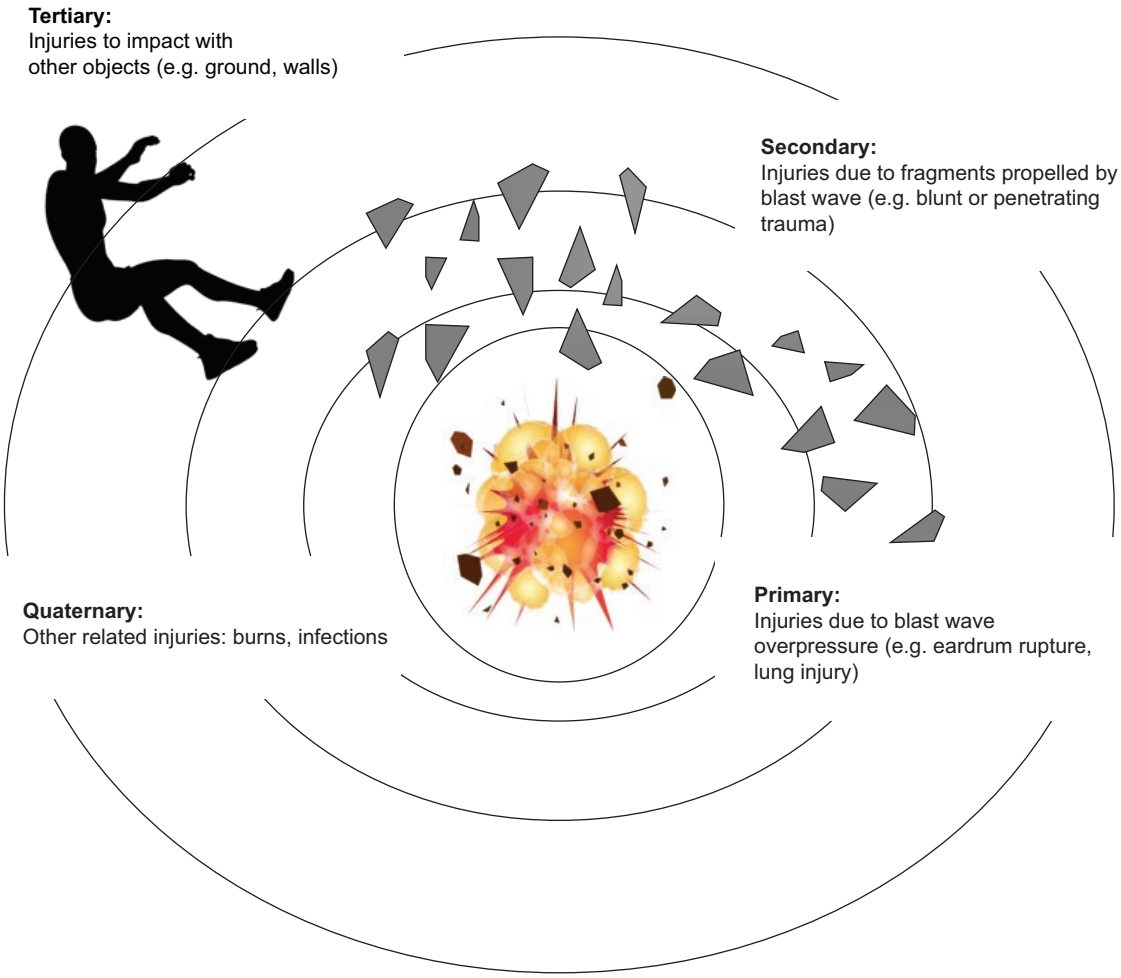

Figure 3. *Type of explosion injuries.*

Conclusions

The findings of this review indicate that clinical experience derived from explosions occurring in one setting – such as military or combat zones – may not be fully generalizable to explosions occurring in other contexts, such as civilian or accidental events, as demographic, environmental, and contextual factors contribute to distinct injury patterns.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. 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 or creation of the content of this manuscript.

