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EDITORIAL

Transcendence of scientific research: dissemination, diffusion, and impact factor

Trascendencia de la investigación científica: divulgación, difusión y factor de impacto

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Scientific research is a valuable activity, whose significance depends on its results reaching the target audience, which assigns importance in a particular area.

There are several reasons why physicians should publish in scientific journals; among the main ones are: knowledge should be the property of all humanity, the importance of providing truthful and reliable information, high professional education, and possibly some benefits such as career promotion or attracting scholarships and resources, among others. The main objective of publishing as physicians should be the dissemination of knowledge[1].

The dissemination of articles can be done through the publishing house, and currently, personally, this activity is facilitated through social networks. More than obtaining a "like" reaction, which can lead to developing "vanity metrics," the dissemination of articles on social networks amplifies reaching out to the public, thus favoring that research results reach those who can use them, as references or for decision-making.

While general networks like Facebook, X (formerly known as Twitter), and Instagram can offer broad exposure of research results, academic networks facilitate access to other communities. Thus, ResearchGate, Academia, and even Mendeley allow access to niches where the target audience of the research may be found, which can determine its significance.

Unlike unrecommended practices, such as citation circles, where authors or journals cite each other, disseminating articles on networks does not imply a response from the target audience. Sharing research results on networks is a proactive way for them to reach their users before they even engage themselves in the search process. Legally recommending or sharing articles from our network extends the dissemination of websites, and this is one of the activities supporting the articles of *Cirugía y Cirujanos.*

The impact factor (IF) of publications refers to the number of citations in the JCR among the overall number articles published in the last 2 years[2]. Although the IF is an important gauge for scientific research to reach target audiences that can use it as a basis for other studies, it is also important to maintain the pursuit of humanity's benefit and not just the numerical value of the impact factor alone[2,3].

More frequently, the IF of journals has been used to guide decisions on appointments, grant allocations, and scientific policies. The true value of the measure lies in evaluating the relative importance of articles published in a journal compared to a different journal with similar content[4]. The primary objective should not only be to have a high IF because to increase academic quality the following is required: 1) attracting quality articles, 2) editorial work, 3) increasing the visibility of the journal, and 4) cooperation between editors and reviewers[2]. To achieve this, it is essential to have a reliable publishing platform, an objective review process, a low acceptance rate (controversial if knowledge dissemination is required), timely work, good professional English editing and proofreading, statistical review, continuous education of editors,

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authors, and reviewers (something that still needs to ne improved), and collaboration with international publishers[2].

The IF of *Cirugía y Cirujanos* has been gradually increasing, reaching 0.5 this year. Editorial work can only be evaluated over time, as changes are slow (after year 4). Annual changes in citable production and the IF are not correlated. The impact of academic work is of utmost importance, so academics and other researchers are invited to continue submitting their high-quality work to *Cirugía y Cirujanos*.

Finally, the objective of writing, publishing, and disseminating in a scientific and academic manner could be driven by the desire to make a change in the world, with compassion and commitment, with something rigorous and valuable to contribute. Writing with the sole purpose of fulfilling the legacy of medicine and serving the goals of academic life[5].

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ORIGINAL ARTICLE

Risk factors for readmission after a cholecystectomy: a case-control study

Factores de riesgo de reingreso hospitalario tras una colecistectomía: un estudio de casos y controles

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Abstract

Objective: *The aim of this study was to assess the risk factors associated with 30-day hospital readmissions after a cholecystectomy.* **Methods:** *We conducted a case–control study, with data obtained from UC-Christus from Santiago, Chile. All patients who underwent a cholecystectomy between January 2015 and December 2019 were included in the study. We identified all patients readmitted after a cholecystectomy and compared them with a randomized control group. Univariate and multivariate analyses were conducted to identify risk factors.* **Results:** *Of the 4866 cholecystectomies performed between 2015 and 2019, 79 patients presented 30-day hospital readmission after the surgical procedure (1.6%). We identified as risk factors for readmission in the univariate analysis the presence of a solid tumor at the moment of cholecystectomy (OR = 7.58), high pre-operative direct bilirubin (OR = 2.52), high pre-operative alkaline phosphatase (OR = 3.25), emergency admission (OR = 2.04), choledocholithiasis on admission (OR = 4.34), additional surgical procedure during the cholecystectomy (OR = 4.12), and post-operative complications. In the multivariate analysis, the performance of an additional surgical procedure during cholecystectomy was statistically significant (OR = 4.24).* **Conclusion:** *Performing an additional surgical procedure during cholecystectomy was identified as a risk factor associated with 30-day hospital readmission.*

Keywords: *Cholecystectomy. Hospital readmission. Risk factor.*

Resumen

Objetivo: *El objetivo de este estudio fue evaluar los factores de riesgo asociados al reingreso hospitalario en los primeros 30 días post colecistectomía.* **Métodos:** *Estudio de casos-controles con datos obtenidos del Hospital Clínico de la UC-Christus, Santiago, Chile. Se incluyeron las colecistectomías realizadas entre los años 2015-2019. Se consideraron como casos aquellos pacientes que reingresaron en los 30 primeros días posterior a una colecistectomía. Se realizó un análisis univariado y multivariado de diferentes posibles factores de riesgo.* **Resultados:** *De un total de 4866 colecistectomías, 79 pacientes presentaron reingreso hospitalario. Los resultados estadísticamente significativos en el análisis univariado fueron; tumor sólido al momento de la colecistectomía (OR = 7.58) bilirrubina directa preoperatoria alterada (OR = 2.52), fosfatasa alcalina preoperatoria alterada (OR = 3.25), ingreso de urgencia (OR = 2.04), coledocolitiasis al ingreso (OR = 4.34) realización de otros procedimientos (OR = 4.12) y complicaciones postoperatorias. En el análisis multivariado sólo la realización de otro procedimiento durante la colecistectomía fue estadísticamente significativa (OR = 4.24).* **Conclusión:** *La realización de otros procedimientos durante la colecistectomía es un factor de riesgo de reingreso hospitalario en los 30 días posteriores a la colecistectomía.*

Palabras clave: *Colecistectomía. Reingreso hospitalario. Factor de riesgo.*

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Introduction

The reduction of hospital readmissions has increasingly attracted public health attention because they are frequent and expensive and a significant percentage of them can be prevented. For some pathologies, percentages as high as 19% at 30 days and 34% at 90 days have been reported[1,2]. Hospital readmissions for post-operative complications are not only associated with adverse health outcomes in patients, but are also often used as an indicator of quality of care, and are considered an opportunity for improvement, reducing health costs[3]. In the United States, hospitals with a percentage of readmission higher than expected can be sanctioned, for this reason; health centers allocate a significant amount of resources to identify modifiable risk factors to decrease readmission rates[1].

Cholelithiasis is one of the most frequent gastrointestinal pathologies, affecting between 10% and 30% of the Western population[4]. In Chile, the incidence of cholelithiasis is even higher compared to other countries, reaching 13.1% in men and 36.7% in women over 20 year's old[5]. For this reason, cholecystectomy is one of the most frequently surgical procedures in our country: in 2016, 59,420 cholecystectomies were performed[6].

Several factors have been associated with readmission after an abdominal surgery, such as age, comorbidities, previous hospitalization for more than 7 days, hospitalization in an intensive care unit, and type of surgery, among others[7,8]. In the case of cholecystectomy, there are some factors that may be associated with readmission, such as emergency cholecystectomy, duration of symptoms before surgery, open surgery, additional procedures, and experience of the surgical team, among others[9-11]. Despite this, there is only low-quality evidence for risk factors associated with readmission after a cholecystectomy. Therefore, the aim of this study was to identify risk factors for 30-day readmission after a cholecystectomy.

Methods

Study design

We conducted a case–control study using data from UC-Christus Clinical Hospital from Santiago, Chile. All patients who underwent a cholecystectomy between January 2015 and December 2019 were included in the study. Authorization was obtained from the Institutional Review Board of the Pontificia Universidad Católica de Chile.

Definitions

Cases

Patients older than 18 year's old underwent a cholecystectomy and presented an unplanned 30-day post-operative hospital readmission. Both elective and emergency cholecystectomies and patients in whom some additional procedure was performed during surgery were included in the study. Controls: patients older than 18 year's old who underwent a cholecystectomy and did not presented an unplanned 30-day post-operative hospital readmission. Both elective and emergency cholecystectomies were included in the study, as well as those patients in whom some additional procedure was performed during surgery. One control was randomly selected for each case from a pool of possible controls.

Exclusion criteria

All patients with severe acute pancreatitis according to the 2012 Atlanta classification, those who had a remnant cholecystectomy, and those who were in critical condition at the time of the cholecystectomy were excluded from the study.

Analyzed data

Medical records were reviewed, registering sociodemographic data (age, gender, and comorbidities); admission type (elective or non-elective); presence of choledocholithiasis; laboratory data (complete blood cell count, liver functional tests, C-reactive protein test, and pre-operative serum lipase); surgical data (surgical approach, intraoperative findings, intraoperative complications; additional procedures, surgical technique and use of abdominal drainage); overall complications; short-term results (any complication or mortality occurring within 30 post-operative days, according to Clavien-Dindo classification), and length of hospital stay. For all cases, we included the cause of readmission.

Source of data and statistical analysis

The data obtained in medical records were collected in a database using Microsoft Excel® software. Statistical analysis was performed using SPSS® software. Qualitative variables were presented using absolute numbers and percentages. Numerical variables

were presented using mean and standard deviation (SD). In the first stage, we performed a univariate analysis to explore the risk factors associated with postoperative 30-day hospital readmission, based on the odds ratio (OR) estimation.

For univariate analysis of laboratory data, we transformed these into qualitative variables using a cut-off value: for hemoglobin, we consider as "low" a level < 10 g/dL and for the white blood cell we consider as "high" a count over 10,000/mL (this cutoff value was described in the 2013 Tokyo guidelines as diagnostic criteria for acute cholecystitis). For the following variables, we consider "high" a level higher than 2 mg/dL for total bilirubin; 0.45 mg/dL for direct bilirubin; 37 IU/L for aspartate aminotransferase (glutamic oxaloacetic transaminase); 45 IU/L for alanine aminotransferase (glutamic pyruvic transaminase); 60 IU/L for gamma-glutamyl transferase and 150 UI/L for alkaline phosphatase (these cutoff values were described in the 2013 Tokyo guidelines as diagnostic criteria for acute choledocholithiasis). Finally, for the C-reactive protein we consider it as "high" a level over than 1 mg/dL, and for the serum lipase a level over than 60 IU/L (these cutoff values are described as pathologic in the laboratory who performed the analysis). Variables with an OR different than the null value were considered as risk factors associated with hospital readmission. Existence of a significant association between the variables was evaluated using the Chi-squared test and 95% confidence interval (CI) for each OR. Standard significance levels ($p < 0.05$) were used for all analyses.

In the second stage, the statistically significant variables found in the univariate analysis were included in a multivariate logistic regression model (Wald forward method) to select the variables associated with the "case" condition and their respective OR and CI 95%.

Results

Between January 2015 and December 2019, a total number of 4866 cholecystectomies were performed at UC-Christus Clinical Hospital. Seventy-nine (1.6%) patients presented a 30-day hospital readmission after cholecystectomy and met the inclusion criteria to be considered as a case for this study.

Description of the cases

Sociodemographic, laboratory, and surgical data are presented in table 1. The mean age of the cases was 47 ± 14 years old). Twenty-six patients (32.9%) were male, 17 (21.5%) had a history of high blood pressure, 11 (13.9%) chronic liver disease, 9 (11.4%) diabetes mellitus, and 7 (8.9%) had a solid tumor at the moment the cholecystectomy was performed. Thirty-six (45.6%) patients had presented an emergency admission, being acute cholecystitis the most frequent cause (n = 27/36; 75%) of this type of admission. Eight (10.1%) patients were admitted for choledocholithiasis and 6 (7.6%) for acute biliary pancreatitis. Minimally invasive approach was performed in all patients and 2 (2.5%) patients required conversion to open technique. The most frequent abnormal intraoperative finding was acute cholecystitis (N: 16/79; 20.3%), half of them edematous.

Intraoperative cholangiogram (IOC) was performed in 12 patients (15.2%) and 20 (25.3%) patients required an additional procedure during the cholecystectomy, the most frequent were endoscopic retrograde cholangiopancreatography (N: 7/20; 35%), liver biopsy (N: 4/20; 20%) and hernioplasty (N: 5/20; 25%) (Table 2). Six patients had an intraoperative complication (6.3%), being the most frequent intraoperative bleeding (N:4/6; 66.7%). Five patients required abdominal drainage. Five patients presented postoperative complications: 1 CD-I, 1 CD-II, 2 CD-IIIa, and 1 CD-IIIb, which required reintervention due to hemoperitoneum. The mean hospital stay for this group was 2.38 ± 2.0 days.

The causes for readmission are presented in table 3. The main cause of readmission was abdominal pain with no presence of evident post-operative complication (N: 17/79; 21.5%), followed by residual choledocholithiasis (N: 16/79; 20.3%), nausea, vomiting, or diarrhea (N: 11/79; 13.9%), presence of intra-abdominal collection (N: 6/79; 7.6%), biliperitoneum (N: 5/79; 6.3%), and acute pancreatitis (N: 5/79; 6.3%). The causes for readmission of patients in whom an additional procedure was performed are detailed in table 4.

Univariate analysis

Table 5 shows the results of the univariate analysis between the different clinical variables and the case or control condition.

There were no significant differences in age, gender, and comorbidities between both groups. The presence of a solid tumor at the time of cholecystectomy was higher in cases than controls ($p = 0.029$). In the preoperative laboratory tests, there were statistically significant differences between both groups in "high pre-operative BD" ($p = 0.042$) and "high pre-operative AF" ($p = 0.024$), both seen more frequently in the case group. The variable "high pre-operative GPT" was

Table 1. Characterization of cases

Sociodemographic data (n = 79)	
Age (mean, SD)	47 ± 14 years-old
Male gender (n, percentage)	26 (32.9%)
High blood pressure (n, percentage)	17 (21.5%)
Chronic liver disease (n, percentage)	11 (13.9%)
Diabetes mellitus (n, percentage)	9 (11.4%)
Solid tumor (n, percentage)	7 (8.9%)
Peripheral artery disease (n, percentage)	4 (5.1%)
Heart failure (n, percentage)	3 (3.7%)
Chronic kidney disease (n, percentage)	2 (2.5%)
Chronic obstructive pulmonary disease (n, percentage)	2 (2.5%)
Coronary heart disease (n, percentage)	1 (1.3%)
Accident cerebrovascular (n, percentage)	1 (1.3%)
Laboratory data (n = 79)	
Hemoglobin (mean, SD)	13.65 ± 1.65 g/dL
White blood cell count (mean, SD)	10499.44 ± 8680.24/mL
Total bilirubin (mean, SD)	0.86 ± 1.3 mg/dL
Direct bilirubin (mean, SD)	0.44 ± 0.61 mg/dL
GOT (mean, SD)	84.18 ± 186.17 UI/L
GPT (mean, SD)	80.63 ± 145.86 UI/L
GGT (mean, SD)	95.12 ± 142 UI/L
ALP (mean, SD)	113.5 ± 67.18 UI/L
CRP (median, range)	0.61 (0.03-30) mg/dL
Serum lipase (median, range)	29.5 (12-649) UI/L
Clinical data (n = 79)	
Emergency admission (n, percentage)	36 (45.6%)
Choledocholithiasis (n, percentage)	8 (10.1%)
Acute pancreatitis (n, percentage)	6 (7.6%)
Laparoscopic approach (n, percentage)	79 (100%)
Conversion (n, percentage)	2 (2.5%)
Intraoperative cholangiogram (n, percentage)	12 (15.18%)
Additional procedures (n, percentage)	20 (25.31%)
Intraoperative complications (n, percentage)	5 (6.3%)
Bleeding (n, percentage)	4 (80%)
D-type bile duct injury (n, percentage)	1 (20%)
Abdominal drain (n, percentage)	5 (6.32%)
Postoperative complication (n, percentage)	5 (6.32%)
Clavien-Dindo I (n, percentage)	1 (20%)
Clavien-Dindo II (n, percentage)	1 (20%)
Clavien-Dindo IIIa (n, percentage)	2 (40%)
Clavien-Dindo IIIb (n, percentage)	1 (20%)
Reoperation (n, percentage)	1 (1.26%)
Length of stay (mean, SD)	2.38 ± 2 days

GOT: glutamic oxaloacetic transaminase; GPT: glutamic pyruvic transaminase; GGT: gamma-glutamyl transferase; ALP: alkaline phosphatase; CRP: C-reactive protein; SD: standard deviation.

Table 2. Additional intraoperative procedures in the cases

Additional procedures (n = 20)	
ERCP (n, percentage)	7 (35%)
Hernioplasty (n, percentage)	5 (25%)
Liver biopsy (n, percentage)	4 (20%)
Previous Roux-en-Y gastric bypass mesenteric defects closure (n, percentage)	1 (5%)
Transcholedochal bile duct exploration (n, percentage)	1 (5%)
Endoscopic EndoBarrier® withdrawal (n, percentage)	1 (5%)
Cervical tumor resection (n, percentage)	1 (5%)

ERCP: endoscopic retrograde cholangiopancreatography.

higher in cases (p = 0.048), although the 95% CI for the OR included the null value (CI 95% 1-5.17).

Emergency initial admission was significantly more frequent in cases than controls (p = 0.033). Cases had significantly more additional procedures during cholecystectomy compared to controls (p = 0.003). Patients who presented post-operative complications also had a higher rate of hospital readmission. Finally, the diagnosis of choledocholithiasis at admission was also higher in cases than controls (p = 0.0499).

Table 3. Causes for readmission

Cause for readmission (n = 79)	
Abdominal pain (n, percentage)	17 (21.5%)
Residual choledocholithiasis (n, percentage)	16 (20.3%)
Nausea, vomiting, and diarrhea (n, percentage)	11 (13.9%)
Intra-abdominal collection (n, percentage)	6 (7.6%)
Acute pancreatitis (n, percentage)	5 (6.3%)
Biliary peritonitis (n, percentage)	5 (6.3%)
Intestinal obstruction (n, percentage)	4 (5%)
Decompensated heart failure (n, percentage)	2 (2.5%)
Thromboembolic disease (n, percentage)	2 (2.5%)
Upper gastrointestinal bleeding (n, percentage)	2 (2.5%)
Pneumonia (n, percentage)	1 (1.2%)
Diabetic ketoacidosis (n, percentage)	1 (1.2%)
Trigeminal neuralgia (n, percentage)	1 (1.2%)
Fecal impaction (n, percentage)	1 (1.2%)
Hemoperitoneum (n, percentage)	1 (1.2%)
Incisional hernia (n, percentage)	1 (1.2%)
Surgical wound infection (n, percentage)	1 (1.2%)
Acute diverticulitis (n, percentage)	1 (1.2%)
Others (n, percentage)	1 (1.2%)

Multivariate analysis

We included in the model eight variables whose $p < 0.05$ in the univariate analysis. The only variable selected by the multivariate model was performance of an additional procedure during cholecystectomy, with p-values 0.015, and OR 4.24 (95 CI% 1.33 and 13.55).

Discussion

The present study identified that the performance of an additional procedure during cholecystectomy is a risk factor associated with readmission after surgery. There are few studies that evaluate risk factors associated with readmission after cholecystectomy. The study performed by Rana et al. (2016) evaluated risk factors associated with 30-day readmission after a laparoscopic cholecystectomy, including 44 readmissions in a 4-year period of 747 patients undergoing laparoscopic cholecystectomy (readmission rate of 5.89%). They concluded that patients with more comorbidities had a higher rate of readmissions, but it was the only variable evaluated in their study[12]. Another study conducted by Manuel-Vásquez et al. (2017) evaluated the causes of hospital readmission at 30 and 90 days after cholecystectomy, during 5 years. Of 1423 cholecystectomies performed, 50 were readmitted within 30 days (readmission rate of 3.5%). In their study, intra-abdominal collections (32%) and choledocholithiasis (10%) were the main causes for readmission, while in our study the main causes were abdominal pain (21.5%) and choledocholithiasis (20.3%). Intra-abdominal collections only represented 7.6% in our series[13].

Awolaran et al. (2017) conducted an observational study evaluating 328 laparoscopic cholecystectomies performed over a period of 6 months. There were 22 readmissions within 30 days after laparoscopic cholecystectomy, with a readmission rate of 6.7%, higher compared to our study. Furthermore, they found that the readmission rate was lower in those patients with longer hospital stays[14], a variable that was not an associated factor in our study.

On the other hand, in the meta-analysis conducted by McIntyre et al. (2020), risk factors associated with 30-day readmission after laparoscopic cholecystectomy were evaluated. Forty-four studies from 25 countries were included in the study, analyzing 1,573,715 cholecystectomies, with a readmission rate of 3.3%. Only seven studies performed a univariate analysis of risk factors, evaluating obesity, use of a single port, and major outpatient surgery, all of them were not significant. When they evaluated the causes of readmission, these were similar to those we found in our study, highlighting biliary complications (46%), abdominal pain (16%), and nausea and vomiting (11.8%)[15].

In the study carried out by Rosero and Joshi, they found a 2.2% readmission rate among 230,745 patients who underwent outpatient laparoscopic cholecystectomy in a 3-year period. In the univariate analysis of this study, they reported as risk factors for 30-day readmission after an outpatient laparoscopic cholecystectomy the following variables: age, male gender, race, health insurance, emergency surgery, IOC, bile duct exploration, chronic obstructive pulmonary disease, heart failure, chronic liver damage, and cancer[16]. Finally, in the study conducted by Altieri et al. (2020), they reported a 30-day readmission rate of 4.58% among 591,627 patients who underwent elective or emergency cholecystectomy in a 6-year period in New York State. They evaluated gender, age, race, and health insurance, type of surgery, comorbidities, and post-operative complications as risk factors for readmission. In the univariate analysis of this study, they reported all these factors as statistically significant but did not perform a multivariate analysis[17].

In our study, we analyzed 4866 elective and emergency cholecystectomies with 1.6% readmission rate, and following a multivariate analysis, we only found the performance of an additional procedure as a risk factor for 30-day readmission.

Table 4. Causes for readmission in patients with an additional procedure

Additional procedure and cause for readmission	Treatment
ERCP (n = 7)	
– Residual choledocholithiasis (n = 3)	Repeat ERCP
– Upper gastrointestinal bleeding (n = 2)	Endoscopic hemostasis
– Acute pancreatitis (n = 1)	Analgesics and bowel rest
– Intestinal obstruction (n = 1)	Analgesics and bowel rest
Hernioplasty (n = 5)	
– Bilateral inguinal hernia repair. Readmission for intestinal obstruction (n = 1)	Analgesics and bowel rest
– Umbilical hernia repair. Readmission for multilobar pneumonia (n = 1)	Antibiotics
– Umbilical hernia repair. Readmission for pain, vomiting, and nausea (n = 1)	Analgesics
– Umbilical hernia repair. Readmission for deep vein thrombosis (n = 1)	Anticoagulation
– Unilateral inguinal hernia repair. Readmission for choledocholethiasis	ERCP
Liver biopsy (n = 4)	
– Intra-abdominal collection (n = 3)	Antibiotics
– Abdominal pain (n = 1)	Analgesics
Choledochoplasty and T-tube insertion for Mirizzi syndrome (n = 1)	
– Biloma (n = 1)	Antibiotics
Cervical tumor resection (n = 1).	
– Biliary peritonitis for Lushka (n = 1)	Exploratory laparoscopy
Endoscopic EndoBarrier® withdrawal (n = 1)	
– Intra-abdominal collection (n = 1)	Antibiotics
Previous Roux-en-Y gastric bypass mesenteric defects closure (n = 1)	
– Abdominal pain (n = 1)	Analgesics

ERCP: endoscopic retrograde cholangiopancreatography.