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Impulsando los hallazgos de índices celulares y reactantes de fase aguda como predictores de absceso tras apendicectomía

Boosting the findings of cellular indices and acute phase reactants as predictors of abscess after appendectomy

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Estimado Editor:

Quisiera felicitarles por la publicación del artículo de Moreno-Alfonso et al.[1] titulado «Índices celulares y reactantes de fase aguda como predictores de absceso tras apendicectomía», el cual definitivamente es relevante tanto para el abordaje de las complicaciones de la apendicitis mencionada en el presente caso como para otras patologías quirúrgicas y no quirúrgicas. Este ejemplar reafirma la importancia del hemograma como principal prueba inicial paraclínica, de muy bajo costo y alto beneficio en el abordaje de los pacientes con apendicitis. Como es bien sabido, la apendicitis tiene una alta incidencia en el mundo actual y es la principal causa de emergencia quirúrgica tanto en adultos como en niños.[2] En estos últimos tiene aún mayor relevancia, pues el abordaje se ve enlentecido por tratarse de un interrogatorio principalmente indirecto y porque las manifestaciones clínicas pueden verse enmascaradas. Esto conlleva la presentación de complicaciones tales como perforación o absceso, antes y después de la intervención quirúrgica, mismas que se mencionan en la publicación.

Previamente se había hablado en la literatura sobre la importancia de los reactantes de fase agudas como predictores de complicaciones en distintas enfermedades; sin embargo, algo que destaca en el artículo es la comparación con tres parámetros que vienen emergiendo en nuestros días, como son el índice neutrófilos-linfocitos, el índice plaquetas-linfocitos y el índice bilirrubina directa-linfocitos. El índice neutrófilos-linfocitos ya había demostrado su utilidad para diferenciar la apendicitis complicada de la no complicada.[3] Esta contribución de los autores sin duda impulsará el desarrollo de nuevos estudios para enriquecer la evidencia hasta ahora disponible sobre dichos marcadores. Para favorecer esto, nos gustaría hacer un par de comentarios acerca de la metodología y los resultados obtenidos en el estudio.

Primero, hacer mención de la selección de los pacientes, incluyendo menores de 15 años, lo cual es esperado, ya que esta población en específico es mayormente susceptible a complicaciones y, por tanto, a mayor morbimortalidad; sin embargo, sería interesante aplicar su método en un grupo etario distinto, como los adultos mayores, que también se consideran de riesgo.

En segundo lugar, en el apartado Método se menciona el tratamiento que se dio a los pacientes de manera homogénea, a base de cefotaxima y metronidazol, lo cual también es una medida estándar en muchos pacientes con esta enfermedad, pero sería bueno mencionar si existe bibliografía acerca de resultados similares brindando otro esquema antibiótico.

Tercero, como parte del abordaje de la apendicectomía se menciona una técnica de mínima invasión, la apendicectomía transumbilical videoasistida, la cual ha demostrado *per se* una menor incidencia de complicaciones, trans- y posquirúrgicas, en

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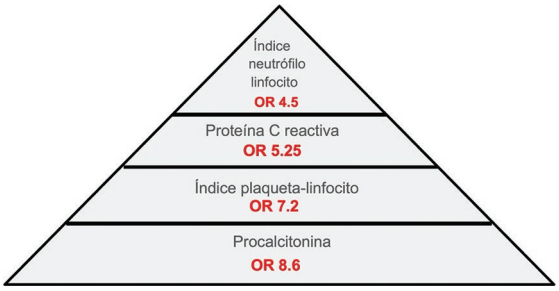

Figura 1. *Pirámide representativa de los hallazgos presentados por los autores sobre el objetivo principal del artículo. OR: odds ratio.*

comparación con las técnicas habituales de laparoscopia y laparotomía. A pesar de mencionar que no hubo diferencias significativas en cuanto a la aparición de absceso tras la apendicectomía, en otras publicaciones sí presentó diferencia, lo que podría significar un sesgo de selección.[4]

Finalmente, queremos resaltar los resultados de los autores mencionados con una figura de elaboración propia (Fig. 1).

Solo nos queda felicitar a los autores por su exitosa e interesante publicación, la cual será considerada para futuros trabajos en la rama de cirugía. Nos mantenemos expectantes de su respuesta.

Financiamiento

Los autores declaran no haber recibido financiamiento para este estudio.

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, historias clínicas ni muestras biológicas humanas, por lo que no requiere aprobación ética. No se aplican las guías SAGER.

Declaración sobre el uso de inteligencia artificial. Los autores declaran que no se utilizó ningún tipo de inteligencia artificial generativa para la redacción ni la creación de contenido de este manuscrito.

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