Table 5. The eight statically significant risk factors for 30-day readmission at univariate analysis and multivariate analysis

Risk factors	Cases (n = 79)	Control (n = 79)	OR (IC 95%)	p	ORad (IC 95%)
Solid tumor	7	1	7.58 (0.91-63.15)	0.029	-
High direct bilirubin	26	13	2.52 (1.01-6.30)	0.042	-
High ALP	16	15	3.25 (1.12-9.44)	0.024	-
High GPT	23	11	2.27 (1-5.17)	0.048	-
Emergency admission	36	23	2.04 (1.06-3.93)	0.033	-
Choledocholithiasis	8	2	4.34 (0.89-21.12)	0.049	-
Additional procedures	20	6	4.12 (1.56-10.93)	0.003	4.24 (1.33-13.55)
Postoperative complications	5	0	-	0.023	-

GPT: glutamic pyruvic transaminase; ALP: alkaline phosphatase; OR: odds ratio; ORad: odds ratio adjusted in a multivariate logistic regression model (Wald forward method).

Thirty-five percent of these procedures were endoscopic retrograde cholangiopancreatography (ERCP), 25% hernioplasty, and 20% liver biopsy. This finding had not been reported in other studies, and it may contribute to reduce hospital readmission. If we analyze the additional procedures performed in these 20 patients, 12 were directly related to the cause of readmission (mainly ERCP and liver biopsy). In these cases, the potential complications of the additional procedures are added to the potential complications of the cholecystectomy itself.

We consider that the strength of our study is the long period of time analyzed (5 years), which included a large number of cholecystectomies performed during this time. In addition, we analyzed multiple variables that could explain the readmission of these patients after cholecystectomy and compared it with a control group. Since readmission is an unusual outcome after a cholecystectomy, the number of patients included in the univariate and multivariate analysis was rather small; this could explain the non-statistically significance of some variables with biological plausibility. Furthermore, a limitation of our study is that data collection was carried out in only

one center and the patients could have been readmitted to another center, being missed as cases. Besides, due to the retrospective nature of this study, the intraoperative findings and the surgical technique were evaluated through the medical records; in this scenario, some relevant details might be missed. In future studies, a prospective multicenter collaboration could be beneficial to reach a greater number of patients.

Conclusion

Our study identified that undergoing an additional procedure during a cholecystectomy is a risk factor for 30-day hospital readmission. The most frequent additional procedures were ERCP, hernioplasty, and liver biopsy.

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Conflicts of interest

There are no conflicts of interest for any author.

Ethical disclosures

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

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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ORIGINAL ARTICLE

The effect of antiangiogenic agent aflibercept on surgically induced endometriosis in a rat model

El efecto del agente antiangiogénico aflibercept sobre la endometriosis inducida quirúrgicamente en un modelo de rata

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Abstract

Objective: *The aim of the study is to show for the first time how aflibercept affects endometriosis lesions.* **Material and methods:** *Surgically induced endometriosis in Wistar albino female rats. Rats with endometriosis were randomly divided into three groups: control (Co), aflibercept (Af), and leuprolide acetate (Le). Then, Af, aflibercept, and Le received leuprolide acetate. The control group was not treated. The weights and changes in intra-abdominal adhesions of the rats before and after treatment were recorded according to the Blauer adhesion score. Blood extracted for sacrifice was analyzed. Endometriotic lesions were evaluated for size, volume, histology, and immunohistochemistry (vascular endothelial growth factor [VEGF] and CD31). Significance level was accepted as p < 0.05.* **Results:** *Aflibercept significantly reduced endometrial implant volume (p = 0.002). The explant epithelial histological score showed a significant difference between aflibercept and leuprolide acetate (p = 0.006) and between aflibercept and control groups (p = 0.002). Aflibercept decreased VEGF-H and CD31 expression (p = 0.001) more than leuprolide acetate. Aflibercept improved adhesions (p = 0.006).* **Conclusion:** *Aflibercept is more successful than leuprolide acetate in the treatment of endometriosis.*

Keywords: *Aflibercept. Leuprolide acetate. Angiogenesis. Endometriosis. Vascular endothelial growth factor.*

Resumen

Objetivo: *Mostrar por primera vez cómo afecta aflibercept a las lesiones de endometriosis.* **Material y métodos:** *Endometriosis inducida quirúrgicamente en ratas hembras albinas Wistar. Las ratas con endometriosis se dividieron aleatoriamente en tres grupos: control (Co), aflibercept (Af) y acetato de leuprolida (Le). Luego, Af, aflibercept y Le recibieron acetato de leuprolida. El grupo de control no fue tratado. Los pesos y cambios en las adherencias intraabdominales de las ratas antes y después del tratamiento se registraron de acuerdo con la puntuación de adherencia de Blauer. La sangre extraída para el sacrificio fue analizada. Las lesiones endometriósicas se evaluaron en tamaño, volumen, histología e inmunohistoquímica (factor de crecimiento endotelial vascular [VEGF] y CD31). El nivel de significación se aceptó como p < 0.05.* **Resultados:** *Aflibercept redujo significativamente el volumen del implante endometrial (p = 0.002). La puntuación histológica epitelial (EHS) del explante mostró una diferencia significativa entre aflibercept y acetato de leuprolida (p = 0.006) y entre los grupos de aflibercept y control (p = 0.002). Aflibercept disminuyó la expresión de VEGF-H y CD31 (p = 0.001) más que el acetato de leuprolida. Aflibercept mejoró las adherencias (p = 0.006).* **Conclusión:** *Aflibercept tiene más éxito que el acetato de leuprolide en el tratamiento de la endometriosis.*

Palabras clave: *Aflibercept. Acetato de leuprolida. Angiogénesis. Endometriosis. Factor de crecimiento del endotelio vascular.*

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Introduction

Endometriosis is defined as the presence of a tissue similar to the endometrium at sites outside the uterine cavity[1]. It is difficult to determine the actual prevalence of endometriosis as it might be aymptomatic in some of the affected women and a biopsy is required for a definitive diagnosis. However, the prevalence among women of reproductive age is estimated to be 10%[2]. Endometriosis frequently presents itself with symptoms such as chronic pelvic pain, infertility, dysmenorrhea, dyspareunia, dysuria, dysgeusia, and fatigue and therefore might have a negative effect on physical, mental, sexual, or social life and productivity. Although the pathophysiology of endometriosis has not yet been fully understood, it is known to be closely related to inflammation and angiogenesis[3,4].

Angiogenesis is necessary for supplying nutrients required for implantation and invasion of endometriotic implants. Vascularization of lesions is mainly regulated by vascular endothelial growth factor (VEGF)[5]. Aflibercept is a recombinant fusion protein containing the second Ig domain and the third Ig domain of the VEGF receptors (VEGFR1 and VEGFR2, respectively), fused to the Fc portion of human immunoglobulin G1 (IgG1)[6-8]. It also binds to VEGF-A, VEGF-B, placental growth factor (PlGF)-1, and PlGF-2. Consequently, aflibercept acts as a trap for VEGFR by preventing the ligands from binding to their respective receptors, and it binds to both ends of VEGF very tightly[6,9]. This binding inhibits the biological action of VEGF and prevents the abnormal development of blood vessels. Aflibercept is also referred to in the literature as "VEGF trap"[7].

Aflibercept monotherapy is used in conjunction with chemotherapy as it significantly inhibits tumor growth and improves survival in various orthotropic animal models. It has been experimentally shown that aflibercept prevents and slows down the formation of choroidal neovascularization[10].

In this pioneering study, we aimed to evaluate the effect of aflibercept, a recombinant fusion protein that has an antiangiogenic effect by inhibiting VEGF on endometriotic foci, and compared the effect of aflibercept with leuprolide acetate, a GnRH agonist currently used in the routine treatment and the no-treatment group.

Materials and methods

The effects of the antiangiogenic agent aflibercept and a gonadotropin analog, leuprolide acetate, on ectopic endometrial lesions were compared to the control group in a rat model.

Ethical approval

This experiment was conducted in accordance with the standards of the Local Ethics Committee Directory of Turkish Ministry of Health, Health Sciences University Gülhane animal experiments. The experimental animals were obtained from Gülhane Experimental Animals Production and Research Unit. As recommended by the Gülhane Animal Studies Ethics Committee (03.03.21/ETİK-2021/07-21/09), a preliminary study was first conducted on two female rats for testing the experimental endometriosis model and the experiment was started after the success of the proposed model was confirmed and an approval from the *Gülhane Animal Studies Ethics Committee* was obtained (25.03.21/ETİK-2021/08-21/10).

Animals

A total of 30 female Wistar albino rats were included in the study. The 8-week-old rats, weighing 250-300 g, were kept in temperature-controlled cages throughout the study with standard rat chow and adequate water. During the day, each rat was kept in special standard cages at 21-24°C and 50% humidity. The automatic 12-h light-dark cycle was maintained. Rats were kept in the same cage for 20 days to ensure estrus.

Surgical procedures

Anesthesia was administered by intraperitoneal administration of 90 mg/kg ketamine hydrochloride (Ketalar; Eczacıbaşı Warner-Lambert pharmaceutical industry, Levent/İstanbul) and 10 mg/kg xylazine hydrochloride (Rompun-Bayer, Şişli/İstanbul) for the operations. In immobilized rats, the surgical area was shaved in the dorsal position and cleaned with povidone-iodine solution for antisepsis.

1ST OPERATION

A rat endometriosis model was developed by the surgical endometriosis induction method defined by Vernon and Wilson[11]. A 3-cm median skin incision was made while protecting the integrity of the intra-abdominal organs, and then, the uterine horns were exposed.

The right uterine horn was excised after ligating both the uterotubal junction and the cervix. The endometrial tissue inside the excised horn section was excised to a 5 × 5 mm piece and then implanted with 4-0 Vicryl sutures into the relatively vascular area on the ipsilateral inner lateral wall of the abdomen, with the endometrium facing the peritoneal surface. After the bleeding was controlled, 1 ml of saline was applied to the abdominal cavity, and the median incision was closed by continuous suturing using 3-0 Vicryl and prolene sutures according to the anatomic plan. Subsequently, all rats were transferred to the post-operative unit in separate cages. Paracetamol (Parol oral suspension; Atabay İlaç, Kadıköy/Istanbul) at a dosage of 100 mg/kg was given to the rats in 500 ml of water for pain control during the post-operative period. Routine daily feeding of the animals was continued during the following 3 weeks.

2ND OPERATION

Twenty-one days after the initial surgery, rats underwent exploratory laparotomy to evaluate endometriotic lesions. One rat died during this operation during anesthesia was given and was excluded from the study. In the remaining 29 rats, the development of endometriotic implants at the transplanted areas was confirmed. Then, the rats were randomly divided into three groups: aflibercept group (Af) n = 12, leuprolide acetate group (Le) n = 12, and the control group (Co) n = 5. The local ethics committee (25.03.21/ETIK-2021/08-21/10) recommended recruitment of a reduced number of rats to the control group. The rats were numbered according to the intra-group tail staining method. The volumes (0.52 × width [mm] × length [mm] × height [mm]) of all tissues transplanted in the abdominal wall 3 weeks before and changed into endometriotic structure were then measured (Fig. 1A). During the examination, intra-abdominal adhesions were scored according to the Blauer scoring system (0-4): 0 = no adhesion, 1 = weak adhesion, 2 = dense adhesion confined to a single area, 3 = dense adhesion over a large area, and 4 = strong adhesions including internal organs[12] (Fig. 1B and C). Surgery was completed with closure of the abdominal cavity with 3-0 Vicryl and prolene. Body weights of all rats were measured and 25 mg/kg aflibercept (Eylea®; Regeneron, NY, USA) was administered intraperitoneally (i.p.) in the Af group, and 1 mg/kg leuprolide acetate (Lucrin Depot; Abbott, Cedex, Istanbul) was administered subcutaneously (s.c.), Turkey, in the Le group. The doses were based on the studies from the literature[13,14]. The co-group received no treatment. The rats received the same post-operative pain control treatment and they were routinely followed up for 21 days until the third operation.

3RD OPERATION

A third laparotomy was performed 21 days after the exploratory laparotomy. During this operation, the diameters of endometriotic lesions were measured as done during the previous operation. The adhesions were scored again according to the "Blauer scoring system" for comparison with the pre-treatment scores[11]. The body weights of all rats were measured again. Subsequently, all rats were sacrificed by exsanguination. Blood samples collected were sent to the laboratory in tubes containing ethylenediaminetetraacetic acid (EDTA) for analysis. Finally, all endometriotic lesions were excised and sent to the pathology laboratory in containers containing 10% formaldehyde solution.

Histopathological evaluation

The excised endometriotic tissues were stored in containers containing 10% formaldehyde, numbered, and sent to the pathology laboratory of Gülhane Training and Research Hospital, where they were examined by the same pathologist (F.A.) who was blinded to the study groups. Sections of 5 μm (microns) were taken by the microtome (Leica-M225-Thermo HM3555-Thermo scientific). Sections stained with hematoxylin and eosin (H&E) were examined under a microscope (Nikon® ECLIPSE 80i, Japan) at ×100, ×200 and ×400 magnifications (Supplementary Figure 1). The persistence of endometrial cells within the endometrial implants was assessed by semiquantitative explant epithelial histological scoring (EHS) (score 0-3): 3 = a well-preserved epithelial layer, 2 = a moderately preserved epithelium with leukocyte infiltration, 1 = a poorly preserved epithelium (containing only occasional epithelial cells), and 0 = no epithelium[15]. The software "NIS-Elements D Ver 5.02.03 for 64-bit edition" was used for photographing from the microscope.

Immunohistochemical evaluation

Immunohistochemical staining was performed automatically using the Ventana BenchMark XT System (Ventana Medical Systems, Roche, Basel, Switzerland). Ultraview universal 3,3′-diaminobenzidine (DAB) detection kit (Ventana®)

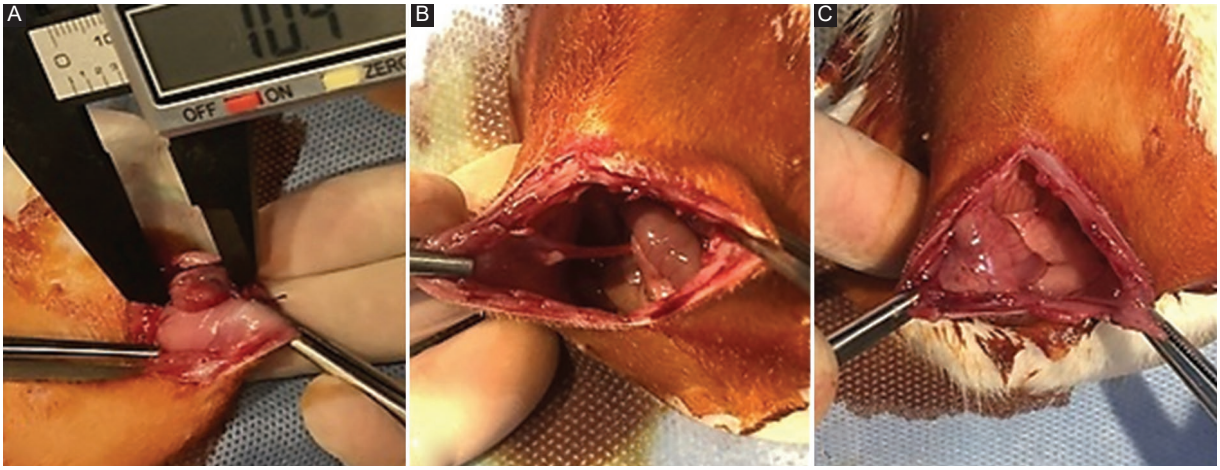

Figure 1. *Several images captured throughout the experiment.* **A:** *appearance compatible with endometriosis on exploration.* **B:** *example of Blauer adhesion score 1.* **C:** *example of Blauer adhesion score 4.*

was used for automatic immunohistochemistry device. The primary antibodies against VEGF (Flt-1/VEGFR1, 0.1 ml concentrate 1:501:200 antibody, GenomeME, Richmond BC, Canada) and CD31 (JC70, 0.1 ml concentrate 1:251:100 antibody, Santa Kruz) were used. The slides were evaluated under the microscope, with histological scoring (H-score) for VEGF as previously described in the literature[16-18]: H-score = ∑Pi i = 0 (negatively stained cells) to i = 3 (highly stained cells), P = 1, 2, 3, 4, 5 values < 15%, 15-50%, 50-85%, > 85%, and 100% positively stained cells, respectively. For the CD31 antibody, the number of CD31-positive stained microvessels (endothelial cells/endothelial cell clusters) was calculated per 1 mm^2 area[5].

Blood parameters

Intracardiac blood samples collected during the sacrifice phase by exsanguination were transferred to EDTA tubes. Unfortunately, clotting abnormalities occurred in 4 tubes (1 tube from the Af group, 2 tubes from the Le group, and 1 tube from the Co group) and these tubes were excluded from the study. The remaining 25 blood samples were sent to laboratory for analysis. An automatic analyzer was used to determine the hemoglobin level (HGB) (gr/dL), total white blood cell count (WBC) (× 10^3 μL), and platelet count (PLT) (× 10^\mm^3), which are among the laboratory complete blood count parameters (Mindray BC-6000).

Statistical analysis

The sample size of the study was calculated by G-power analysis, and the number of rats required for the study was set at 30. Normality assumptions of the continuous variables were tested using the Shapiro–Wilk test. The mean ± standard deviation of the normally distributed variables and the median values (25^{th}-75^{th} percentiles) of the non-normally distributed variables are indicated. The Wilcoxon signed-rank test was used to compare the parameters of the rats before and after treatment. One-way analysis of variance (one-way ANOVA) was used to compare the normally distributed parameters between groups. In case of a significant difference, the *post hoc* Tukey or Games-Howell test was used according to the result of Levene's test for homogeneity of variance. The Kruskal–Wallis test was used to compare the parameters that were not normally distributed between groups. In the case of a significant difference, the Mann–Whitney test with Bonferroni correction was used to determine from which groups the difference originated. IBM SPSS 25 program was used in all analyses, and $p < 0.05$ was accepted as the significance level.

Results

Weight of the rats and volume of the endometriotic tissue measured at the time of the 2^{nd} and 3^{rd} operations (pre and post-treatment) were compared in the Af, Le, and the control groups. The post-treatment weight of both the Co group and the Af group was significantly lower than that of the Le group ($p < 0.001$) (Table 1). The weight of the rats increased significantly in all groups; 14.89% in the Co group, 8.3% in the Af group, and 27.7% in the Le group (Table 1). However,

Table 1. Comparison of groups in terms of weight, endometriotic lesion width, length, height, volume, and Blauer adhesion score

Variables	Group Co (n = 5)	Group Af (n = 12)	Group Le (n = 12)	p value	Difference among groups
Weight (gr)					
Before treatment	235.00 (215.00-242.50)	242.50 (235.00-253.75)	235.00 (235.00-247.50)	0.282†	-
Post-treatment	270.00 (245.00-277.50) c	262.50 (255.00-273.75) a	300.00 (290.00-305.00) b	**< 0.001**†	**a < b; c < b**
p value	**0.042***	**0.002***	**0.002***		
Endometriotic lesion width (mm)					
Before treatment	6.00 (4.00-8.00)	9.00 (5.40-9.10)	5.55 (3.80-6.68)	0.153†	-
Post-treatment	8.60 (6.15-10.05)	5.60 (2.95-7.15)	5.00 (3.58-5.52)	0.067†	-
p value	**0.043***	**0.002***	**0.036***		
Endometriotic lesion length (mm)					
Before treatment	4.00 (2.15-5.05) c	7.40 (5.55-8.00) a	4.45 (2.82-5.23) b	**0.004**†	**b < a; c < a**
Post-treatment	4.50 (3.05-6.55)	4.65 (4.00-6.30)	3.45 (2.58-4.40)	0.175†	-
p value	**0.042***	**0.012***	**0.006***		
Endometriotic lesion height (mm)					
Before treatment	1.50 (1.25-2.45) c	3.65 (2.90-4.57) a	2.05 (1.45-2.88) b	**0.002**†	**b < a; c < a**
Post-treatment	2.50 (1.65-5.10)	1.85 (1.55-2.08)	1.50 (1.00-2.50)	0.230†	-
p value	**0.043***	**0.002***	**0.016***		
Endometriotic lesion volume (mm^3)					
Before treatment	18.00 (10.00-35.50) c	134.50 (59.75-170.25) a	21.00 (15.25-46.75) b	**0.013**†	**b < a**
Post-treatment	78.00 (24.50-107.50)	27.50 (10.75-43.00)	12.50 (7.00-27.25)	0.106†	-
p value	**0.043***	**0.002***	0.084*		
Blauer adhesion score					
Before treatment	2.00 (1.00-2.00)	2.00 (2.00-3.00)	2.00 (2.00-3.00)	0.145†	-
Post-treatment	2.00 (1.50-3.50)	1.00 (1.00-2.00)	2.00 (1.00-4.00)	0.091†	-
p value	0.102*	**0.006***	1.000*		

*Wilcoxon signed-rank test.
†Kruskal–Wallis test.
gr: grams; mm: millimeters; mm^3: cubic millimeters.
Blauer adhesion score; (0-4): 0 = no adhesion; 1 = weak adhesion; 2 = dense adhesion limited to a single area; 3 = dense adhesion over a large area; 4 = dense adhesion involving internal organs.
Parameters are expressed as mean±standard deviation or median (25^{th}-75^{th} percentile) taking into account normality assumptions. Values in bold are statistically significant.

the increase in weight was statistically significant in the Af and Le groups. The endometriotic foci volume of the Co group was found to be increased by 333.3% during the 3rd operation. However, the volume of the endometriotic foci was found to be decreased by 40.4% in the Le group and 79.5% in the Af group. Although endometriotic foci volume regressed in both Af and Le groups, the reduction in the Af group was statistically significantly higher (p = 0.002) (Table 1).

Intraabdominal Blauer adhesion scores of the three groups recorded during the 2nd and 3rd operations were compared. No change in the Blauer adhesion score was observed in the Le and Co groups, while there was a statistically significant decrease in Blauer score after treatment with Af (p = 0.006) (Table 1).

Histology of the excised endometriotic tissue obtained during the 3rd operation and the immunohistochemical assessment of VEGF and CD31 expression in excised tissues were compared in the control group with the two intervention groups (Table 2). Explant epithelial histological scoring (EHS) difference among groups was significant (p = 0.002) (Table 2). When the persistence of endometrial cells within the endometrial implants was assessed by semiquantitative explant EHS, none of the specimens in the intervention and control groups had a score of 0. In the control group, 40% had a score of 2 and 60% had a score of 3. In the Le group, the distribution of the scores 1, 2, and 3 was 25.0%, 16.7%, and 58.3%, respectively. In the Af group, none of the specimens had a score of 3, 75% received a score of 1 while the remaining 25% had a score of 2 (Table 3). According to Chi-square analysis, when three groups were compared, the p value was 0.07 (Table 3). When the median EHS scores were compared, there was a significant

Table 2. Comparison of groups in terms of explant epithelial histological score, VEGF H score, and CD31 expression

Variables	Group Co (n = 5)	Group Af (n = 12)	Group Le (n = 12)	p value	Difference among groups
EHS	3.00 (2.00-3.00) c	1.00 (1.00-1.75) a	3.00 (1.25-3.00) b	**0.002***	a < b **(p = 0.006)**† a < c **(p = 0.002)**†
CD31	154.00 (105.50-286.50) c	75.50 (62.25-85.00) a	144.00 (112.75-198.25) b	**< 0.001***	a < b **(p < 0.001)**† a < c **(p = 0.001)**†
VEGF	6.00 (6.00-6.00) c	2.00 (2.00-3.00) a	4.00 (2.00-6.00) b	**0.002***	a < c **(p = 0.001)**†

*Kruskal–Wallis test.
†Mann–Whitney test with Bonferroni correction.
EHS: Explant epithelial histological scoring "semi-quantitative" (0-3); 0: no epithelium, 1: poorly preserved (only occasionally) epithelium, 2: moderately preserved epithelium with leukocyte infiltrates, 3: well-preserved epithelial layer; CD31: microvessel density; The number of CD31 positive-stained microvessels (endothelial cell/endothelial cell clump) per 1 mm^2 area; VEGF: H score = $\sum Pi$; i = 0 (stained negatively) to 3 (stained heavily), P = 1, 2, 3, 4, 5 values < 15%, 15-50%, 50-85%, > 85%, and 100%, respectively, positively stained cells. Parameters are expressed as mean±standard deviation or median (25^{th}-75^{th} percentile) taking into account the assumptions of normality.
a: median value for the Af group (25^{th}-75^{th} percentile), b: median value for the Le group (25^{th}-75^{th} percentile), c: median value for the control group (25^{th}-75^{th} percentile).

Table 3. Distribution of explant epithelial histological scores in Study Groups

Groups	Score 0	Score 1	Score 2	Score 3	p value
Number of EHS					**0.007***
Group Af	-	9 (75.0%)	3 (25.0%)	-	
Group Le	-	3 (25.0%)	2 (16.7%)	7 (58.3%)	
Group Co	-	-	2 (40.0%)	3 (60.0%)	

*Chi-square analysis.
Group Le < group Af at score 1 (p < 0.001); group Le < group Co at score 2 (p < 0.001).
EHS: explant epithelial histological scoring "semi-quantitative" (0-3); 0: no epithelium, 1: poorly preserved (only occasionally) epithelium, 2: moderately preserved epithelium with leukocyte infiltrates, 3: well-preserved epithelial layer.
Number of EHS: it refers to the number of rats in the score groups according to the EHS. Values in bold are statistically significant.

difference between the groups, and Af group had the lowest median score when compared to Le and Co groups. (p = 0.002). The Bonferroni-corrected Mann–Whitney test showed a significant difference between the Af group and the Le group (p = 0.006) and between the Af group and the Co group (p = 0.002) (Table 2).

When glandular, stromal, and epithelial cells were stained for calculation of microvessel density for the VEGF-H immunohistochemical score and CD31 antibody evaluation, Co group was found to have a stronger staining in comparison to the Af and Le groups. In the Af group, staining for both VEGF and CD31 antibodies was much weaker than that observed in the Co and Le groups (Fig. 2). Counting CD31 and VEGF-H scores revealed a significant difference between the groups (p < 0.001 and p = 0.002, respectively) (Table 2 and Fig. 3). In the Bonferroni-corrected Mann–Whitney test, both CD31 and VEGF H scores were significantly lower in the Af group than the Co group (p = 0.001) and the Le group (p < 0.001) (Table 2).

Out of the 29 blood samples obtained during the 3^{rd} operation, four samples could not be processed due to the hemolysis. Analysis from the remaining samples (Co group: [n = 4], Af group: n = 11, Le group: n = 10) demonstrated no significant difference between the three groups in terms of WBC counts and hemoglobin levels. The platelet counts in Af, Le, and Co groups (median [25^{th}-75^{th} percentile]) were 999.50 (R: 886.75-1002.25) × 10^3 μL, 978.00 (R: 936.00-993.75) × 10^3 μL, and 870.00 (R: 805.00-890.50) × 10^3 μL, respectively. The Kruskal–Wallis test revealed a significant difference in the platelet counts among the groups (p = 0.032) (Table 4).

Discussion

Although more than a decade passed since the universally accepted definition of endometriosis, there is not a consensus about the pathogenesis and a set protocol for the diagnosis and treatment of this disease[19]. Endometriosis has a negative impact on education, employment, and social relations of the women of reproductive age due to its effect on physical, sexual, and reproductive health and thus is called as a "social disease"[20,21]. The researchers working in this field have proposed different theories for the explanation of various forms of endometriosis.

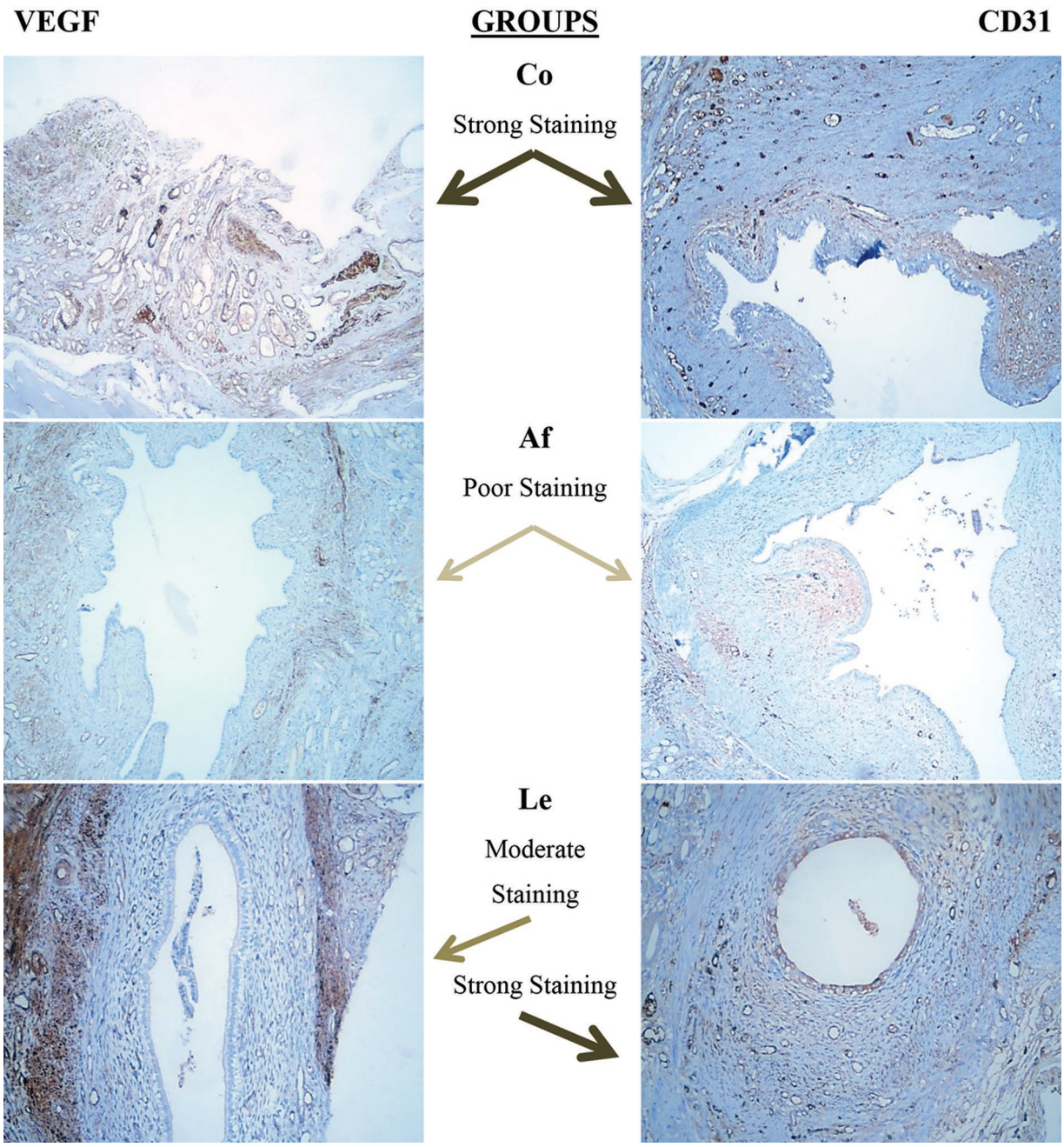

Figure 2. *Immunohistochemical examination of endometriotic lesions. Image for Group Co CD31 is at ×100 magnification. All other images are at ×200 magnification. VEGF: vascular endotelial growth factor.*

Besides lymphangiogenesis and neurogenesis, angiogenesis plays an important role in the pathophysiology of endometriosis[22]. The nutrients and oxygen required for the development of endometriotic lesions are provided by angiogenesis and thus neovascularization[23]. The presented study is a pioneering study that aims to investigate aflibercept, an antiangiogenic agent in the treatment of endometriosis in a surgically induced rat model. In the present study, aflibercept was more efficient in the regression of endometriotic lesions and treating adhesions than the control group and the leuprolide acetate group.

Changes in implant volume have been reported mostly as a marker for treatment efficacy of induced endometriotic foci in animal studies[24,25]. Bakacak et al. reported a significant reduction in the endometrial implant volume after treatment with the antiangiogenic agent thalidomide ($p = 0.001$)[26]. Aflibercept group had

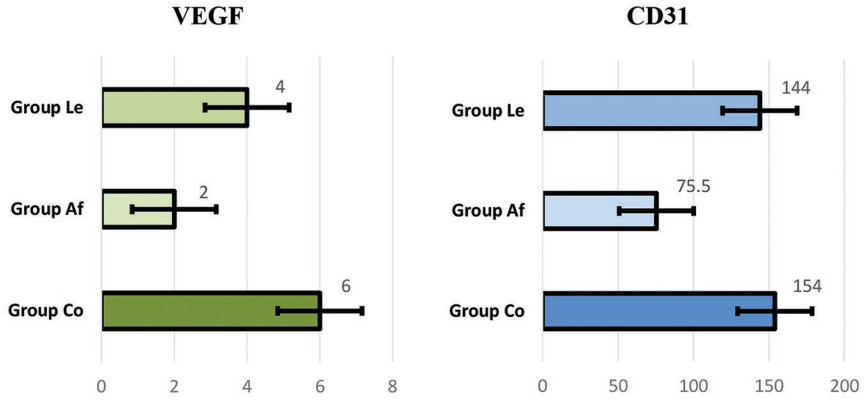

Figure 3. *Results of CD31 and vascular endothelial growth factor H score by groups. CD31: microvessel density: number of CD31-positive stained microvessels (endothelial cell/endothelial cell clump) per 1 mm²; VEGF: H score = ∑Pi; i = 0 (stained negatively) to 3 (stained heavily), p = 1, 2, 3, 4, 5 values < 15%, 15-50%, 50-85%, > 85%, and 100, respectively, % positively stained cells.*

Table 4. Comparison of intra-group and inter-group blood parameters

Parameters	Group Co (n = 4)	Group Af (n = 11)	Group Le (n = 10)	p value	Difference among groups
WBC (× 10^3 µL)	5196.00±930.61	6870.00±1552.26	7870.00±2531.40	0.061*	-
HGB (gr/dL)	13.38±0.36	13.94±0.27	14.06±0.79	0.097*	-
PLT (× 10^\mm^3)	870.00 (805.00-890.50) c	999.50 (886.75-1002.25) a	978.00 (936.00-993.75) b	**0.032**†	**c < b** **c < a**

*One-way ANOVA analysis.
†Kruskal–Wallis test.
WBC: white blood cell count; HGB: amount of hemoglobin; PLT: platelet count.
Parameters are expressed as mean±standard deviation or median (25th-75th percentile) taking into account normality assumptions. Values in bold are statistically significant.

a significant reduction in the volume of the endometriotic implants (p = 0.002) (Table 1). The significant increase in the total body weight of the rats in all groups after treatment could be speculated as the rats being in their growth period during the experimental study. However, the weight gain in the group receiving leuprolide acetate was more significant than the other groups (Table 1).

Ozer et al. analyzed and compared the effect of two antiangiogenic agents – bevacizumab and sorafenib on the volume of the endometriotic foci[5] and the changes in VEGF and CD31.The reported results of this study were similar to our results. In contrast, Ozer et al. observed that sorafenib cleared some endometriotic lesions entirely. For aflibercept, we did not meet such a circumstance in our research. They compared two anti-angiogenic drugs while in the present study, the efficacy of aflibercept; an antiangiogenic drug was compared with a GnRH agonist leuprolide acetate in the treatment of endometriosis. Because, in addition to its hypoestrogenic impact, leuprolide acetate has a demonstrated anti-VEGF activity[27]. In our study, with leuprolide acetate, VEGF expression decreased when compared with the control group but this decrease was not significant. In our study, aflibercept statistically significantly reduced VEGF expression. This indicates that aflibercept has a stronger antiangiogenic effect than leuprolide acetate.

Adhesion formation was decreased with two anti-VEGF agents bevacizumab[28] and sunitinib[29] in two animal studies presented by Moraloglu and Pala. According to the Blauer scoring system, we also found that aflibercept reduced adhesion after treatment. Consistent with the literature our study demonstrated that anti-VEGF agents have a reducing effect on adhesions.

Siracusa et al observed to have a significant reduction in both markers of angiogenesis – VEGF and CD34 expression on the endometriotic surfaces with another anti-VEGF agent, rapamycin[30]. In the present study, besides VEGF expression levels, another endothelial marker, CD31 was also evaluated in the endometriosis rat model and the findings with aflibercept were similar to those obtained with rapamycin.

Zhang et al studied rosiglitazone, an antiangiogenic PPARγ (peroxisome proliferator-activated receptor γ) agonist that acts by inhibiting macrophage activation in endometriotic lesions in a surgically induced rat model[4]. The expression of VEGF and caspase-3 immunohistochemically in endometriotic tissue was evaluated, and expression of VEGF and caspase-3 was significantly reduced by rosiglitazone ($p < 0.05$, $p < 0.05$)[4]. Zhang et al. compared rosiglitazone with the control (no treatment) and saline groups without comparing it with any other agent currently being used in the treatment of endometriosis. In the present study, the efficacy of aflibercept was compared with leuprolide acetate in a rat model, to demonstrate its potential in comparison to an agent that has been currently being used.

Yıldız et al. studied imatinib, a tyrosine kinase receptor inhibitor, and obtained a significant improvement ($p < 0.05$) compared with the control group using VEGF-H score system[31]. However, in our study, aflibercept reduced VEGF expression more prominently, therefore it can be speculated that the antiangiogenic effect of aflibercept might be stronger that of imatinib ($p = 0.01$).

In the study performed by Ozdemir et al on ranibizumab which has an antiangiogenic effect, the percentage of specimens with an epithelial histological score of 0 was 33.3%. In our study, there were no specimens in any of the groups with a score of 0; however, the rates of the other scores were similar. Ozdemir et al reported score 1 in 66.7% of the ranibizumab-treated group[32]. In our study, 75% of the aflibercept group received a score of 1. This suggests that aflibercept does not completely eradicate endometriotic lesions but can destroy the protective epithelium of the lesion similar to ranibizumab.

It is well known that antiangiogenic agents may cause thromboembolic complications[30]. In the present study, the blood samples taken at the final phase of the study were analyzed and complete blood count results showed that the platelet count was higher in the aflibercept group than in the other groups. This result was significant when compared with the control group but not significant compared with the leuprolide acetate group. These findings suggest that aflibercept may cause thrombocytosis.

Studies with experimental animals cannot be directly applied to humans. Therefore, acceptance of aflibercept as a treatment option for endometriosis depends on more comprehensive animal studies and clinical studies. Any results we obtained should be carefully evaluated because the number of rats was restricted due to the regulations of the local ethics committee for animal studies and the parameters studied to determine the side effect profile were limited.

Conclusion

It is necessary to suppress the process of angiogenesis to achieve effective results in the treatment of endometriosis. The anti-angiogenic agent aflibercept was used for the first time in the present study for the treatment of endometriosis. Aflibercept proved more successful than the control group and leuprolide acetate in both regression of endometriotic lesions and treatment of adhesions.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Supplementary data

Supplementary data are available at DOI: 10.24875/CIRUE.M23000605. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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ORIGINAL ARTICLE

Evaluation of the possible effects of the COVID-19 period on the clinical outcomes of acute mesenteric ischemia

Evaluación de los posibles efectos del periodo COVID-19 en los resultados clínicos de la isquemia mesentérica aguda

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Abstract

Objective: *The objective of the study was to investigate the possible effects of the coronavirus disease 2019 (COVID-19) period on the frequency and clinical course of acute mesenteric ischemia (AMI) cases.* **Material and methods:** *A total of 35 patients who were treated and followed up with a diagnosis of AMI over 44 months were included.* **Results:** *The mean age of the patients was 69 ± 12 years. Of these patients, 22 were male (63%). The most common cause of AMI in the patients was arterial embolism/thrombosis (68.6%). Thirty-three (94%) of the patients underwent surgical intervention. The duration of the pre-COVID-19 and COVID-19 periods was equal as 22 months, and 18 (51%) of the patients were admitted during the pandemic period. The mortality rate of the patients admitted during the COVID-19 period was also significantly higher than that of the patients admitted during the pre-COVID-19 period (61% and 29%) (p = 0.05).* **Conclusions:** *Although the COVID-19 period did not cause a significant increase in the number of AMI cases when compared to the pre-COVID-19 period, the mortality rate was higher in this period. It is thought that further studies are required to investigate the cause of this increased mortality rate during the pandemic period.*

Keywords: *Acute mesenteric ischemia. Coronavirus. COVID-19. Mortality. Pandemic.*

Resumen

Objetivo: *Investigar los posibles efectos del período COVID-19 en la frecuencia y el curso clínico de los casos de isquemia mesentérica aguda (IAM).* **Material y métodos:** *Se incluyeron un total de 35 pacientes tratados y seguidos con diagnóstico de IAM durante 44 meses.* **Resultados:** *La edad media de los pacientes fue de 69 ± 12 años. De estos pacientes, 22 eran hombres (63%). La causa más frecuente de IAM en los pacientes fue la embolia/trombosis arterial (68.6%). Treinta y tres (94%) de los pacientes fueron intervenidos quirúrgicamente. La duración de los períodos pre-COVID-19 y COVID-19 fue igual a 22 meses, y 18 (51%) de los pacientes ingresaron durante el período pandémico. La tasa de mortalidad de los pacientes ingresados durante el periodo COVID-19 también fue significativamente mayor que la de los pacientes ingresados durante el periodo pre-COVID-19 (61% y 29%) (p = 0.05).* **Conclusiones:** *Si bien el período COVID-19 no provocó un aumento significativo en el número de casos de IAM en comparación con el período pre-COVID-19, la tasa de mortalidad fue mayor en este período. Se cree que se requieren más estudios para investigar la causa de este aumento en la tasa de mortalidad durante el período pandémico.*

Palabras clave: *Isquemia mesentérica aguda. Coronavirus. COVID-19. Mortalidad. Pandemia.*

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Introduction

Acute mesenteric ischemia (AMI) is an important medical emergency caused by insufficient blood flow to the small intestine that can result in mortality. Late diagnosis and treatment negatively affect the prognosis of the disease. Despite advanced technological devices used in its diagnosis and various surgical and/or interventional treatment methods, AMI remains a condition with a high mortality rate[1,2].

Computed tomography (CT) angiography is the golden standard of imaging methods used for the diagnosis of AMI. The dilatation of the intestinal lumen, pneumatosis intestinalis, superior mesenteric vein thrombosis, intraperitoneal fluid, portal vein thrombosis, and splenic vein thrombosis seen on CT angiography results indicate intestinal necrosis[3]. The incidence rates of arterial embolism, arterial thrombosis, non-occlusive mesenteric ischemia (NOMI), and vein thrombosis in AMI have been reported as 50%, 15-25%, 20%, and 5-15%, respectively[4].

The World Health Organization declared that coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, was a pandemic on March 11th, 2020. It is known that COVID-19 not only affects the respiratory system but also can affect all the systems. It has been reported that two-thirds of the patients who have contracted COVID-19 also showed gastrointestinal system symptoms[5,6].

Coronavirus disease 2019 causes systemic inflammation, platelet activation, and endothelial damage and thus increases the tendency of thrombosis in both the venous and arterial systems[5]. Accordingly, it has been established that thromboembolic complications, such as pulmonary embolism, acute myocardial infarction, deep vein thrombosis, and AMI, can be observed in patients with COVID-19[7]. Intestinal necrosis due to thrombosis of small arterioles in the submucosal areas has been detected in histopathological examinations of the gastrointestinal tract of patients infected with the SARS-CoV-2 virus[8]. It has also been reported that AMI can manifest as an early or late complication of COVID-19[9].

The indirect effects of COVID-19 pandemic cause delayed admission of non-COVID-19 emergency cases to the emergency department. It has been suggested that this situation may cause an increase in mortality and morbidity in these cases[10,11]. In addition, Reschen et al. showed that in the first wave of the COVID-19 pandemic, there was a significant decrease in the daily number of non-COVID-19 cases admitted to the emergency department compared to the pre-COVID-19 period. It is thought that this may increase the delay in diagnosis or the missed case rates in non-COVID-19 emergency cases[12]. When the literature was examined, it was seen that studies on the clinical course of AMI, a serious medical emergency, during the COVID-19 pandemic period are limited[7].

In this study, it was aimed to compare the incidence and clinical course of AMI cases during the COVID-19 pandemic period and the pre-COVID-19 period.

Materials and methods

Patients who were followed up with a diagnosis of AMI in the General Surgery Clinic of Bursa Yüksek İhtisas Training and Research Hospital, between 01 May 2018 and 31 December 2021 were included in this retrospective study. The pre-COVID-19 period group was composed of patients diagnosed with AMI over a total of 22 months, between May 2018 and February 2020 (n = 17). The COVID-19 period group was composed of patients diagnosed with AMI over an equal period of 22 months, between March 2020 and December 2021 (n = 18). The demographic (age and gender) and laboratory data (pH, lactate, C-reactive protein (CRP), platelet, ferritin, D-dimer, white blood cell, creatinine, transaminases, lactate dehydrogenase, total bilirubin, and neutrophil-to-lymphocyte ratio) of the patients were obtained from the patient files. In addition, the clinical data (intensive care Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, surgery types, comorbidities, COVID-19 vaccination status, Sars-CoV-2 virus positivity, mortality, length of hospital stay, and abdominal CT and/or CT angiography) of the patients were also recorded. The patients had been diagnosed with AMI according to a combination of clinical, laboratory, radiological, and histopathological findings. The patients were divided into two groups as those who died and those who survived. While the patients who died during their hospitalization were defined as the exitus group, the patients who were discharged as healthy were defined as the survivors group. Individuals aged 18 years and over who were diagnosed with AMI were included in the study. Patients who had prior cases of AMI, intravascular involvement, chronic mesenteric ischemia, inflammatory bowel disease or intestinal masses, were pregnant, or diagnosed with thrombophilia were excluded from the study. All of the patients

were checked for COVID-19 infection by real-time polymerase chain reaction (RT-PCR) tests on combined nasal and oropharyngeal swabs.

Ethical approval

Ethics committee approval for the study was obtained from the Ethics Committee of Bursa Yüksek İhtisas Training and Research Hospital, under decision number 2011-KAEK-25 2022/02-08, on February 9th, 2022. The study was carried out by the Declaration of Helsinki.

Statistical analysis

For statistical evaluation of data obtained in the study, IBM SPSS Statistics 21.0 (IBM Corp., Armonk, NY, USA) was used. The study population was checked for normal distribution with the Shapiro–Wilk test. Values were expressed as mean ± standard deviation (SD) for normally distributed variables, as median (min-max) for non-normally distributed variables, and count and percent for categorical variables. In the comparison of the data between the two groups, the independent samples t-test was used for the parametric data, and the Mann–Whitney *U*-test was used for the non-parametric data. The chi-square test was used to compare the categorical variables. For all analyses, a $p < 0.05$ was considered to be statistically significant.

Results

The mean age of the patients included in the study was 69 ± 12 years. Of the patients, 13 (37%) were female and 22 were male (63%). The duration of the pre-COVID-19 and COVID-19 periods was equal, as 22 months. The number of patients admitted during the COVID-19 period was 18 (51%). While small intestine resection was performed in 12 (34%) patients, colon resection was performed in 1 (3%) patient. Combined small intestine and colon resection were performed in 20 patients (57%). Two (6%) patients underwent no resection. A total of 16 (46%) patients were lost (Table 1). The COVID-19 RT-PCR tests performed during the hospitalization and follow-up of the patients were all negative.

Table 1. Clinical, demographic, and laboratory data of the patients (n = 35)

Variables	Value
Age, year*	69 ± 12 (range: 44-90)
Gender, F/M, n (%)	13/22 (37/63)
pH*	7.34 (± 0.1)
Lactate*, mmol/L	4.8 ± 3.6
CRP*, mg/L	172 ± 130
APACHE II*	20 ± 9
Platelet*, (× 10^3) (cells/mm^3)	283 ± 106
Ferritin†, ml/ng	147 (11-750)
D-dimer†, mg/dL	7 (1-66)
WBC†, (× 10^3)	14 (3-24)
Creatinine†, mg/dl	1.4 (0.5-4.7)
AST†, (U/L)	37 (5-4113)
ALT†, (U/L)	20 (6-3717)
LDH†, (U/L)	302 (144-1303)
Total bilirubin†, mg/dl	0.8 (0.2-4)
N/L†	10 (1-57)
Total hospital stay†, days	10 (1-49)
Intensive care unit stay†, days	3 (0-35)
Pre-COVID-19/COVID-19 period, n (%)	17/18 (49/51)
Cause of mesenteric ischemia, n (%)	
Arterial embolism/thrombosis	24 (68.6)
Venous	3 (8.6)
Non-occlusive	8 (22.9)
Operation status, n (%)	
Small bowel resection	12 (34)
Colon resection	1 (3)
Small intestine + colon resection	20 (57)
No resection	2 (6)
Comorbid disease, n (%)	
AF	4 (11)
HT	8 (23)
DM	11 (31)
CAD	17 (49)
Mortality, n (%)	16 (46)

*mean (± standard deviation).
†median (minimum-maximum).
F: female; M: male; CRP: C-reactive protein; WBC: white blood cell; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; N/L: neutrophil/lymphocyte; SMA: superior mesenteric artery; AF: atrial fibrillation; DM: diabetes mellitus; HT: hypertension; CAD: coronary artery disease.

When the demographic, clinical, and laboratory parameters of the AMI patients admitted during the pre-COVID-19 and COVID-19 periods were compared, no significant differences were found in terms of age, gender, comorbidities, or etiology. However, patients admitted during the COVID-19 period had significantly

higher aminotransferase aspartate (AST) and lactate dehydrogenase (LDH) values ($p < 0.05$). While the total duration of hospital stay in both groups was similar, the median duration of intensive care unit (ICU) stay for the patients admitted during the COVID-19 period was significantly longer ($p = 0.02$). In addition, the mortality rate of the patients admitted during the COVID-19 period was significantly higher (61% and 29%) ($p = 0.05$) (Table 2).

When the demographic, clinical, and laboratory parameters of the patients who were lost and the patients who survived were compared, it was found that the patients who were lost had significantly higher arterial blood gas pH, lactate, ferritin, creatinine, ALT, and AST values when compared to the patients who survived ($p < 0.05$). It was found that the mean duration of hospital stay was significantly shorter in the patients who were lost when compared to the patients who survived ($p = 0.001$), but their duration of ICU stay was significantly longer ($p = 0.01$) (Table 3).

Discussion

The absence of a specific laboratory parameter that can be used in the diagnosis of AMI and the indefinite abdominal examination findings in AMI patients may cause a delay in the diagnosis. Moreover, AMI is more common in the elderly and patients with comorbid diseases. As a result, AMI has a high mortality rate. The COVID-19 pandemic, the effects of which are still ongoing, has caused an important public health problem that has given rise to medical and socioeconomic problems all over the world[13]. COVID-19 is a multisystemic disease with reported thromboembolic complications developing during and after its course[14]. During the course of COVID-19, it has been reported that the virus causes thrombosis in the microvascular system secondary to the colonization of the intestinal mucosa[15].

The number of studies in the literature on the possible effect of COVID-19 infection on AMI is limited, and most of them have been presented in the form of case reports[16,17]. Thus, it is thought that this study will make an important contribution to the literature.

AMI is a disease that affects the elderly and is observed at a higher rate in females[18]. Similar to the literature, in the present study, most of the patients were elderly. Unlike the results presented in the literature, however, most of the patients in this study were male. AMI most often develops secondary to thromboembolic events in the superior mesenteric artery.

Table 2. Comparison of clinical, demographic, and laboratory data of the patients diagnosed before and during the COVID-19 period

Variables	Pre-COVID-19 period (n = 17)	COVID-19 period (n = 18)	p
Age, year	72 ± 11	66 (± 12)	0.1
Gender, F/M, n (%)	6/11 (35/65)	7/11 (39/61)	0.8
pH*	7.33 (± 0.1)	7.35 (± 0.1)	0.6
Laktate*, mmol/L	4.7 ± 3.1	4.8 ± 4.1	0.9
CRP*, mg/L	156 ± 139	187 ± 124	0.5
APACHE II*	19 ± 8	21 ± 10	0.5
Platelet*, ($\times 10^3$)/mcL	285 ± 100	282 ± 113	0.9
Ferritin†, ml/ng	163 (17-405)	147 (11-750)	0.8
D-dimer†, mg/dL	9 (5-10)	7 (1-66)	0.7
WBC†, ($\times 10^3$)/mcL	15 (4-24)	15 (3-21)	0.6
Creatinine†, mg/dl	1.2 (0.5-2.7)	1.3 (0.6-4.7)	0.7
AST†, (U/L)	22 (5-1209)	48 (20-4113)	**0.002**
ALT†, (U/L)	16 (6-1664)	30 (10-3717)	0.1
LDH†, (U/L)	230 (144-653)	341 (182-1303)	**0.02**
Total bilirubin†, mg/dl	0.7 (0.2-2.8)	0.9 (0.4-4)	0.5
N/L†	11 (1-57)	10 (1-55)	0.9
Total hospital stay†, days	10 (1-30)	10 (1-49)	0.9
Intensive care unit stay†, days	2 (0-10)	4 (1-35)	**0.02**
Cause of mesenteric ischemia, n (%)			0.8
Arterial embolism/	12 (71)	12 (67)	
thrombosis	1 (6)	2 (11)	
Venous	4 (23)	4 (22)	
Non-occlusive			
Operation status, n (%)			0.08
Small bowel resection	9 (53)	3 (17)	
Colon resection	0	1 (6)	
Small intestine + colon resection	8 (47)	12 (67)	
No resection	0	2 (11)	
Comorbid disease, n (%)			0.4
AF	2 (12)	2 (11)	
HT	6 (35)	2 (11)	
DM	6 (35)	5 (28)	
CAD	8 (47)	9 (50)	
Mortality, n (%)	5 (29)	11 (61)	**0.05**
Past COVID-19 infection, n (%)	-	4 (22)	-
Covid-19 vaccine status, n (%)	-	2 (11)	-

*mean (± standard deviation).
†median (minimum-maximum).
F: female; M: male; CRP: C-reactive protein; WBC: white blood cell; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; N/L: neutrophil/lymphocyte; SMA: superior mesenteric artery; AF: atrial fibrillation; DM: diabetes mellitus; HT: hypertension; CAD: coronary artery disease.

Table 3. Comparison of demographic, clinical, and laboratory data of the patients with and without exitus

Variables	Exitus (n = 16)	Survivors (n = 19)	p
Age, year	70 ± 11	68 (± 13)	0.7
Gender, F/M, n (%)	4/12 (25/75)	9/10 (47/53)	0.8
pH*	7.26 (± 0.1)	7.40 (± 0.1)	**< 0.001**
Laktate*, mmol/L	6.5 ± 3.9	3.3 ± 2.5	**0.007**
CRP*, mg/L	170 ± 139	173 ± 127	0.9
APACHE II*	26 ± 8	15 ± 5	**< 0.001**
Platelet*, (× 10^3)/mcL	252 ± 83	309 ± 117	0.1
Ferritin†, ml/ng	269 (85-750)	118 (11-405)	0.05
D-dimer†, mg/dL	12 (4-66)	6 (1-19)	**0.5**
WBC†, (× 10^3)/mcL	14 (3-24)	15 (9-21)	0.5
Creatinine†, mg/dl	1.8 (0.6-4.7)	1.1 (0.5-2.3)	**0.03**
AST†, (U/L)	102 (5-4113)	30 (8-81)	**0.02**
ALT†, (U/L)	47 (10-3717)	16 (6-88)	**0.01**
LDH†, (U/L)	335 (144-1303)	247 (171-653)	0.2
Total bilirubin†, mg/dl	0.8 (0.3-4)	0.5 (0.2-2.8)	0.9
N/L†	10 (1-57)	11 (1-26)	0.9
Total hospital stay†, days	6 (1-35)	11 (8-49)	**0.001**
Intensive care unit stay†, days	5 (1-35)	2 (0-7)	**0.01**
Patients in the COVID-19 period, n (%)	11 (69)	7 (37)	**0.05**
Cause of mesenteric ischemia, n (%) Arterial embolism/thrombosis Venous Non-occlusive	12 (75) 1 (6) 3 (19)	12 (63) 2 (11) 5 (26)	0.7
Operation status, n (%) Small bowel resection Colon resection Small intestine + colon resection No resection	2 (13) 1 (6) 12 (75) 1 (6)	10 (52) 0 8 (42) 1 (5)	0.07
Comorbid disease, n (%) AF HT DM CAD	 0 3 (19) 6 (38) 9 (56)	 4 (21) 5 (26) 5 (26) 8 (42)	0.3
Past COVID-19 infection, n (%)	1 (6)	3 (16)	0.4
COVID-19 vaccine status, n (%)	0	2 (11)	0.2

*mean (± standard deviation).
†median (minimum-maximum).
F: female; M: male; CRP: C-reactive protein; WBC: white blood cell; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; N/L: neutrophil/lymphocyte; SMA: superior mesenteric artery; AF: atrial fibrillation; DM: diabetes mellitus; HT: hypertension; CAD: coronary artery disease.

The incidence rates of arterial embolism/thrombosis, venous thrombosis, and NOMI in AMI have been reported in the literature as 65-75%, 5-15%, and 25%, respectively[19]. In this study, a result similar to that in the literature was obtained in terms of etiology.

AMI is an important medical emergency that may often require surgical resections involving the colon and/or small intestine for its treatment. It is seen that the small intestine is included in the resection in most cases[13]. In the present study, surgical intervention was

performed in 33 (94%) of the patients and small intestine resection was performed in 32 (91%) patients. Moreover, 2 (6%) patients who did not undergo resection were patients who were admitted during the COVID-19 period. One of them died. It was reported that AMI has a mortality rate of 26-97%[20]. It is thought that the most important reasons for these high mortality rates are late diagnosis and the fact that this disease most often affects the elderly and individuals with comorbidities[13]. In this study, the overall mortality rate was 46%, which is consistent with the literature.

According to the current information, there are no studies on the possible effects of the COVID-19 period on the frequency and clinical course of AMI cases. When the number and demographic data of AMI patients admitted to our hospital during the pre-COVID-19 and COVID-19 pandemic periods were compared, it was found that the number of patients admitted to our hospital in both periods was similar (17 patients and 18 patients, respectively), and no significant differences were found between the mean age and gender distributions of the groups. However, the mortality rate in the COVID-19 period was significantly higher than in the pre-COVID-19 period (61% and 29%). The mortality rate of patients diagnosed with AMI during COVID-19 infection was reported as 62.5%. It was also reported that these patients had a worse prognosis[16]. When the literature searched, it was suggested that the COVID-19 pandemic may indirectly increase mortality and morbidity in emergency cases. It has been stated that the reason for this may be due to the delay in the admission of these patients to the emergency department during the COVID-19 period[10-12]. In this study, the rate of patients who were vaccinated and had previous COVID-19 infection during the COVID-19 period was 33%. It is thought that the cause of the higher mortality rate, when compared to the pre-COVID-19 period, is not related to the direct effects of the virus, since the 2 patients who were vaccinated survived, only one of the 4 patients with prior COVID-19 infection was lost, and none of the patients were infected with COVID-19 during this treatment period. It is suggested that this increased mortality may have been caused by the late admission of these patients with AMI to the hospital during the COVID-19 period and delays in the treatment. However, multicentered studies with large patient populations are needed to confirm this hypothesis.

Leukocytosis and increased serum lactate values can be observed in 88-90% of patients with AMI[21]. Serum lactate values of > 2 mmol/L have been associated with intestinal ischemia. In addition, a positive correlation was found between serum lactate values and mortality rate[22]. In the present study, increased lactate values and leukocytosis were also observed. CRP and ferritin are acute-phase reactants, and high serum levels of CRP and ferritin are observed in cases of inflammation and ischemia[23]. It has also been reported that D-dimer values are increased in thromboembolic events and a high D-dimer value is an independent risk factor for intestinal ischemia[24,25]. In this study, high serum CRP, D-dimer, and ferritin values were observed in the patients, similar to the literature. It has been reported that there is a positive correlation between the neutrophil-to-lymphocyte ratio (NLR) and mortality in AMI[26]. The mean NLR has been reported to be quite high (19.5) in patients with AMI who had a prior COVID-19 infection[16]. In the present study, although it was observed that the NLR was increased in patients with AMI, no significant differences in the NLR were found between patients who were admitted in the different periods, and between patients who were lost and those who survived.

Lactic dehydrogenase and AST are laboratory parameters that increase during tissue ischemia and cell destruction. Serum levels of lactic dehydrogenase and AST also increase in systemic viral infections[27]. In a study conducted during the pre-COVID-19 period, the mean LDH level in AMI patients was 365 U/L[28]. LDH levels were found to have increased to 623 U/L in AMI patients in the COVID-19 period[16]. Serum AST values were found to be significantly higher in patients with intestinal ischemia when compared to those who did not have intestinal ischemia[29]. It was also reported that serum AST levels were increased during the COVID-19 infection due to both increased viral load and tissue hypoperfusion[30]. In the present study, the serum LDH and AST levels during the COVID-19 period were significantly higher than those during the pre-COVID period. Since patients admitted during the COVID-19 period were not infected with COVID-19 during their AMI clinic periods and only 22% had a prior COVID-19 infection, it is thought that these high LDH and AST levels could not be directly associated with the viral infection. In addition, there was no significant difference among the serum lactate, CRP, ferritin, D-dimer, and white blood cell levels of patients admitted in either period. There was also no significant difference between the two groups in terms of AMI etiologies, total duration of hospital stay, and comorbidities. However, the median duration of ICU stay for the patients admitted during the COVID-19

period was significantly higher than for the patients admitted during the pre-COVID-19 period. This is also an indirect indicator of high mortality during the COVID-19 period.

In the study, no significant differences were found between the patients who were lost and the patients who survived in terms of age, gender, comorbidities, causes of AMI, or surgical treatment methods. However, the blood pH, serum ferritin, and lactic acid levels were significantly higher in the patients who were lost. In addition, the median duration of hospital stay was significantly higher in the patients who survived, while the duration of ICU stay was significantly lower. It is thought that the increase in the duration of ICU stay negatively affects the mortality rates in AMI patients. Sepsis is a serious clinical condition that is frequently seen in the patients admitted to ICU and causes mortality. The risk of sepsis increases as the length of stay of the patient in the ICU is prolonged[31,32]. In our cohort, the fact that the ICU stay was longer in the exitus group compared to the survivor group was found to be compatible with the literature. A high APACHE-II score is an important parameter that indicates mortality in AMI[33]. In this study, the patients who were lost had a higher APACHE-II score when compared to the patients who survived, similar to the literature.

Limitations

The most important limitation of this study was its single centered and retrospective. Another limitation was the small number of our cohort.

Conclusion

AMI is an important condition affecting the elderly and patients with comorbidities and it still has high mortality rates. Although there has been no significant increase in the number of AMI cases during the COVID-19 period when compared to the pre-COVID-19 period, there has been a statistically significant increase in mortality in the COVID-19 period. It is thought that multicentered studies that include large patient populations are required to conclude the cause of increased mortality during the pandemic period in the patients with AMI.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

Ethical disclosures

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

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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ORIGINAL ARTICLE

Efficacy of diltiazem 2% rectal gel in the treatment of chronic anal fissure: a retrospective observational study

Eficacia de diltiazem 2% gel rectal en el tratamiento de la fisura anal crónica: un estudio observacional retrospectivo

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Abstract

Objective: *The aim of this study is to describe the effectiveness and safety of a magistral formulation of diltiazem 2% rectal gel as a treatment for chronic anal fissure.* **Material and methods:** *A retrospective observational study of all patients that began treatment with diltiazem 2% gel during 2019. The primary endpoint of the study was anal fissure healing. We also looked for differences in effectiveness between those initiating treatment and those who had been previously treated, long-term effectiveness through a 2-year follow-up and frequency of adverse effects.* **Results:** *Of the 166 patients included in the study, anal fissure healed in 72.9%. We detected adverse effects in 12 patients, the most common was local irritation. After 2 years of follow-up, 88% of patients did not relapse.* **Conclusion:** *In this study, use of topical diltiazem 2% has been shown to be effective and safe in the treatment of anal fissure and should be considered as the first line of therapy.*

Keywords: *Diltiazem. Fissure in Ano. Administration. Topical.*

Resumen

Objetivo: *El objetivo de este estudio es describir la efectividad y la seguridad de una fórmula magistral de diltiazem 2% gel rectal, como tratamiento de la fisura anal crónica.* **Material y métodos:** *Un studio observacional retrospectivo de todos los pacientes que comenzaron a ser tratados con diltiazem 2% gel durante el año 2019. La variable principal del estudio fue la cicatrización de la fisura anal. También se buscaron diferencias de efectividad entre aquellos que iniciaban el tratamiento y los que ya habían sido tratados previamente, efectividad a largo plazo mediante un seguimiento de 2 años y frecuencia de aparición de efectos adversos* **Resultados:** *De los 166 pacientes incluidos en el estudio, el 72,9% cicatrizaron la fisura anal. No detectamos diferencias estadísticamente significativas de efectividad entre los pacientes naive y aquellos que ya habían sido tratados. Detectamos efectos adversos en 12 pacientes, siendo el más frecuente la irritación local. Tras 2 años de seguimiento, el 88% de los pacientes no presentaron ninguna recaída.* **Conclusión:** *En este estudio, el uso de diltiazem 2% tópico ha mostrado ser efectivo y seguro en el tratamiento de la fisura anal y debería considerarse como primera línea terapéutica.*

Palabras clave: *Diltiazem. Fisura Anal. Administración Tópica.*

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Introduction

Chronic anal fissure is a lesion of the mucosa lining the anus in which there is an epithelial tear that persists for more than 6 to 8 weeks. It is usually located in the posterior raphe and the most common symptoms are pain during or after defecation that may last for minutes or hours, anal pruritus and rectorrhagia[1].

The etiology of chronic anal fissure is unclear. The traditional theory is that inadequate fiber intake generates hard stool, which, upon defecation, causes a tear in the anal mucosa[2]. However, though constipation may contribute to the development of chronic anal fissure, it is not the only factor involved. These patients have been found to have elevated resting internal anal sphincter pressure[2,3], which reduces posterior midline arterial flow, causing ischemia and thus entering a continuous cycle of pain, sphincteric spasm, and ischemia.

The goal of treatment is to reduce anal muscle tone and improve local vascularization, stopping the vicious cycle. According to the Clinical Practice Guidelines of the American Society of Colon and Rectal Surgeons[4], anal fissure should initially be treated conservative, combining pharmacological treatment (topical nitrates, calcium antagonists or botulinum toxin) with hygienic-dietary measures; such as the intake of a diet rich in fiber to avoid constipation, the use of fecal bolus softeners or warm water baths.

Lateral internal sphincterotomy (LIS) is a surgical procedure that reduces sphincteric hypertonia by sectioning the internal anal sphincter and is considered the treatment of choice in chronic anal fissure due to its high cure rate[5-7]. However, a percentage of patients develop irreversible incontinence after the procedure[6,8], so this technique is limited to patients with chronic anal fissure who have not responded to pharmacological treatment[9].

Calcium antagonists, such as diltiazem or nifedipine, are used as an alternative to LIS in the conservative treatment of chronic anal fissure, avoiding the risk of incontinence that this procedure can lead to. They are associated with a low incidence of adverse effects, the most frequent being headache or pruritus. They act by blocking L-type calcium channels in the muscle fibers of the internal anal sphincter, decreasing resting pressure and reducing sphincteric spasm, improving posterior midline blood flow[10,11].

Although there are pharmaceutical forms for oral administration, they usually produce systemic adverse effects such as orthostatic hypotension, nausea or headache. This has led to the development of topical forms for the treatment of chronic anal fissure. Jonas et al[12]. conducted a randomized clinical trial to compare the efficacy of topical versus oral diltiazem in the treatment of chronic anal fissure and observed that topically administered diltiazem was more effective, with 65% of patients resolving the fissure after 8 weeks of treatment versus 38% who received oral treatment.

To date, there is no topical pharmaceutical form of diltiazem approved by the Spanish Agency of Medicines and Medical Devices for the treatment of chronic anal fissure. Therefore, it is necessary to develop an extemporaneous preparation to be able to use a topical calcium antagonist in the treatment of this disease. This increases the risk of differences in composition and potency of the preparation when performed in different centers, which favors different results in patients receiving the same treatment.

The aim of this study is to describe the short- and long-term effectiveness and safety of a magistral formulation of diltiazem 2% rectal gel as a treatment for chronic anal fissure.

Material and methods

We conducted a retrospective observational study during 2019, which was approved by the local Drug Research Ethics Committee. We included all patients who attended the outpatient unit of a county hospital during the study period and who started treatment with a magistral formulation of diltiazem 2% gel (Table 1). All patients under 18 years of age, who did not have a diagnosis of anal fissure, if they received other additional topical treatment in the first 4 weeks of follow-up and those who had previously undergone a LIS were excluded.

The main study variable was anal fissure healing, considering as treatment failure those patients who did not achieve complete healing of the anal fissure, did not resolve the clinical condition or required additional topical treatment after the fourth week. We also looked for differences in effectiveness in naïve patients versus those who had been previously treated with topical diltiazem, appearance of adverse effects (headache, nausea, dizziness, local irritation or orthostatic hypotension) and long-term effectiveness, through a two-year follow-up of those patients who achieved complete healing, considering as relapse the appearance of symptoms suggestive of anal fissure. Other variables included in the study were

sociodemographic data (sex and age) and the number of containers collected.

The patients treated with diltiazem 2% were obtained from an internal registry of the pharmacy service. The clinical and sociodemographic variables were extracted from the patients' medical records using Abucasis® software. We used Microsoft Excel® software as a worksheet, while the statistical analysis was performed using IBM SPSS Statistics ver.23®.

We performed a statistical analysis using measures of centralization (median and mean), dispersion (interquartile range) and frequency. To determine differences in effectiveness between naive patients and those previously treated with diltiazem, we used Fisher's exact test.

To ensure patient privacy, a double-entry table was established that related the SIP number of each patient analyzed to a study number that was randomly assigned using the Excel® program. This list was kept in a locked cabinet in a password-protected worksheet and only the principal investigator had access to it.

No data that could identify the patient were recorded in the data collection sheet.

Table 1. Composition of topical diltiazem 2%

Components	Quantity
Diltiazem CLH	2g
Hydroxyethylcellulose	2g
Propylene glycol	10mL
Preserved water csp.	100mL

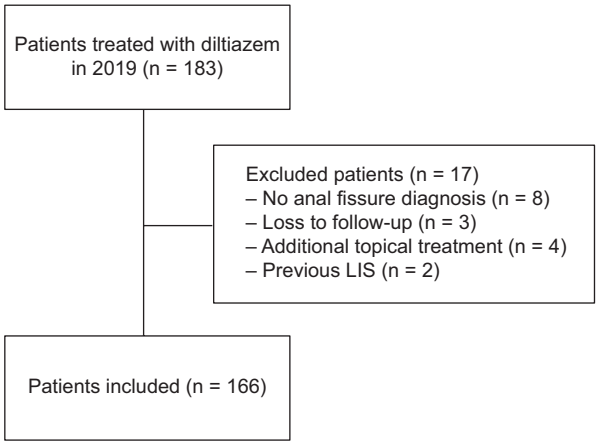

Figure 1. *Flow diagram of the patients included in the study.*

Results

Of the 183 patients studied, we excluded 17 patients from the study (Fig. 1). We included 166 patients (Table 2), of whom 81% had never been treated with topical diltiazem 2% and 19% had been treated previously.

Fifty-five percent were women, with a median age of 52 years (RIQ: 42-64).

Patients collected a median of 2 containers of diltiazem (range: 1-14) during treatment.

As for the primary study endpoint, anal fissure healing occurred in 72.9% of patients using topical diltiazem.

The anal fissure healed in 75.6% of the naive patients compared to 80.7% of those patients who had been previously treated with diltiazem. After performing Fisher's statistical test, we did not observe significant differences in the effectiveness of treatment between both groups (p = 0.329).

Regarding the 45 patients who did not heal their anal fissure, 53% received additional topical treatment, 18% were given botulinum toxin and 22% were treated with LIS.

We detected adverse effects in 12 naïve patients, and it was necessary to exchange the treatment in 11 of them for another topical drug. The most frequent was local irritation (42%), followed by headache (33%), dizziness (17%) and nausea (17%).

After 2 years of follow-up of the 121 patients who achieved complete healing of the anal fissure after completing treatment with topical diltiazem 2%, we observed that 88% of the patients did not present another episode of anal fissure, 10% suffered a relapse and 2% died.

Discussion

The aim of this study is to describe the efficacy and safety of the administration of an extemporaneous compound of Diltiazem 2% rectal gel in the management of anal fissure.

In anal fissure there is a tearing of the mucosa lining the anus, and it can be considered chronic when it persists for more than 6 weeks.

One of the most commonly used therapeutic options for chronic anal fissure is LIS, since it allows reducing the tone of the internal sphincter with a low rate of recurrence. However, several studies show that a high proportion of these patients develop irreversible fecal incontinence after surgery, which limits its use[6,8].

The use of calcium antagonists reduces sphincter hypertonia, improves local vascularization and

Table 2. Characteristics of patients treated with topical diltiazem 2%

	Naive (n = 135), n(%)	No Naive (n = 31), n(%)	Total (n = 166), n(%)
Women	72 (53)	19 (61)	91 (54,8)
Age (years), median (IQR)	49 (42-65)	52 (42-64)	52 (42-64)
No. of containers, median (range)	2 (1-14)	2 (1-10)	2 (1-14)
Healing	102 (75.6)	25 (80.7)	121 (72.9)
Therapeutic failure	33 (24.4)	6 (19)	45 (27.1)
Other topical treatment	21 (15.6)	3 (10)	24 (14.5)
Botox	5 (4)	3 (10)	8 (17.8)
LIS	7 (5)	3 (10)	10 (22.2)
ADR	12 (8.9)	0	12 (7.2)
Local irritation	5 (3.7)		5 (3)
Headache	4 (3)		4 (2.4)
Dizziness	2 (1.5)		2 (1)
Nausea	1 (0.7)		1 (0.6)

IQR: interquartile range; LIS: lateral internal sphincterotomy; ADR: adverse drug reaction.

constitutes an alternative to LIS, thus avoiding the risk of fecal incontinence. However, oral administration of calcium antagonists has been associated with the appearance of adverse effects such as nausea, vomiting and headache. For this reason, several formulations have been designed which allow their use topically, such as diltiazem 2% rectal gel that, thanks to its easy handling, acceptable efficacy and low incidence of adverse effects, is one of the most widely used options in the management of anal fissure.

In our study, 72.9% of patients treated with a compounded preparation of diltiazem 2% rectal gel achieved healing of anal fissure. These results are in agreement with a meta-analysis by Edward J et al[13]. which collected 9 clinical trials studying the efficacy of topical diltiazem 2%. Of the 379 patients included, 73.1% of patients successfully healed their anal fissure. Moreover, we observed no significant differences between those patients who were receiving the treatment for the first time and those who had already been treated.

The treatment was well tolerated by most patients. We observed the appearance of adverse effects in 7% of the patients, although all of them were mild, such as headache, nausea, vertigo or local irritation, the latter being the most frequent. It should be noted that all the adverse effects were detected in patients who had never been treated with diltiazem.

After two years of follow-up, 87.6% of the 121 patients who managed to heal their anal fissure did not experience any relapse. This implies that, taking into account the 155 patients included in the study, 68.3% were free of disease after two years. Nash et al[14]. obtained similar results when followed up for two years where 67.9% of the patients resolved the anal fissure after being treated with diltiazem.

In our experience, the results we have obtained in this study are similar to those of other investigators and support the use of topical diltiazem as first line in the treatment of anal fissure in order to avoid the need for LIS in the short term.

However, this study is not free of limitations. The observational design of the study and the absence of a control group makes it difficult to extrapolate these results to the population. In addition, the data were not obtained directly from the patients, but from the clinical history, which increases the risk of measurement bias.

Conclusions

In conclusion, in this study, treatment with topical diltiazem 2% has resulted in healing of 72.9% of anal fissures, with infrequent and mild adverse effects, so we consider it to be an effective and safe initial alternative to LIS in the treatment of anal fissure, thus avoiding the risk of fecal incontinence that this procedure implies.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of humans and animals. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed their center's protocols on the publication of patient data.

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ORIGINAL ARTICLE

Relation between neutrophil-to-lymphocyte ratio with epidural analgesia timing and thoracotomy pain

Relación entre la proporción neutrófilos/linfocitos con el momento de la analgesia epidural y el dolor de la toracotomía

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Abstract

Objective: *This study investigated the relationship of the pre-operative neutrophil/lymphocyte ratio (NLR) to the timing of epidural analgesia administration and post-operative acute and chronic pain in thoracotomy.* **Materials and methods:** *The study was conducted on 60 patients, with NLR ≥ 2 (Group A) and NLR < 2 (Group B). Each group was divided into subgroups pre-emptive analgesia (Group P) and control group (Group C). Epidural analgesic solution was administered as a bolus before the surgical incision in Group P and at the end of the operation in Group C. NRS was questioned postoperatively at the 2nd, 4th, 8th, 12th, 24th h, 1st, and 3rd months and also additional analgesic needs were recorded.* **Results:** *In Group A, the pain scores of the patients who received pre-emptive epidural analgesia were lower at the post-operative 2nd, 4th, and 8th h and analgesic consumption was less in the post-operative first 24 h.* **Conclusion:** *It was observed that pre-emptive epidural analgesia reduced pain levels and additional analgesic consumption in the acute post-operative period in patients with pre-operative NLR ≥ 2.*

Keywords: *Pre-emptive epidural analgesia. Neutrophil/lymphocyte ratio. Post-operative pain. Chronic pain.*

Resumen

Objetivo: *Este estudio investigó la relación de la relación neutrófilos/linfocitos (NLR) preoperatoria con el momento de la administración de la analgesia epidural y el dolor agudo y crónico posoperatorio en la toracotomía.* **Materiales y métodos:** *El estudio se realizó en 60 pacientes, como NLR ≥ 2 (Grupo A) y NLR < 2 (Grupo B). Cada grupo se dividió en subgrupos de analgesia preventiva (Grupo P) y grupo control (Grupo C). La solución analgésica epidural se administró en bolo antes de la incisión quirúrgica en el Grupo P y al final de la operación en el Grupo C. La NRS se cuestionó posoperatoriamente a las 2, 4, 8, 12, 24 horas, 1 y 3 meses también adicionales Se registraron las necesidades analgésicas.* **Resultados:** *En el Grupo A, los puntajes de dolor de los pacientes que recibieron analgesia epidural preventiva fueron menores a las 2, 4 y 8 horas postoperatorias y el consumo de analgésicos fue menor en las primeras 24 horas postoperatorias.* **Conclusión:** *Se observó que la analgesia epidural preventiva redujo los niveles de dolor y el consumo adicional de analgésicos en el postoperatorio agudo en pacientes con NLR preoperatorio ≥ 2.*

Palabras clave: *Analgesia epidural preventiva. Relación neutrófilos/linfocitos. Dolor posoperatorio. Dolor crónico.*

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Introduction

Post-operative pain is an acute type of pain that starts with surgical trauma and ends with wound healing. Prevention of post-operative pain is very important in terms of patient satisfaction and prevention of possible complications[1].

Thoracotomy is one of the surgical procedures in which post-operative pain is most common. Inadequate pain control after thoracic surgery, insufficient respiratory effort, inability to cough, and the development of atelectasis may cause thromboembolism due to decreased mobilization[2], cardiovascular side effects with increased catecholamine release, and lung infections such as pneumonia and bronchitis[3].

Inflammation triggered by surgery is one of the most important mechanisms of post-operative pain[4]. Neutrophil/lymphocyte ratio (NLR), a marker closely related to systemic inflammation, has been associated with post-operative edema and ecchymosis in rhinoplasty[5] and with post-operative wound infection in spinal surgery[6]. In addition, NLR has been used as a prognostic factor in various malignancies such as rectum[7], lung[8], and breast[9] cancers and as a diagnosis and response criterion in various diseases such as diabetes mellitus[10] and acute appendicitis[11].

Although NLR is used as a marker of inflammation in various diseases in the literature, studies investigating its effects on post-operative pain, which is closely related to acute inflammation, and its effectiveness in the timing of analgesia management are limited. The primary aim of this study is to evaluate the relationship of NLR, an inflammation marker in thoracic surgery, with the timing of epidural analgesia and, second, to investigate the relationship of NLR level with post-operative acute and chronic pain.

Materials and methods

A total of 60 patients between the ages of 18 and 75 years and in the ASA I-III risk group who underwent elective thoracotomy between March 2020 and June 2021 were included in the study. Patients with a body mass index (BMI) > 30 kg/m^2, those with local anesthetic or opioid allergy, those who continue to use opioids, those with active infections, those with neurological disease, abnormal coagulation tests, patients with renal or hepatic insufficiency, patients who used any medication for the diagnosis of chronic pain, could not cooperate, patients who had a previous thoracotomy, and patients who were unable to compare physical and verbal performance were excluded from the study.

One day before the operation, pre-anesthetic examinations of all patients were performed. Patients with suitable conditions for the study were informed about the study, and their written consent was received. The numeric rating scale (NRS) score was explained in detail to the patients to evaluate their acute and chronic post-operative pain levels. NLR, age, gender, weight, and ASA risk scores of the patients were recorded before the operation.

Electrocardiography (ECG), peripheral oxygen saturation (SpO_2), and non-invasive blood pressure monitoring were performed on the patients who were taken to the operating table. Thoracic epidural catheter T_{4-5} was inserted at the level of the intervertebral space. After IV administration of propofol (2-3 mg/kg) and fentanyl (2 μg/kg), muscle relaxation was achieved with IV rocuronium (0.6 mg/kg). All patients were intubated with an appropriately sized left double-lumen tube for one-lung ventilation. After the tube position was confirmed with a fiberoptic bronchoscope, mechanical ventilation was started. After the patients were placed in the lateral decubitus position for surgery, the tube position was confirmed again with a fiberoptic bronchoscope. Anesthesia was maintained with 50% O_2/air and 2% sevoflurane in both groups. Muscle relaxant maintenance was provided with an additional dose of 0.25 mg/kg rocuronium according to the neuromuscular monitoring response.

Patients were divided into two groups as NLR level above 2 (Group A) and NLR level below 2 (Group B). After the epidural catheter was inserted, an equal number of subgroups were differentiated into groups A and B, and a bolus of 0.25% bupivacaine 0.1 ml/kg was administered through the epidural catheter 20 min before the surgical incision in the group to be administered pre-emptive analgesia (Group P), and an infusion of 0.1% bupivacaine was started at a rate of 0.1 ml/kg/h for 48 h. In the control group (Group C), a bolus of 0.25% bupivacaine 0.1 ml/kg was administered through the epidural catheter 20 min before awakening, and an infusion of 0.1% bupivacaine at a rate of 0.1 ml/kg/h for 48 h was started. In Group C, intraoperative analgesia was provided with 0.1-0.25 mcg/kg/min remifentanil infusion. Intramuscular pethidine (Aldolan-Gerot®, LibaLab.) was given at a dose of 1 mg/kg to all patients with a post-operative NRS value above 3. If the pain did not decrease, intramuscular diclofenac 75 mg (Diclomec®, Abdi İbrahim)

was administered. Application time and doses were recorded. NRS and additional analgesia needs were recorded for all patients at the post-operative 2nd, 4th, 8th, 12th, and 24th h. In the 1st and 3rd months postoperatively, the patients were contacted by phone, and their NRS scores were recorded.

Statistics

SPSS for Windows 17.0 program was used for statistical analysis. Descriptive variables are given as median (minimum-maximum), mean ± SD, and, if needed, as % (frequency) values. The conformity of the data to the normal distribution was evaluated with the Shapiro–Wilk test. During the data analysis, cases with Chi-square and Mann–Whitney U test $p < 0.05$ were considered statistically significant. G Power 3.1.9.4 (HHU, Germany) program was used to calculate the sample size. Based on the study of Öner et al.[12], alpha error = 0.05, beta error = 0.20, and effect size 0.8, it was concluded that a total of 52 patients, at least 26 for each group, would be sufficient. However, considering possible data loss, a total of 60 patients were included in the study.

Results

There was no significant difference between the groups in terms of demographic data ($p > 0.05$) (Table 1). There was no significant difference in pain scores and analgesic consumption between the patient groups with and without pre-emptive epidural analgesia in the pre-operative NLR < 2 group (Table 2). However, in the group with pre-operative NLR ≥ 2, the pain scores of the patients who received pre-emptive epidural analgesia were lower at the post-operative 2nd, 4th, and 8th h (respectively, $p < 0.001$, $p = 0.005$, $p = 0.006$) (Table 3) compared to the patients who did not receive pre-emptive epidural analgesia. Analgesic consumption was less in the post-operative first 24 h ($p < 0.05$) (Table 3). It has been observed that pre-emptive epidural analgesia has no effect on the chronicity of pain in patients with both NLR ≥ 2 and NLR < 2 (Tables 2 and 3).

Discussion

Thoracotomy is considered the most painful of all surgical procedures and must be treated with effective analgesia. In addition to the surgical incision, damage to the ribs and intercostal nerves, cutting of the major muscles, and placement of the chest tube play a role in the formation of this pain. It has been reported that eliminating this pain is very important in increasing patient comfort and contributes to both rapid recoveries of respiratory functions and reduction of complications[13,14].

Table 1. Demographic data (min-max, mean ± SD, n [%])

	Group A (NLR ≥ 2) (n = 32)	Group B (NLR < 2) (n = 28)	p
Age	66 41-75	62 23-74	0.213
Gender (M/F)	24 (75)/8 (25)	25 (89)/3 (11)	0.472
BMI	24.8 21.9-29.1	24.7 20.3-29.4	0.779
ASA (I, II, III)	5 (16)/16 (50)/9 (34)	6 (22)/15 (53)/7 (25)	0.068
NLR	3.45 ± 2.84	1.45 ± 0.445	**< 0.0001**

p values in bolds are statistically significant at $p < 0.05$. NLR: neutrophil/lymphocyte ratio.

Some patients may be at greater risk for post-operative pain. Determining this risk or patient group will help establish the analgesia and anesthesia strategy. Identifying patients with this risk group, particularly in cases that may cause severe pain, such as post-thoracotomy pain, may help us prevent post-operative pain-related complications. Patients with high baseline inflammation, such as those with high NLR levels, can be included in this risk group for post-operative pain.

With this current study, we accepted our hypothesis that if we detect the pre-operative NLR level, a risk factor for post-thoracotomy pain, in advance, we can reduce the severity and chronicity of acute post-operative pain by making the timing of epidural analgesia correct.

In our study, we found that the NRS levels at the post-operative 2nd, 4th, and 8th h and the amount of additional analgesic consumed in the first 24 h post-operatively in the control group in pre-operative NLR ≥ 2 patients were higher than the group in which pre-emptive thoracic epidural analgesia was administered. However, there was no difference between the subgroups in terms of pain scores and analgesic consumption in patients with pre-operative NLR < 2. This has shown us that patients with pre-operative high NLR may benefit from pre-emptive thoracic epidural analgesia. However, we observed that pre-emptive thoracic epidural analgesia had no effect on the chronicity of post-thoracotomy pain in both NLR ≥ 2 and NLR < 2 patient groups.

Table 2. Comparison of the effects of epidural analgesia application times on post-operative NRS and analgesic consumption in patients with pre-operative NLR < 2

Pre-operative NLR < 2 (n: 28)	Group P (n: 14)		Group C (n: 14)		p
	Median	Min-Max	Median	Min-Max	
Post-operative 2nd h NRS	2	2-4	3	2-4	0.282
Post-operative 4th h NRS	2	1-3	1.5	1-3	0.953
Post-operative 8th h NRS	2	0-2	2	1-3	0.805
Post-operative 12th h NRS	1	0-2	1	0-2	0.700
Post-operative 24th h NRS	0	0-1	0	0-2	0.923
Post-operative 1st-month NRS	0	0-3	1	0-5	0.303
Post-operative 3rd-month NRS	0	0-3	1	0-4	0.361
Post-operative first 24 h Additional analgesic consumption					
Meperidine (mg)	40	0-50	50	30-60	0.123
Diclofenac (mg)	0	0-75	37.5	0-150	0.711

NLR: neutrophil/lymphocyte ratio.

Table 3. Comparison of the effects of epidural analgesia application times on post-operative NRS and analgesic consumption in patients with pre-operative NLR ≥ 2

Pre-operative NLR ≥ 2 (n: 32)	Group P (n: 16)		Group C (n: 16)		p
	Median	Min-Max	Median	Min-Max	
Post-operative 2nd h NRS	3	1-5	5	3-7	**< 0.001**
Post-operative 4th h NRS	3	0-5	4	1-6	**0.005**
Post-operative 8th h NRS	1	0-3	3	1-5	**0.006**
Post-operative 12th h NRS	1	0-3	1	0-3	0.945
Post-operative 24th h NRS	0	0-3	1	0-2	0.716
Post-operative 1st-month NRS	1	0-5	1	0-4	0.390
Post-operative 3rd-month NRS	0	0-3	0	0-5	0.737
Post-operative first 24 h Additional analgesic consumption					
Meperidine (mg)	40	0-60	85	30-100	**< 0.001**
Diclofenac (mg)	75	0-75	75	0-225	**0.014**

p values in bold are statistically significant at p < 0.05. NLR: neutrophil/lymphocyte ratio.

It has been shown that patients with high NLR levels have pre-operative widespread systemic inflammation and may experience more pain due to the altered inflammatory balance[8]. Many studies in the literature show the relationship between pre-operative NLR level and post-operative pain. It has been shown that post-operative analgesic need and pain scores are higher in patients with a pre-operative NLR level above two after orthognathic surgery[15], arthroscopic shoulder surgery[16], and thoracotomy[17]. In our study, we determined the threshold value for NLR as 2 while forming our groups in accordance with the literature. We found that pre-emptive analgesia reduced the amount of post-operative analgesic and decreased pain scores in patient groups with NLR levels above 2.

In another study on thoracotomy surgery, it has been suggested that epidural analgesia can be chosen in patients with high NLR[18]. In this study, we chose epidural analgesia as the method of analgesia; however, we have demonstrated that patients with high

basal inflammation levels, such as high NLR levels, are at greater risk and that pre-emptive epidural analgesia will make a difference in preventing post-operative pain in this risk group.

Pre-emptive analgesia is defined as the prevention of central sensitization by applying painkillers or methods before the causes of pain occur and, thus, the cessation of pain before it starts[19]. In studies investigating the effects of pre-emptive thoracic epidural analgesia on acute post-thoracotomy pain, lower post-operative pain scores and analgesic consumption were found in the pre-emptive epidural analgesia method[20,21]. However, none of these studies evaluated pre-operative NLR levels. In the study of Neustein et al., it was shown that the pain levels in the first 6 h were statistically lower in patients who underwent pre-emptive epidural analgesia in thoracic surgery. They did not detect a significant difference in pain scores after 6 h[22]. In our study, NRS scores in the first 8 h were statistically lower in patients who underwent pre-emptive analgesia, in line with the literature. However, we observed that this change was only in the patient group with NLR levels above 2. There was no significant difference in NRS scores at other hours, and more analgesic consumption was observed in this patient group.

Unlike our study, the study investigating the relationship between chronicity of post-operative pain and NLR in the literature was conducted in lumbar disc surgery. They examined VAS levels at 6 months post-operatively to assess pain. It was found that the pre-operative NLR level showed a positive correlation with the pain at the post-operative 6th month[23]. In our study, we evaluated the NRS levels at the 1st and 3rd months to evaluate the relationship between the pre-operative NLR level and chronic post-thoracotomy pain; however, we could not find a relationship between the pre-operative NLR level and the NRS values at the 1st and 3rd months. We thought that this difference was due to the different duration of evaluation of chronicity and the fact that pain evaluation is a subjective method.

There are some limitations in our study. The most important limitation is that there are factors that affect the inflammatory response to surgery other than pain. Since our study was a single-center study, the results are limited to a certain region. Therefore, multicenter studies with larger patient groups are needed. Although there are many methods for measuring post-operative pain since pain is a subjective symptom, our study is also limited by the lack of a precise and objective method for measuring pain.

As a result, in our study, we concluded that the pre-emptive epidural analgesia method has a high inflammatory activity, and the pre-operative NLR level of patients above 2 is suppressed with the pre-emptive analgesia method, and their pain is better controlled in the post-operative acute period. We observed that the post-operative pain level and analgesic consumption of patients with low inflammatory activity and a pre-operative NLR level below 2 did not change with the application of pre-emptive analgesia. Thus, we provided sufficient analgesia by minimizing the unnecessary use of local anesthetic and the dose of local anesthetic to reduce the side effects in pain management. We believe that the NLR level, one of the parameters with pre-operative inflammatory activity in thoracotomy surgeries, may guide our choice of pre-emptive epidural analgesia.

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Conflicts of interest

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Ethical disclosures

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Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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ORIGINAL ARTICLE

Effects of different surgical treatments on pain, disability, anxiety and quality of life in lumbar disc herniation

Efectos de diferentes tratamientos quirúrgicos sobre el dolor, la discapacidad, la ansiedad y la calidad de vida en la hernia de disco lumbar

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Abstract

Objective: *This study aims to compare the effects of microscopic microdiscectomy and microendoscopic discectomy on pain, disability, fear of falling, kinesiophobia, anxiety, quality of life in patients with lumbar disc herniation (LDH).* **Methods:** *A total of 90 patients who underwent microscopic microdiscectomy (n = 40) and microendoscopic discectomy (n = 50) for LDH were included in this study. The patients' pain, disability, fear of falling, kinesiophobia, anxiety, and quality of life were evaluated before the surgery, in the early postoperative period and three months after.* **Results:** *In patients who underwent microendoscopic discectomy, the results of pain, disability, fear of falling, kinesiophobia and anxiety were statistically decreased compared with the microscopic microdiscectomy in the early postoperative period and three months later ($p < 0.05$). Also, a statistically higher increase was observed in the general health perception of patients who underwent microendoscopic discectomy three months after the operation ($p < 0.01$).* **Conclusion:** *Microendoscopic microdiscectomy, remains the most effective and widely applied method with advantages on pain, quality of life, and improved physical functions.*

Keywords: *Lumbar disc herniation. Microscopic microdiscectomy. Microendoscopic discectomy. Pain. Disability.*

Resumen

Objetivo: *Este estudio tiene como objetivo comparar los efectos de la microdiscectomía microscópica y la discectomía microendoscópica sobre el dolor, la discapacidad, el miedo a caer, la kinesiofobia, la ansiedad y la calidad de vida en pacientes con hernia de disco lumbar (LDH).* **Métodos:** *Se incluyeron en este estudio un total de 90 pacientes sometidos a microdiscectomía microscópica (n = 40) y discectomía microendoscópica (n = 50) por LDH. Se evaluó el dolor, la discapacidad, el miedo a caer, la kinesiofobia, la ansiedad y la calidad de vida de los pacientes antes de la cirugía, en el postoperatorio temprano y tres meses después.* **Resultados:** *En los pacientes sometidos a discectomía microendoscópica, los resultados de dolor, discapacidad, miedo a caer, kinesiofobia y ansiedad disminuyeron estadísticamente en comparación con la microdiscectomía microscópica en el postoperatorio temprano y tres meses después ($p < 0.05$). Además, se observó un aumento estadísticamente mayor en la percepción de salud general de los pacientes sometidos a discectomía microendoscópica tres meses después de la operación ($p < 0.01$).* **Conclusión:** *La microdiscectomía microendoscópica sigue siendo el método más eficaz y ampliamente aplicado con ventajas sobre el dolor, la calidad de vida y la mejora de las funciones físicas.*

Palabras clave: *Hernia discal lumbar. Microdiscectomía microscópica. Discectomía microendoscópica. Dolor. Discapacidad.*

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Introduction

Lumbar disc herniation (LDH) is characterized by the change in the normal location of the discs because of excessive load on the vertebral discs and usually occurs during the degeneration process[1]. It is frequently observed between the ages of 30-50 and mostly in men[2]. The sedentary lifestyle we frequently encounter today causes many health problems[3,4]. It is generally accepted that the etiology of disc degeneration is multifactorial and related to physical activity, lifestyle factors, and other individual characteristics[5,6].

Physical inactivity can lead to a narrowing of the distance between the intervertebral discs, an increase in the fat content of the multifidus muscle, and high-intensity low back pain[7]. In addition, due to the very low activation of the lumbar muscles while sitting, the load may be transmitted to passive structures such as ligaments and intervertebral discs, causing degenerative changes in the lumbar spine. This may cause an increase in the prevalence of lumbar disc herniation[8].

Low back pain is one of the most common health problems, causing severe disability in lumbar disc herniation patients, and 70-80% of people experience low back pain at some point in their lives. It is seen as an expensive sociomedical problem due to the need for recurrent treatments, long-term job loss, and social support[1,7].

Lumbar disc herniation is usually seen in L4-L5 and L5-S1 localizations. Displacement of the intervertebral disc causes compression on spinal nerve roots, spinal cord, and pain-sensitive structures. The patient may have lower back-leg pain, pain and limitation in lower back movements, spasms in the lumbar muscles, positive nerve stretching tests, and sensory, motor, and reflex defects due to the sliding disc pressing on the nerve root[9,10]. Most patients with lumbar disc herniation respond well to conservative treatment; hence only 5-10% of patients require surgery[9].

MRI is a valuable, non-invasive tool for demonstrating disc herniation and identifying pathological changes in the disc due to its superiority in soft tissues[11,12]. Contrast-enhanced MRI may also reveal inflammation in the nerve root. Sequestered disc hernias, differentiation of hernias and other lesions, and peridiscal degeneration assessment can be conducted more efficiently with MRI[12].

Following the diagnosis, the treatment in herniation patients is primarily conservative, and options such as medical treatment, physical therapy, and rest are usually advised. In addition, the definitive surgical indication is sacral root paralysis due to massive midline disc herniation. Relative indications are progressive neurological loss, motor weakness, severe excruciating pain, frequent recurrences, and unresponsiveness to appropriate conservative treatment[13]. Microscopic discectomy and endoscopic discectomy options are available as surgical treatments. Recently, the preference for endoscopic discectomy has been increasing because it is less invasive[14].

In previous literature, limited evidence has been published about the effectiveness of these two surgeries on functional parameters such as pain, disability, fear of falling and kinesiophobia in individuals with lumbar disc herniation. Additionally, no research has been published that compared the efficacy of microscopic microdiscectomy treatment and microendoscopic discectomy surgeries. The aim of this study is to compare the effects of microscopic microdiscectomy surgical treatment and micro endoscopic discectomy on pain, disability, fear of falling, kinesiophobia, anxiety and quality of life in patients scheduled for lumbar disc herniation surgery. Secondly, it is aimed to illuminate the disability and loss of quality of life caused by lumbar disc herniation.

Materials and methods

A total of 90 patients who were admitted to two institutions with lumbar disc pathologies between March 2023 to May 2023 enrolled in this prospective study. Ninety patients over 18, who were diagnosed with lumbar disc pathology requiring surgical treatment according to MRI results, and volunteered to participate in the study, were included in the study. Patients who had undergone surgery in the lumbar region previously had lumbar degenerative changes (spondylolisthesis, scoliosis, malignancy status, vertebral fracture, osteoporosis, lumbar osteoarthritis) in the MRI, individuals who were not able to cooperate, pregnant, and did not require surgical treatment were excluded.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the Ethics Committee of the University (2023/1282) and written informed consent has been obtained from all patients.

Patients diagnosed with lumbar disc and scheduled for microscopic discectomy and microendoscopic

discectomy were included in the study and divided into two groups: Microendoscopic discectomy (endoscopic surgery) and microscopic discectomy (surgery). The patients were evaluated in their routine outpatient clinic controls, and the patients whose symptoms were compatible with the lumbar disc pathologies were included in the study. The study was conducted on patients diagnosed with a lumbar disc in two hospitals (Karabük University Training and Research Hospital Neurosurgery Department and Malatya Private Gözde Academy Hospital). Demographic characteristics of the patients such as age, genders were recorded. Pain (Numeric Rating Scale), disability (Oswestry Disability Index), fear of falling (Falls Efficacy Scale-International), kinesiophobia (Tampa Scale for Kinesiophobia), anxiety (Beck Anxiety Inventory), and quality of life (Short Form-36) were evaluated to patients who decided to undergo surgical treatment in the preoperative, early postoperative periods, and three months.

Outcome measures

Numeric rating scale

Low back pain severity of individuals was evaluated with the 'Numbered Rating Scale (NRS)'. This scale is horizontally scored between 0-10 (0 = no pain, 10 = unbearable pain). Pain intensity was evaluated for the low back during rest[15].

Oswestry disability index

The Turkish version of the Disability Index (ODI) was used to evaluate the degree of loss of function associated with low back pain. The ODI, developed to assess functional disability in low back pain, has ten items (pain intensity, personal care, lifting, walking, sitting, standing, sleeping, social life, travelling, and changing the degree of pain). Pain-related disability ranges from 0 to 100 points. As the total score increases, the level of disability also increases[16].

Falls efficacy scale-international

Falls Efficacy Scale-International (FES-I) is a scale that evaluates individuals' self-confidence while performing their daily activities. Thus, it aims to predict the probability of falling concerning balance and gait. This scale assesses individuals' fear of falling in daily activities with 16-item questions. Individuals get a score between 16-65. It is observed that the probability of falling increases as the total score increases[17]. Turkish validity and reliability were performed by Ulus et al[18].

Tampa scale for kinesiophobia

The Tampa Scale for Kinesiophobia (TSK) measures individuals' fear of movement and re-injury. The Turkish version of the TSK was used to measure kinesiophobia in the study. The TSK consists of 17 questions and a 4-point Likert score, including the attitudes of individuals (1 = strongly agree, 4 = strongly disagree). When calculating the total score, items 4, 8, 12 and 16 be reversed to obtain a score. The individual gets a score between 17-68, and an increase in the score means an increase in kinesiophobia[19].

Beck anxiety inventory

The Turkish version of the Beck Anxiety Inventory (BAI) was used to measure the anxiety symptoms level of the participants. The BAI is a 21-item questionnaire to reflect the severity of somatic and cognitive anxiety symptoms during the previous week. Items are scored on a 4-point scale (0-3), and the total score ranges from 0 to 63[20].

Short form-36

The Turkish version of Short Fom-36 (SF-36) was used to measure changes in quality of life-related to chronic low back pain. This scale consists of 36 items and includes physical function, physical role difficulty, pain, general health, energy, social function, emotional role difficulty, mental health, etc. It evaluates various sub-parameters. Each sub-parameter is scored out of 0 is the lowest, and 100 is the highest[21,22].

Statistical analysis

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 23.0 (IBM Corp., Armonk, NY) package program. Based on the pain results from the pilot study, we estimated that a sample size of at least 35 individuals in each group would have 80% power for an α value of 0.05 and an effect size d = 0.60. Considering there would be data loss, 10% more individuals were planned to participate in the study, and at least 40 individuals for each group participated.

Frequency and percentage were given for categorical data, and median, minimum, and maximum descriptive values for continuous data. The "Mann Whitney U-Test" was used to compare the groups, and the "Pearson Chi-Square Test" was used to compare the categorical variables. The results were considered statistically significant when the p-value was less than 0.05.

Results

Within the scope of this prospective research, 90 patients who had undergone lumbar herniation surgeries in two different centers were enrolled in the study. Endoscopic surgery was performed in 55.6% (n = 50) of the patients, and lumbar discectomy was performed in 44.4% (n = 40). The distribution of demographic findings according to the type of surgery of the patients is presented in table 1. Regarding gender, 51.1% (n = 46) of the patients were female, and 48.9% (n = 44) were male. The median age of the study population was 41 years (range 21 to 73 years).

The outcomes of the NRS pain scores, ODI, FES-I, TSK, and BAI were measured before the surgery, after the surgery, and at the three months after the surgery, according to the surgical types of the patients were elaborated in table 2. When the table is examined, it is seen that there was no statistically significant difference in the preoperative NRS pain scores and TSK between the two surgical methods. All other scales showed a statistically significant difference between the two surgical methods before, after, and during the three months after the surgery ($p < 0.05$; table 2).

The distribution of SF-36 quality of life scale scores according to surgery methods measured before, after, and during the three months after the operation has been presented in table 3. When the table is examined, it is seen that there was a statistically significant difference before the surgery in the "Physical Function" sub-dimension scores between the two methods ($p < 0.05$). Although this difference disappeared after the surgery, there was a statistically significant difference in the three months after the surgery ($p < 0.05$). The difference between the two methods before the surgery in the sub-dimensions of "Physical Role Difficulty" and "Emotional Role Difficulty" disappeared in the postoperative period.

A statistically significant difference has been achieved between the two methods in the preoperative, postoperative, and postoperative three-month measurements in the "Energy/Vivacity/Vitality" sub-dimension ($p < 0.05$). In terms of the "Mental Health" and "Pain" sub-dimensions, although a difference has been observed before and after the surgery, no statistically significant difference was detected in the three months after the surgery. While there was no difference in the "Social Functioning" sub-dimension before the surgery,

Table 1. Baseline demographics of the study population

	Total (n = 90)	Endoscopic Surgery (n = 50)	Surgery (n = 40)	p
	Median (Min-Max) n (%)	Median (Min-Max) n (%)	Median (Min-Max) n (%)	
Age (years)	41 (21-73)	35 (21-73)	49 (23-72)	< 0.001
Gender				
Female	46 (51.1)	25 (50)	21 (52.5)	0.981
Male	44 (48.9)	25 (50)	19 (47.5)	

Min: minimum; Max: maximum.

Table 2. Distribution of the variables according to groups

	Endoscopic surgery (n = 50)	Surgery (n = 40)	p
	Median (Min-Max)	Median (Min-Max)	
NRS			
Before the operation	7 (6-9)	7 (4-9)	0.401
Post-operative	1 (0-4)	1 (0-2)	0.024
3rd month after the surgery	0 (0-3)	1 (0-2)	< 0.001
ODI			
Before the surgery	15.5 (11-15.5)	20 (12-29)	< 0.001
Post-operative	0.8 (0-8.1)	2.5 (0-5.5)	0.002
3rd month after the surgery	0 (0-8.1)	1.5 (0-5)	< 0.001
FES-I			
Before the surgery	35 (30-36)	43 (27-60)	< 0.001
Post-operative	18 (16-33)	23 (16-38)	< 0.001
3rd month after the surgery	16 (16-33)	19.5 (14-34)	< 0.001
TSK			
Before the surgery	49 (46-49)	48 (33-55)	0.761
Post-operative	21 (17-58)	26 (14-40)	< 0.001
3rd month after the surgery	17 (17-58)	20 (14-30)	< 0.001
BAI			
Before the surgery	29 (15-29)	11 (7-19)	< 0.001
Post-operative	4 (0-16)	9 (7-14)	< 0.001
3rd month after the surgery	0 (0-10)	8 (7-12)	< 0.001

Min: minimum; Max: maximum.

there was a statistically significant difference between the two methods in the postoperative and postoperative three-month measurements ($p < 0.05$). On the contrary, the 'General Health Perception" sub-dimension presented a difference between the two methods before the surgery; this difference disappeared after the surgery, and there was a difference again in the three-month measurements after the surgery ($p < 0.05$; Table 3).

Table 3. Distribution of SF-36 Quality of Life Scale Scores by groups

SF-36 Quality of Life Scale	Endoscopic Surgery (n = 50)	Surgery (n = 40)	
	Median (Min-Max)	Median (Min-Max)	
Physical Function			
Before the surgery	65 (65-65)	50 (0-85)	< 0.001
Post-operative	92.5 (45-100)	90 (50-100)	0.055
3rd month after the surgery	100 (45-100)	90 (65-100)	0.023
Physical Role Difficulty			
Before the surgery	0 (0-0)	0 (0-100)	0.002
Post-operative	100 (25-100)	100 (0-100)	0.468
3rd month after the surgery	100 (25-100)	100 (0-100)	0.490
Emotional Role Difficulty			
Before the surgery	33.3 (0-33.3)	0 (0-100)	< 0.001
Post-operative	100 (34.3-100)	100 (0-100)	0.442
3rd month after the surgery	100 (34.3-100)	100 (0-100)	0.447
Energy/Vitality/Viability			
Before the surgery	35 (30-45)	30 (5-45)	< 0.001
Post-operative	50 (0-70)	55 (35-80)	< 0.001
3rd month after the surgery	50 (45-65)	55 (35-80)	< 0.001
Mental Health			
Before the surgery	48 (44-56)	52 (32-64)	0.002
Post-operative	52 (0-60)	56 (40-80)	< 0.001
3rd month after the surgery	52 (40-64)	56 (40-80)	0.201
Social Functioning			
Before the surgery	50 (25-50)	50 (0-62.5)	0.085
Post-operative	37.5 (0-75)	75 (62.5-100)	< 0.001
3rd month after the surgery	62.5 (37.5-87.5)	81.3 (62.5-100)	< 0.001
Pain			
Before the surgery	22.5 (12.5-45)	45 (10-67.5)	< 0.001
Post-operative	35 (0-77.5)	90 (52.5-100)	< 0.001
3rd month after the surgery	78.8 (22.5-100)	90 (52.5-100)	0.071
General Health Perception			
Before the surgery	35 (35-45)	45 (15-65)	0.013
Post-operative	60 (10-85)	55 (30-75)	0.957
3rd month after the surgery	62.5 (40-95)	55 (30-75)	< 0.001

Min: minimum; Max: maximum.

Discussion

This study showed that microendoscopic surgery is more effective than microscopic surgery in reducing pain, disability, fear of falling, and kinesiophobia in the early and long term. It also showed that micro-endoscopic surgery improves the quality of life in a long time.

Herniated intervertebral disc disease is the most common reason for lumbar spinal surgery. In the early 1980s, there was an increasing use after Caspar described the technique and instrumentation for the use of the microscope in the surgery of disc herniations. This technique is still the gold standard in disc surgery today. Although most lumbar disc herniations benefit from conservative treatments, surgical treatment is required in patients with cauda equina syndrome, sudden or progressive loss of strength, failure to respond to conservative treatment for 4-6 weeks, and frequent recurrent disc herniation attacks[1,14].

The anatomical structure of the lumbar spinal column, such as midline, paraspinal and posterolateral, reliably allows minimally invasive surgical intervention with the posterolateral approach. One of these different approaches is the transforaminal approach. If necessary, it is applied for discectomy with the help of an endoscope or microscope[1,21]. Required revision can be achieved by using different angle endoscopy optics. It is known that open surgery in extraforaminal disc herniations causes more anatomical damage than intracanal herniations. Since facetectomy is usually performed in open surgery, 25% instability due to anatomical damage is always one of the topics discussed[3,5]. Microdiscectomy is a modification of the standard open discectomy. Smaller skin incision, less muscle dissection, preservation of the ligamentum flavum and ultimately faster recovery are the advantages of this technique. However, transforaminal and extraforaminal endoscopic methods are minimally invasive[1]. In a study, transforaminal endoscopic discectomy was found to be effective in reducing pain and disability in LDH[23]. In our study, the comparison between endoscopic discectomy and microscopic microdiscectomy on the SF-36 Quality of Life scale revealed favorable outcomes for microendoscopic microdiscectomy. Postoperative pain is the most important complaint of lumbar disc herniation patients, and it was clinically significantly lower in the

microendoscopic microdiscectomy group. Additionally, general health status, which indicated the degree of healing, was also clinically higher in individuals operated via microendoscopic microdiscectomy. Similar to this parameter, social functioning was also significantly better in these patients in the postoperative period and three months after the surgery. Energy–vitality and viability sub-dimensions have also indicated significantly improved outcomes in the preoperative and postoperative period and three months after the surgery. The preoperative results may be attributed to the patient's motivation for a microendoscopic microdiscectomy. The physical functioning scores also revealed statistically significantly higher results in the preoperative period and three months after the surgery[24]. In addition, injections used before surgery also increase the effectiveness of treatment after LDH surgery[25]. Therefore, its use in the microendoscopic surgery process may be important in making healing more effective.

Lew et al. stated that transforaminal percutaneous endoscopic discectomy results have been 85% successful in foraminal and extraforaminal disc herniation[26]. Similarly, Yang reported a success rate of 85.7% with transforaminal endoscopic discectomy[27]. He stated that these rates were comparable to foraminal and extraforaminal disc hernias treated with traditional surgical methods[28]. Yeung reported excellent and good results in 83.6%, poor results in 9.3%, and reoperation in 5% of 307 patients with primary lumbar disc herniation who underwent posterolateral endoscopic discectomy with a minimum follow-up of 1 year[28]. In this study, 80% success was achieved with the full endoscopic method in lumbar disc disease despite the inexperience of the surgeons. It was determined that the success rate obtained in this study was comparable to the studies in the literature. More importantly, 93.3% of cases reported that the same surgery could be repeated despite recurrence[28].

Recurrence is an inevitable complication of disc surgery. Even in microsurgery series, recurrence rates between 5% and 18% have been reported. The recurrence rate in endoscopic discectomy surgery is between 0% and 12%[26]. Many authors have reported it completing the learning curve with increased cases recommended to avoid recurrence[28,29].

While microdiscectomy was widely used for the surgical treatment of soft sequestered disc herniations, it was later used frequently in treating pathologies associated with advanced degeneration. Microendoscopic microdiscectomy performed in lumbar disc herniation surgery may have many advantages compared to open standard discectomy, such as being a minimally invasive method, using a small incision, very little subperiosteal muscle dissection, good, and less. In addition, this surgical method has less postoperative pain. The period includes many postoperative advantages, such as more comfortable mobilization and early return to work. Considering the length of hospital stay and the amount of blood loss, some studies reported results favoring microendoscopic microsurgery[30].

The results of our study supported the advantages of microscopic microdiscectomy. Although there was no statistically significant difference between the two surgical methods in the preoperative NRS pain scores and TSK, they favored the microendoscopic microdiscectomy group in the postoperative period and three months after the surgery. Additionally, ODI scores have also denoted clinically significant results in the postoperative period and three months after the surgery. Falls Efficacy Scale-International and BAI scores were statistically significantly better in all three measurements in the microendoscopic microdiscectomy group.

Regarding the outcomes of this research, it was shown that microendoscopic microdiscectomy surgical treatment is more effective in reducing pain than endoscopic discectomy. Additionally, microendoscopic microdiscectomy surgical treatment is more effective in reducing disability and increasing quality of life. Microendoscopic microdiscectomy surgical treatment effectively reduces kinesiophobia, anxiety, and fear of falling.

Conclusion

In conclusion, microendoscopic discectomy surgery performed in patients with lumbar disc hernia reduces pain, disability, fear of falling, kinesiophobia and anxiety more than microscopic microdiscectomy surgery in both the early and long term after surgery. Also, microendoscopic discectomy is more effective in improving quality of life. In this context, microendoscopic microdiscectomy, a minimally invasive method, continues to be the most effective and widely applied method with the advantages of improving pain, quality of life and physical functions.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

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

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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ORIGINAL ARTICLE

The mediating role of physician trust in the relationship between medical mistrust and health-care system distrust

El papel mediador de la confianza del médico en la relación entre la desconfianza médica y la desconfianza en el sistema de salud

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Abstract

Objective: *This study was carried out to determine the mediating role of physician trust in the relationship between medical mistrust and health-care system distrust.* **Materials and methods:** *The "Health Care Systems Distrust Scale", which consists of 10 questions, the "Medical Mistrust Scale", which consists of 17 questions, the "Physician Trust Scale", which consists of 11 questions. The statistical analysis was performed using the SPSS 26.0 program.* **Results:** *Health-care system distrust was positively correlated with medical mistrust and negatively correlated with physician trust. There was a negative relationship between medical mistrust and physician trust. Physician trust mediates the effect of medical mistrust on health-care system distrust. In other words, it was determined that the mediating effect of physician trust was significant.* **Conclusion:** *Addition of physician trust to medical mistrust decreases the negative effects of health-care system distrust. Medical mistrust must be addressed at multiple levels of society, including government, policy, and health-care systems.*

Keywords: *Trust. Mistrust. Distrust. Physician. Health-care system.*

Resumen

Objetivo: *Este estudio se llevó a cabo para determinar el papel mediador de la confianza del médico en la relación entre la desconfianza médica y la desconfianza en el sistema de salud.* **Materiales y Métodos:** *La "Escala de desconfianza en los sistemas de atención médica", que consta de 10 preguntas, la "Escala de desconfianza médica", que consta de 17 preguntas, la "Escala de confianza del médico", que consta de 11 preguntas. El análisis estadístico se realizó mediante el programa SPSS 26.0.* **Resultados:** *La desconfianza en el sistema de salud se correlacionó positivamente con la desconfianza médica y negativamente con la confianza en los médicos. Hubo una relación negativa entre la desconfianza médica y la confianza en el médico. La confianza del médico media el efecto de la desconfianza médica en la desconfianza de los sistemas de atención médica. En otras palabras, se determinó que el efecto mediador de la confianza en el médico fue significativo.* **Conclusión:** *La adición de la confianza del médico a la desconfianza médica disminuye los efectos negativos de la desconfianza en el sistema de atención médica. La desconfianza médica debe abordarse en múltiples niveles de la sociedad, incluido el gobierno, las políticas y los sistemas de atención médica.*

Palabras clave: *Confianza. Desconfianza. Médico. Sistema de salud.*

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Introduction

Trust, mistrust, and distrust reflect people's ability to utilize resources and make the best decisions for their health care and well-being[1]. Trust is a defining concept in any relationship but is especially central to the patient–physician relationship. The crucial role of trust in medical relationships has long been adopted[2,3]. However, medical trust has not been systematically measured and analyzed until recently. Trust has been shown to influence a variety of attitudes and behaviors including patient's willingness to seek care, adhere to treatment, remain with a physician, and recommend physicians to others[4]. Trust plays a critical role in the health-care system where entire arrangements are largely relational[5]. Physician trust is shaped by various factors including the professional caring relationship. Physician trust depends on professional experience, professionalism, competence, availability, and credibility[6].

In recent years, there has been an increased awareness of mistrust that people exhibit toward medical advances, medical professions, and medical approaches[7]. Medical mistrust is an important barrier to a strong patient–physician relationship. Patient mistrust in health-care clinicians and health-care system distrust influence patient behaviors and health outcomes[8,9]. Negative health consequences of medical mistrust include lower utilization of health-care systems and poorer management of health conditions such as diabetes mellitus, cancers, and HIV[10-13]. Medical mistrust is consequently the tendency to distrust medical institutions, including medical personnel and clinicians.

Recently, a growing body of evidence suggests that health-care-related distrust may avoid patients from seeking appropriate medical care, adherence to medical recommendations, and maintaining continuity of care[14]. Patients with high levels of health-care system distrust are more likely to avoid health care, less likely to maintain continuity of care, and more likely to need monitoring and verifying their health-care decisions[15].

Physician trust is central to medical mistrust and health-care system distrust. The best example of physicians' mediating role has been seen during the last outbreak. Physician trust has played a major mediating role during COVID-19 pandemic by promoting people to get vaccinated, reducing medical mistrust, and health-care system distrust. There is no study in the literature investigating the mediating role of physician trust in the context of medical mistrust and health-care system distrust. Therefore, the objective of this study was to investigate the mediating role of physician trust in the relationship between medical mistrust and health-care system distrust.

Materials and methods

The survey method was preferred in this study. "Demographic Characteristics", "Health Care Systems Distrust Scale", "Medical Mistrust Scale", and "Physician Trust Scale" were applied face to face to the individuals over the age of 18 who received health services from any health institution in 2022 in Turkey and accepted to participate in our study. The study protocol was approved by the Dicle University Social and Human Sciences Ethics Committee with the 29/08/2022 dated and 343937 numbered decision.

The "Health Care Systems Distrust Scale" was developed by Rose et al. in 2004, and the scale was adapted into Turkish by Yeşildal et al.[16,17]. The scale consists of 10 statements. The statements in the scale were structured as a 5-point Likert scale, ranging from "1: strongly disagree to 5: strongly agree". As the scores obtained from the scale approach 5, it shows that health systems distrust increases and distrust decreases as it decreases toward 1. As a result of the reliability analysis of the scale, Cronbach's alpha coefficient was determined as 0.79[17]. In our study, Cronbach's alpha coefficient was determined as 0.82.

There are a total of 17 statements in the "Medical Mistrust Scale" adapted into Turkish by Şengül and Bulut[18]. For these statements, the participants were allowed to answer between "Strongly Disagree (1), Disagree (2), Agree (3), and Strongly Agree (4)". As a result of the reliability analysis of the scale, Cronbach's alpha coefficient was determined as 0.67[18]. In our study, Cronbach's alpha coefficient was determined as 0.87.

There are a total of 11 statements in the "Physician Trust Scale" developed by Şengül and Bulut[18]. For these statements, the participants were allowed to answer between Strongly Disagree (1), Disagree (2), Undecided (3), Agree (4), and Strongly Agree (5). 1st and 5th statements in the scale are coded in reverse. As a result of the reliability analysis of the scale, Cronbach's alpha coefficient was determined as 0.87[18]. In our study, Cronbach's alpha coefficient was determined as 0.86.

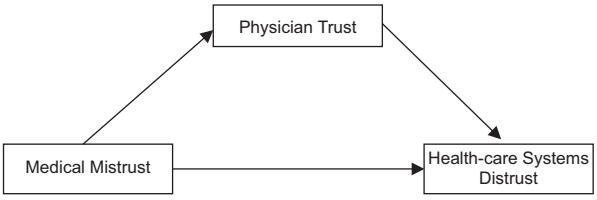

Figure 1. *Research model.*

Exploratory factor analysis was first applied for scale construct validity. The relationship between the variables (medical mistrust, health-care systems distrust, and physician trust) was examined by calculating the correlation coefficient of the Pearson product of moments. The reliability coefficient of the scale was determined by the Cronbach's alpha value. The normality distribution was examined by calculating the coefficient of the skewness and kurtosis values. Finally, the mediation test was applied with SPSS Process Macro.

In this study, the medical mistrust was considered as independent variable, the health-care systems distrust as dependent variable, and the physician trust as mediating variable. The model created in this context is presented in figure 1.

Hypotheses of the study:

- H1: Medical mistrust positively affects health-care systems distrust
- H2: Medical mistrust negatively affects physician trust
- H3: Health-care systems distrust negatively affects physician trust
- H4: There is a significant relationship between medical mistrust and health-care system distrust
- H5: Physician trust has a mediating role in the relationship between medical mistrust and health-care system distrust

Results

In this study, which included 808 participants, the mean age was 34.96 years (standard deviation was 10,36). It is seen that 62.4% of the participants are male and 37.6% are female. 63.1% of them are married and 36.9% are single. 83.9% of them had no chronic disease, and 51.2% had no family member with chronic disease. Finally, 79.7% of them were not using a drug regularly (Table 1).

In the study, the kurtosis and skewness coefficients were examined to determine the conformity of the scale scores to the normal distribution. It is considered sufficient for normal distribution that the kurtosis and skewness values obtained from the scales are between +3 and −3[19-22]. It is seen that the kurtosis and skewness coefficients of each score are between −3 and +3 (Table 2). According to this result, it was concluded that the scores showed a normal distribution. Parametric test techniques were used in the study due to the normal distribution of scores.

Correlation analysis was applied to determine the relationship between medical mistrust, health-care system distrust, and physician trust. The health-care system distrust and the medical mistrust were found to be positively correlated ($r = 0.761$, $p < 0.01$). The health-care system distrust and physician trust were found to be negatively correlated ($r = -0.637$, $p < 0.01$). The medical mistrust and the physician trust were found to be negatively correlated ($r = -0.738$, $p < 0.01$) (Table 3).

Table 1. Demographic data

Variables	Mean	SD
Age	34,96	10,36
	n	**%**
Gender		
Male	504	62.4
Female	304	37.6
Marital status		
Single	298	36.9
Married	510	63.1
Chronic disease		
Yes	130	16.1
No	678	83.9
Chronic disease in the family		
Yes	394	48.8
No	414	51.2
Regular drug usage		
Yes	164	20.3
No	644	79.7

Table 2. Kurtosis and skewness values

Variables	Skewness	Kurtosis
Health-care system distrust	−0.057	−0.008
Physician trust	−0.494	0.154
Medical mistrust	0.099	0.167

Table 3. Relationships between variables included in the study

	Mean	SD	Health-care system distrust	Physician trust	Medical mistrust
Health-care system distrust	3.04	0.66	-		
Physician trust	3.05	0.50	0.761*	-	
Medical mistrust	3.16	0.63	–0.637*	–0.738*	-

*Correlation is significant at the 0.01 level (two-tailed).

Table 4. The mediating role of physician trust in the relationship between medical mistrust and health-care system distrust

Variables	Bootstrap estimations		95% confidence ınterval		r^2	F
	B	SE	LLCI	ULCI		
MM > HCSD	1.007	0.030	0.948	1.067	0.578	1105.6294*
MM > PT	–0.935	0.030	–0.994	–0.876	0.544	962.2654*
MM > HCSD	0.845	0.044	0.759	0.932	0.591	581.3487*
PT > HCSD	–0.173	0.035	0.242	–0.105		
Indirect effect PT	0.162	0.038	0.089	0.236		
Completely standardized effect PT	1.007	0.030	0.948	1.067		

*$p < 0.05$.
MM: medical mistrust; HCSD: health-care system distrust; PT: physician trust.

Process analysis was applied to determine the mediating role of physician trust in the relationship between medical mistrust and health-care system distrust. Indirect effects were examined in the process analysis conducted to determine the mediating role of the physician trust in the relationship between the medical mistrust and the health-care system distrust. It is seen that medical mistrust has a statistically significant effect on health-care system distrust ($\beta = 1.007$, $p < 0.05$) (Table 4).

Medical mistrust has a statistically significant effect on physician trust ($\beta = -0.935$, $p < 0.05$). According to the model in which the independent, dependent, and mediation variables are together, the coefficient of medical mistrust decreased from 1.007 to 0.845 when the mediating variable was added to the model. Accordingly, the impact of medical mistrust on health system care distrust decreased (Table 4).

In the modern approach, it is decided whether there is a mediating effect or an indirect effect by looking at the values in the 95% confidence interval obtained as a result of the bootstrap analysis. Accordingly, if the lower and upper confidence interval values corresponding to the indirect effect value do not include the zero value, the indirect effect is considered significant and it is understood that the mediation effect occurs[23].

According to these results, physician trust mediates the effect of medical mistrust on health-care system distrust. In other words, it was determined that the mediating effect of physician trust was significant.

Discussion

In this study, the health-care system distrust and medical mistrust were found to be positively correlated. The health-care system distrust and the physician trust were found to be negatively correlated. In addition, the medical mistrust and the physician trust were found to be negatively correlated. The increase in medical mistrust decreased physical trust. Physician trust mediates the effect of medical mistrust on health-care system distrust. The mediating effect of physician trust was significant. The addition of physician trust to medical mistrust reduced the effect of health-care system distrust. In a study by Cavellos et al., medical mistrust and perceived discrimination significantly contributed to lower satisfaction with health-care system among young adult Latinos living in a rural region[24]. Similarly, in our study, health-care distrust increased as medical mistrust increased.

Some researchers demonstrated the beneficial effects of physician trust on specific health behaviors and outcomes. Physician trust increased the probability of patient satisfaction, treatment adherence, and improved health outcomes, while it decreased the likelihood of leaving physician's practice or withdrawing from a health plan, suggesting the positive and mediating effect of physician trust on the health-care system. In our study, adding physician trust on medical mistrust decreased the effect of health-care system distrust.

Health-care system distrust is a form of institutional trust related to the institutions of health-care systems including hospitals, insurers, pharmaceutical companies,

etc. In contrast, physician trust is a form of interpersonal trust specific to a physician[25]. Rose et al. investigated physician trust and health-care system distrust among patients receiving adjuvant therapy and found significant correlation between health-care system distrust, physician trust, and treatment discordance[16]. However, in this study, the relationship between health-care system distrust and treatment discordance was not mediated by physician trust. The authors attributed these findings to the fact that addressing health-care system distrust may be an important and distinct effort from strategies focused on the lack of physician trust. In a study by Sengul et al., medical mistrust decreased as trust in the physician increased as was the case in our study. In the same study, it was found that dissatisfaction with the health service increases medical mistrust, while also reducing trust in the physician[18]. Whereas, in our study, trust in the physician decreased both medical mistrust and dissatisfaction with the health service.

In a study by Zhang et al. conducted during COVID-19 period, medical mistrust has played a mediating role in vaccine hesitancy. There was an indirect relationship between mistrust and confidence, complacency, and knowledge of vaccines[26]. Similarly, in the present study, there was a significant positive correlation between medical mistrust and health-care system distrust.

In a study by Adams et al., it was reported that higher scores on medical mistrust scale were associated with lower incidence of colorectal cancer screening[27]. In a study by Griffith et al., it was stated that certain race groups including African American, Latins, and other marginalized groups as well as members of lesbian, gay, bisexual, transgender, and queer community have a long history of receiving inferior quality of care even when they have a comparable level and type of insurance and access to care with those of more privileged groups, which increased medical mistrust and health-care system distrust[1]. In the present study, however, we did not group the participants according to various characteristics.

Conclusions

Medical mistrust is positively correlated with health-care system distrust and negatively correlated with physician trust. Physician trust plays a mediating role in the relationship between medical mistrust and health-care system distrust. The addition of the physician trust on medical mistrust decreases the negative effects of the health-care system distrust. Medical mistrust must be addressed at multiple levels of society, including government, policy, and health-care systems.

The number of our sample is relatively large and this is the first study in the literature investigating the mediating role of the physician trust in the relationship between the medical distrust and the health-care system distrust using process analysis, as the strengths. Further studies with wider populations are needed to better enlighten the relationship between trust, mistrust, and distrust in the field of medicine. Additional questions such as COVID-19 and HIV could be included.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

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

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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ORIGINAL ARTICLE

Can platelet activation markers predict preeclampsia and/or its severity?

¿Pueden los marcadores de activación plaquetaria predecir la preeclampsia y/o su gravedad?

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Abstract

Objective: *This study aimed to evaluate the value of platelet activation markers in predicting preeclampsia and its severity. Preeclampsia is a serious pregnancy complication that affects 3-5% of pregnancies and can lead to significant morbidity and mortality for both the mother and the fetus.* **Methods:** *The study included 99 patients diagnosed with preeclampsia and 60 healthy pregnant women as a control group. Platelet activation markers such as mean platelet volume (MPV), platelet distribution width (PDW), platelet count, and plateletcrit were evaluated along with other clinical parameters.* **Results***: The results of the study showed that platelet activation markers, particularly PDW and MPV, are valuable in the diagnosis and follow-up of preeclampsia. However, they are not sufficient to predict the severity of the disease.* **Conclusion:** *The study suggests that platelet activation markers could aid in predicting, diagnosing, and managing preeclampsia. However, further research is needed to determine the role of these markers in predicting the severity of the disease. The findings of this study could contribute to the development of more effective strategies for the prevention and management of preeclampsia, which could ultimately improve maternal and fetal outcomes.*

Keywords: *Mean platelet volume. Plateletcrit. Platelet activation markers. Preeclampsia.*

Resumen

Objetivo: *El estudio tuvo como objetivo determinar el valor de los marcadores de activación plaquetaria en la predicción de la preeclampsia y su gravedad.* **Método:** *Se incluyeron 99 pacientes diagnosticadas con preeclampsia, incluyendo 36 casos graves, y un grupo control de 60 mujeres embarazadas sanas. Se evaluaron diversas variables, como el volumen plaquetario medio, el recuento de plaquetas, el hematocrito plaquetario y la amplitud de distribución plaquetaria.* **Resultados:** *Los resultados mostraron que el volumen plaquetario medio y la amplitud de distribución plaquetaria son parámetros valiosos en el diagnóstico y seguimiento de la preeclampsia, aunque no son suficientes para predecir su gravedad. El análisis estadístico reveló que la edad, el volumen plaquetario medio, la amplitud de distribución plaquetaria, la semana de gestación y los puntajes de Apgar al primer y quinto minuto fueron significativamente diferentes en el grupo de preeclampsia en comparación con el grupo control.* **Conclusiones:** *En conclusión, estos resultados sugieren que los marcadores de activación plaquetaria pueden ser útiles para el diagnóstico y seguimiento de la preeclampsia, y que el volumen plaquetario medio y la amplitud de distribución plaquetaria, por ser parámetros económicos y accesibles, podrían ayudar a predecir, diagnosticar y manejar esta complicación durante el embarazo.*

Palabras clave: *Volumen plaquetario medio. Critocitos plaquetarios. Marcadores de activación plaquetaria. Preeclampsia.*

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Introduction

Preeclampsia, the etiology and pathogenesis of which have not been fully elucidated, is a serious complication that is seen in 3-5% of all pregnancies and threatens the life of both the fetus and the mother[1]. One view locates its pathogenesis in placental ischemia due to abnormalities in the location of the placenta, remodeling of the spiral artery, and invasion of the extravillous trophoblast. As a result of this ischemia, vasoactive substances are released into the maternal circulation, which may cause maternal endothelial activation and endothelial dysfunction[2].

Microangiopathy in preeclampsia affects all cells circulating in the vessel, such as leukocytes, neutrophils, lymphocytes, and platelets. The hematological abnormality observed in preeclampsia depends on platelet consumption and the activation of the coagulation system. An increase in platelet function has also been reported in pregnant women with preeclampsia[3]. A damaged endothelium due to defective placental trophoblastic invasion leads to the activation of platelets and inflammation[4].

The mean platelet volume (MPV) increases when platelets are activated. Large platelets are stickier than small ones and likelier to aggregate. Platelet activation markers include MPV; platelet distribution width (PDW), which corresponds to the size distribution of platelets; plateletcrit (PCT), which corresponds to the volume of platelets in 100 mL of total blood; and the platelet large cell ratio, which reflects the percentage of platelets > 12 fL indirectly by calculating various indices, including PDW, which measures platelet size distribution. MPV, PCT, and PDW are potential and easily measurable *in vivo* markers of platelet activation[5].

Platelet activation markers may be more sensitive than platelet counts, which may change during normal pregnancy and as a result of preeclampsia. Physiologically, MPV decreases from the 20th week of pregnancy to the 31st week and increases after the 38th week. Increased platelet activity may contribute to the formation of microthrombi in the placenta and exacerbate the vascular dysfunction seen in preeclampsia. Therefore, platelet activation markers may have the potential to aid in the early prediction of preeclampsia and prognosis[6].

Platelet activation markers are routine parameters in complete blood counts. Measurement of platelet activation markers is an easily accessible, reproducible, simple, and inexpensive test. In this study, we investigated the differences between platelet activation markers in healthy pregnant women and pregnant women with preeclampsia and these markers' prognostic effects on the group with preeclampsia.

Methods

This was a retrospective, descriptive, and cross-sectional study. A total of 99 patients diagnosed with preeclampsia were included in the study, 36 of whom were diagnosed with severe preeclampsia. The control group consisted of 60 patients. Patients diagnosed with preeclampsia between May 2020 and November 2022 were retrospectively included in the study. Relevant demographic data, such as maternal age, parity, complete blood count results, and gestational age at birth, were recorded from hospital records and hospital automation systems for analysis.

We compared platelet counts and platelet indices first MPV, and then PDW and PCT values in patients diagnosed with preeclampsia and the control group. We then investigated the differences in platelet activation markers between patients with severe and non-severe preeclampsia.

Venous blood samples of the patients were collected in tubes containing ethylenediaminetetraacetic acid (EDTA) in the first trimester of pregnancy (12-14 weeks) during routine controls, and complete blood counts of all patients included in the study were performed in our hospital laboratory using the same automatic analyzer. The blood sample was taken and studied at the first moment of diagnosis. Blood samples of 2 mL were collected in vacuum tubes (purple cap) containing 2.0 mg/mL EDTA and stored at 37°C for platelet analysis. The samples were measured using an LH 755 automated quantitative hematology analyzer (BECKMAN COULTER Inc., USA). All tubes were mixed by being inverted 5-10 times immediately after blood collection and analyzed within 1 h.

Urine protein levels were measured with a measuring stick at the time of admission. Complete urinalyses were studied using a FUS-200/H-800 Fully Automatic Urine Analysis System. Proteinuria was measured turbidimetrically in spot and 24-h urine samples. Neonatal outcomes at the 1st and 5th min of life were recorded. Apgar scores and delivery patterns were noted.

The diagnoses of preeclampsia and its severity were made according to the criteria in The American College of Obstetricians and Gynecologists Practice Bulletin No. 222[7].

Preeclampsia was diagnosed if a patient previously had normal blood pressure, a systolic blood pressure of ≥ 140 mmHg, and/or a diastolic blood pressure of 90 mmHg at least 4 h apart after the 20th gestational week in addition to one of the following criteria: proteinuria (with a dipstick reading ≥ 2+ and protein/creatinine ratio ≥ 0.3 or ≥ 0.3 g in a 24-h urine sample), thrombocytopenia (with a platelet count ≤ 100,000/mL), a renal failure serum creatinine concentration > 1.1 mg/dL (97.2 μmol/L), a blood concentration of liver transaminases at twice the normal concentration, pulmonary edema, visual symptoms (blurred vision, flashing lights or sparks, or scotoma), or the new onset of a persistent headache unexplained by alternative diagnoses and unresponsive to routine doses of analgesics.

A patient was diagnosed with severe preeclampsia if they had a systolic blood pressure ≥ 160 mmHg and/or a diastolic blood pressure ≥ 110 mmHg in two measurements at rest at least 4 h apart, symptoms of central nervous system dysfunction (new-onset cerebral or visual impairment), hepatic abnormality (unresponsive to medication), severe and persistent right upper quadrant or epigastric pain, a serum transaminase concentration ≥ 2 times the upper limit of the normal range or both, thrombocytopenia (< 100,000 platelets/microL), a renal abnormality (serum creatinine > 1.1 mg/dL), or pulmonary edema. If there was more than one, it was diagnosed as severe preeclampsia.

All of the control group members were healthy women with single pregnancies, no history of systemic disease, and no fetal or chromosomal abnormalities. The blood pressure of the women in this group was below 140/90 mmHg, and none had proteinuria. They all had healthy live births at term. This control group was randomly selected from patients who were followed up and treated in our hospital, were in their third trimesters of pregnancy, and did not have preeclampsia or systemic disease.

To avoid any possible interaction with the incidence of preeclampsia or fetal growth restriction (FGR) and platelet changes caused by the use of drugs that may affect platelet activity, such as aspirin, we excluded patients using these drugs. Patients with previous kidney disease, insulin-dependent diabetes, asthma requiring steroid therapy, chronic hepatitis (with or without liver dysfunction), chronic kidney disease, a history of severe trauma, a history of anticoagulant drug use, a history of oral contraceptive use, a history of smoking, immune thrombocytopenic purpura, hemolysis, elevated liver enzymes, and low platelets syndrome, gestational thrombocytopenia, or any hematological disease were excluded. The exclusion criteria were strictly maintained, and we attempted to increase the working power.

The study was carried out in accordance with the ethical regulations and permission of the hospital's Ethics Committee (2022-42) and conducted in accordance with the Declaration of Helsinki.

The Number Cruncher Statistical System 2007 (Kaysville, Utah, USA) program was used for the statistical analysis. When evaluating the study data, the descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, and maximum) and distribution of the data were determined using the Shapiro–Wilk test. The Mann–Whitney U test was used to compare two groups of quantitative data. Chi-square analysis was used to determine the relationships between the qualitative data. Receiver operating characteristic (ROC) analysis was used to determine the predictive value of the variables. Spearman's correlation test was used to determine the relationships between the quantitative data. Multiple logistic regression analysis was used to determine the factors affecting the dependent variable. Significance was evaluated at the $p < 0.01$ and $p < 0.05$ levels.

Results

A total of 99 pregnant women diagnosed with preeclampsia were included in the study. Of these, 63.6% (n = 63) were not severe preeclampsia cases, while 36.4% (n = 36) were severe. In the preeclampsia group, 54.5% (n = 54) of the patients received magnesium treatment, while 45.5% (n = 45) did not. The rates of protein in the complete urinalyses of the preeclamptic pregnant women were as follows: 24.2% (n = 24) were negative, 29.3% (n = 29) were 1+, 7.1% (n = 7) were 2+, and 39.4% (n = 39) were 3+. Of the patients, 51.5% (n = 51) had primary cesarean sections, 28.3% (n = 28) had previous cesarean sections, 11.1% (n = 11) had induced labor, and 9.1% (n = 9) gave birth spontaneously. While 45.5% (n = 45) of the preeclamptic patients' babies were female, 54.5% (n = 54) were male, and 45.5% (n = 45) had FGR, while 54.5% (n = 54) did not.

The age, MPV, platelet count, PCT, PDW, red cell distribution width coefficient of variation (RDW-CV), red cell distribution width standard deviation (RDW-SD), hemoglobin, week of birth, gravida, parity, abortion number, and Apgar score 1st- and 5th-min values

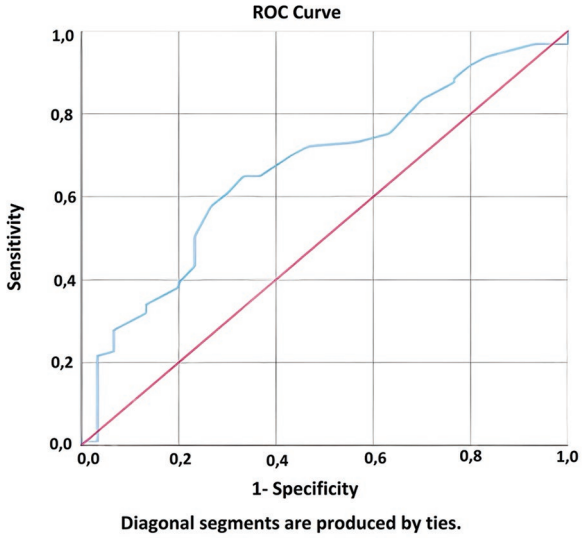

Figure 1. *Receiver operating characteristic curve of mean platelet volume parameter.*

of the patients and control group are given in table 1. The age, MPV, PDW, week of birth, and APGAR score 1st- and 5th-min values were found to be statistically significant in the preeclampsia group compared to the control group ($p = 0.001$; $p < 0.05$). PLT, PCT, RDW-CV, RDW-SD, hemoglobin, gravida, parity, and number of abortions did not show any statistically significant difference ($p > 0.05$).

As shown in table 2, when the patients with preeclampsia were divided into severe and non-severe groups, there were no statistically significant differences between MPV, PLT, PCT, PDW, RDW-CV, RDW SD, hemoglobin, or Apgar score 1st- and 5th-min values and the week of birth ($p > 0.05$). Moreover, there was no statistically significant relationship between the severity of preeclampsia and FGR ($p > 0.05$).

In this study, 64.8% (n = 35) of the patient group and 35.2% (n = 19) of the control group had female fetuses. There was no statistically significant relationship between the severity of preeclampsia and fetal gender ($p > 0.05$).

Upon applying Spearman's correlation analysis, no correlation was found between MPV, PLT, PCT, PDW, RDW-CV, RDW SD, hemoglobin, or APGAR 1st- and 5th-min scores and the week of birth ($p > 0.05$).

A statistically significant correlation in complete urinalysis protein was found between the groups ($p = 0.001$; $p < 0.01$). In those with complete urinalysis protein 3+, the patients had higher values than the control group by a statistically significant amount ($p = 0.001$; $p < 0.01$).

Table 1. Comparison of measurements by group

Parameters	n	Mean ± SD	Min-Max (Median)	p-value
Age (year)				
Preeclampsia	99	30.99 ± 6.06	18-45 (31)	0.001*
Control	60	26.77 ± 5.15	20-37 (26)	
MPV (fL)				
Preeclampsia	99	11.3 ± 1.1	9-14 (11.2)	0.006*
Control	60	10.71 ± 0.94	9.6-13.7 (10.5)	
PLT (10^3/μL)				
Preeclampsia	99	256.13 ± 70.06	139-501 (245)	0.640
Control	60	247.43 ± 63.93	138-410 (234.5)	
PCT (%)				
Preeclampsia	99	0.29 ± 0.07	0.16-0.53 (0.28)	0.124
Control	60	0.26 ± 0.06	0.16-0.43 (0.26)	
PDW (%)				
Preeclampsia	99	13.91 ± 2.73	9.1-21.9 (13.6)	0.048*
Control	60	12.94 ± 2.41	10-19.4 (11.95)	
RDW-CV (%)				
Preeclampsia	99	14.22 ± 1.88	11.9-22.7 (13.7)	0.759
Control	60	14.77 ± 2.92	12.1-26 (13.9)	
RDW-SD (fL)				
Preeclampsia	99	43.16 ± 4.85	36.2-63.7 (42.5)	0.113
Control	60	44.73 ± 5.94	37.6-67.5 (44.3)	
Hemoglobin (g/dL)				
Preeclampsia	99	12.01 ± 1.44	7.1-15.4 (12)	0.290
Control	60	11.63 ± 1.76	6.9-14.7 (11.85)	
Birth week (day)				
Preeclampsia	99	188.57 ± 89.03	0-275 (222)	0.001*
Control	60	275.23 ± 9.79	254-294 (274.5)	
Gravida (number)				
Preeclampsia	99	2.35 ± 1.74	1-9 (2)	0.155
Control	60	2.67 ± 1.58	1-7 (2)	
Parity (number)				
Preeclampsia	99	0.89 ± 1.13	0-5 (0)	0.055
Control	60	1.33 ± 1.27	0-4 (1)	
Abortion (number)				
Preeclampsia	99	0.48 ± 1.06	0-6 (0)	0.646
Control	60	0.33 ± 0.71	0-3 (0)	
Apgar score 1st min				
Preeclampsia	99	5.99 ± 1.89	0-9 (6)	0.001*
Control	60	7.93 ± 0.87	5-9 (8)	
Apgar score 5th min				
Preeclampsia	99	7.78 ± 1.49	0-10 (8)	0.001*
Control	60	9.17 ± 0.59	8-10 (9)	

*Mann Whitney U Test $p < 0.05$.
fL: femtoliter; MPV: mean platelet volume; PLT: platelet; PCT: plateletcrit, PDW: platelet distribution width; RDW-CV: red cell distribution width coefficient of variation; RDW-SD: red cell distribution width standard deviation.

Cutoff and AUC value of ROC analysis

When the cutoff point of the MPV value was taken as 10.85, the sensitivity was 98.7%. The specificity

Table 2. Comparison of measurements by preeclampsia severity

Parameter	n	Mean ± SD	Min-Max (Median)	p-value
MPV (fL)				
Non-severe	63	11.33 ± 1.09	9.4-13.6 (11.3)	0.922
Severe	36	11.32 ± 1.07	9-14 (11.25)	
PLT (10^3/μL)				
Non-severe	63	256.48 ± 67.15	139-383 (245)	0.904
Severe	36	257.81 ± 71.91	164-501 (252)	
PCT (%)				
Non-severe	63	0.29 ± 0.07	0.16-0.45 (0.28)	0.968
Severe	36	0.29 ± 0.07	0.2-0.53 (0.28)	
PDW (%)				
Non-severe	63	13.87 ± 2.6	9.9-21.9 (13.8)	0.644
Severe	36	14.14 ± 2.83	9.1-21.5 (13.9)	
RDW-CV (%)				
Non-severe	63	14.56 ± 2.1	12.2-22.7 (14)	0.134
Severe	36	13.77 ± 1.1	11.9-17 (13.7)	
RDW-SD (fL)				
Non-severe	63	43.83 ± 5.35	36.8-63.7 (43.2)	0.174
Severe	36	42.15 ± 3.39	36.2-50 (41.75)	
Hemoglobin (g/dL)				
Non-severe	63	11.74 ± 1.45	7.1-14.1 (11.9)	0.059
Severe	36	12.39 ± 1.12	10.6-15.2 (12.4)	
Apgar score 1st min				
Non-severe	63	6.06 ± 1.51	1-9 (6)	0.727
Severe	36	5.83 ± 1.58	1-8 (6)	
Apagr score 5th min				
Non-severe	63	7.92 ± 1.2	3-10 (8)	0.342
Severe	36	7.83 ± 0.91	5-9 (8)	
Birth week				
Non-severe	63	33.07 ± 2.95	25.43-39.29 (33)	0.079
Severe	36	32.08 ± 2.13	25-35.57 (32.5)	

FL: femtoliter; MPV: mean platelet volume; PLT: platelet, PCT: plateletcrit, PDW: platelet distribution width; RDW-CV: red cell distribution width coefficient of variation; RDW-SD: red cell distribution width standard deviation.

was determined to be 98.5%, and a reliable cutoff point was determined (Fig. 1)

Table 3 shows, when multiple logistic regression analysis was performed to determine the effect of the independent variables on disease status, it was found to be statistically significant (X2 = 43,738; $p < 0.001$). There was a positive and weakly significant relationship between the independent variables and disease status ($R = 0.29$, $p < 0.001$). The independent variables in the model explain 8.5% of the total variance in disease status ($p < 0.01$).

When the regression coefficients were examined, the complete urinalysis protein-negative ($\beta = -0.085$, $p < 0.001$) variable was a negative effect on disease status, while age ($\beta = 1.177$, $p < 0.001$) and MPV ($\beta = 2.021$, $p < 0.001$) seemed to have positive and significant effects.

Discussion

The results of our study are similar to those in the literature. We found platelet activation markers to be valuable parameters in the diagnosis and follow-up of preeclampsia but insufficient for predicting the intake of preeclampsia. After the continuous consumption of platelets in the peripheral blood in preeclamptic pregnant women, a rapid platelet turnover occurs as a result of the continuous production in the bone. Järemo and colleagues explained the increase in platelet volume by the presence of vessels rather than platelet changes and attributed it to those that dispersed to the surrounding platelet densities[8]. Highly dispersed platelets have high volumes, which limits the assumption that platelet lines and subsequent granule release disrupt platelet distribution[9].

After the release of vasoactive amines, the prolongation and swelling of platelets occur, and new platelets are released into the blood. This leads to an increase in MPV and PDW. A single platelet count may be misleading in early prognosis. Therefore, platelet activation parameters should be used. Reddy and Rajendra Prasad argued that the spread of preeclampsia aggressively occurs on 10.95 fL cut-off travelers in the MPV they bring[10,11]. In our study, the cut-off point for MPV surveillance between the patient and control groups was 10.85, leading to a protective value of 98.7%; ownership was determined as 98.5%, the reliable cutoff point. Our study is consistent with the literature and suggests that MPV is valuable in the diagnosis of preeclampsia in pregnancy.

Yang et al. stated that the PDW value in women with preeclampsia is a valid measurement tool for predicting severe preeclampsia[12]. In our study, the PDW values of the patient group were also higher than those of the control group and were statistically significant.

PCT is calculated by multiplying the platelet count by the MPV and dividing the result by 10,000. Thalor et al. reported in their study that PCT, a marker of platelet activation, showed a slight decrease in patients with preeclampsia, but not at a statistically significant level[13]. In our study, there was no statistically significant relationship between PCT values and preeclampsia. We believe that this may be because the platelet count tends to approach normal in preeclampsia patients, as stated in Thalor et al., and because PCT is calculated using platelet counts[13].

Çintesun et al. looked at the difference between PCT values in preeclamptic pregnant women with different degrees of preeclampsia and could not obtain a significant result[14]. In our study, we did not find a statistically significant difference between PCT values in the severe and

Table 3. Logistic regression analysis findings for ınterpretation of disease status with ındependent variables

Model	Variables	Univariable					Multivariable				
		B	SD	Wald	Exp (B)	p	B	SD	Wald	Exp (B)	p
1	Age (year)	0.129	0.040	10.148	1.137	0.001*	0.163	0.052	9.659	1.177	0.001*
	MPV (fL)	0.568	2.454	6.347	1.765	0.001*	0.703	0.275	6.528	2.021	0.001*
	Complete Urinalysis Protein-Negative	−2.264	0.478	22.400	0.104	0.001*	−2.462	0.552	19.867	−0.085	0.001*

*$p < 0.05$.

mild preeclampsia groups. Although these differences are well known and defined, one factor that may be relevant here is the activation of the bone marrow with an unknown stimulus due to the individuality of the inflammatory and coagulant responses of each pregnant woman.

In their meta-analysis, Bellos et al. suggested that MPV should be evaluated together with conventional markers of preeclampsia and included in combined models that would provide optimum efficiency in the prediction of the disease[15,16]. Based on our results, we think that platelet activation markers, especially MPV and PDW, are valuable. However, we believe that it is necessary to be aware that they are systemic markers.

The MPV measurement method should be standardized to eliminate inconsistent results. It is known that MPV increases with time when the sample is exposed to EDTA[9]. We tried to achieve standardization by sending our samples to the laboratory to be examined as soon as possible. In addition, we made sure to take all measurements on the same device and tried to increase the working power by eliminating possible differences.

The relationship between RDW and preeclampsia has been investigated in many studies. Yücel et al. found that the RDW was significantly higher in severely preeclamptic pregnant women compared to their control group. RDW indicates a change in erythrocyte volume called anisocytosis. High RDW levels are believed to reflect increased inflammation, but this mechanism has not been elucidated[17]. The RDW-CV is found by dividing the histogram width of erythrocytes in 1 SD by the MCV. The RDW-SD is the difference in volume between the largest and smallest erythrocytes at the level of 20% of the erythrocyte population in the erythrocyte histogram. RDW-SD and RDW-CV are parameters that can generally be used to evaluate RDW[18]. We did not find a statistically significant difference in RDW-SD, RDW-CV, or hemoglobin between preeclampsia patients and the control group. Likewise, when we divided the preeclampsia group into severe and non-severe cases, there was no statistical difference. Since the data on the patients' folate and iron levels were not routinely checked, we attributed the different levels to the activation of the patients' red blood cell series.

MPV is a measurement of the average size of platelets. Under conditions of increased platelet turnover, an increase in MPV produces larger and more reactive platelets, possibly affecting megakaryocyte ploidy. Because the MPV increase reflects increased platelet turnover, it precedes the clinical onset of disease symptoms. An identified increase in the MPV of these platelets in the pathogeneses of hypertensive disorders of pregnancy should be carefully monitored to aid in early diagnosis so that appropriate management can be enacted and a thrombotic event leading to maternal and neonatal morbidity or mortality can be prevented[19,20]. We administered magnesium treatment to 54.5% (n = 54) of the patients to avoid complications.

Several studies have investigated the relationship between preeclampsia and neonatal respiratuar distress syndrom in preterm infants, but definitive conclusions have not been reached. The mechanism underlying the association between preeclampsia and neonatal respiratory disorders is unclear. It has been suggested that preeclampsia causes a degenerative change in placental villi and a continuous spasm of maternal whole-body arterioles. In this case, it may cause long-term chronic hypoxia in the fetus, leading to neonatal respiratory disorders. As a second mechanism, it may cause pulmonary hypertension by causing neonatal pulmonary vasculature and systemic vascular dysfunction[21,22]. We found that Apgar scores were significantly lower at the 1st and 5th min in the preeclampsia group than in the control group. However, there was no statistically significant difference between the severe and non-severe groups. When we looked at the correlations of these Apgar scores with platelet activation markers, we could once again find no statistical significance. The increased risk of preeclampsia is caused by incomplete lung maturation due to preterm labor, which may also exacerbate the severity of the preeclampsia.

Limitations

Platelet indices have different normal ranges, as they are determined by different laboratory machines used for analysis. Therefore, the data need to be adjusted to allow for these differences in the normal ranges determined by different machines. Further multicenter studies with larger numbers of patients are required to resolve the contradictions in the literature and achieve definitive results.

Conclusion

Preeclampsia can lead to serious complications if not properly diagnosed. It is a multi-organ disease; therefore, it is difficult to establish severity markers for its development. However, the development of these markers may assist clinicians in determining the timing of delivery for women with preeclampsia. PDW and MPV, which are platelet activation markers that are economical and easily available, can be used in the prediction, early diagnosis, and management of the disease. It would be ideal to create functional systemic indices to predict the onset and severity of PE, which is a systemic disease.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

Ethical disclosures

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

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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ORIGINAL ARTICLE

Comparison of perioperative outcomes in obese and non-obese patients subjected to open lumbar spine surgery

Comparación de los resultados quirúrgicos en pacientes obesos y no obesos sometidos a cirugía de columna lumbar abierta

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Abstract

Objective: *Obesity is a global epidemic affecting developing countries. The relationship between obesity and perioperative outcomes during elective lumbar spine surgery remains controversial, especially in those without morbid disease.* **Materials and methods:** *We retrospectively revised the medical records of patients with lumbar spine degeneration subjected to elective surgery. The data retrieved included demographic and clinical characteristics, body mass index (BMI), obesity status (BMI ≥ 30), surgical interventions, estimated blood loss (EBL), operative time, length of stay (LOS), and postoperative complications. Perioperative outcomes were compared between Grade I-II obese and non-obese individuals.* **Results:** *We enrolled 53 patients, 18 with Grade I-II obesity. Their median age was 51, with no differences in gender, comorbidities, laboratory parameters, and surgical procedures received between groups. No clinically relevant differences were found between grade I-II obese and non-obese participants in EBL (300 mL vs. 250 mL, p = 0.069), operative time (3.2 h vs. 3.0 h, p = 0.037), and LOS (6 days vs. 5 days, p = 0.3). Furthermore, BMI was not associated with the incidence of significant bleeding and long stay but showed a modest correlation with operative time.* **Conclusion:** *Grade I-II obesity does not increase surgical complexity nor perioperative complications during open lumbar spine surgery.*

Keywords: *Obesity. Body mass index. Spine surgery. Lumbar decompression and fusion. Transforaminal lumbar interbody fusion.*

Resumen

Objetivo: *La obesidad es una epidemia mundial que afecta a países subdesarrollados. Su relación con los resultados de la cirugía de columna lumbar electiva sigue siendo controvertida, especialmente en obesos sin enfermedad mórbida.* **Métodos:** *Se revisaron los expedientes de pacientes con degeneración de la columna lumbar sometidos a cirugía. Los datos recuperados incluyeron características demográficas y clínicas, índice de masa corporal (IMC), estado de obesidad (IMC > 30), intervenciones quirúrgicas, sangrado estimado, tiempo operatorio, tiempo de estancia y complicaciones. Los resultados se compararon entre individuos obesos grado I-II y controles.* **Resultados:** *Se incluyeron 53 pacientes, 18 con obesidad de grado I-II. La edad media fue de 51 años, sin diferencias en el sexo, las comorbilidades, los parámetros de laboratorio y los procedimientos quirúrgicos recibidos entre grupos. No se encontraron diferencias relevantes entre los participantes obesos y los no obesos en sangrado (300 vs. 250 mL, p = 0.069), tiempo operatorio (3.2 vs. 3.0 horas, p = 0.037) y estancia (6 vs. 5 días, p = 0.3).*

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El IMC no se asoció con hemorragia y larga estancia, pero mostró una correlación modesta con el tiempo operatorio. **Conclusiones:** *La obesidad grado I-II no predispone a complicaciones durante la cirugía de columna lumbar.*

Palabras clave: *Obesidad. Índice de masa corporal. Cirugía de columna. Descompresión y fusión lumbar. Transforaminal lumbar interbody fusion.*

Introduction

Obesity is a global public health problem in many regions of the globe carrying a wide range of complications[1,2]. Among morbidities related to a higher body mass index (BMI), lower back pain, and lumbar spine degeneration are gaining attention due to their increasing prevalence among overweight persons[3]. Indeed, several risk factors for obesity also contribute to the origin of musculoskeletal abnormalities of the lumbar spine, including poor diet habits, scarce physical activity, and postural problems related to sedentarism. Notably, up to a third of individuals subjected to operative procedures for lumbar decompression are obese[4]. Hence, some of the interests of spine surgeons are focused on elucidating the effects of obesity on surgical outcomes after lumbar spine operations.

At present, the findings of several investigations are contradictory, with opposite results regarding the possible impact of obesity on perioperative outcomes during open and minimally-invasive lumbar spine surgery, including the surgical estimated blood loss (EBL), operative time, length of hospital stay length of stay (LOS), rates of complications, and functional status after a variable period of follow-up[4]. This is especially true among individuals without morbid disease since it is not completely known whether their surgical risk is similar to individuals with more severe obesity. In contrast, the literature clearly shows an increased propensity of patients with morbid obesity (BMI > 40 kg/m^2 or > 35 kg/m^2 with cardiovascular/metabolic comorbidities) to perioperative adverse outcomes, postoperative complications, and long-term morbidity after lumbar decompression and fusion[4,5]. Thus, minimally invasive procedures have been recently advocated for this population with commendable results.

Importantly, minimally invasive approaches for lumbar decompression and fusion are not widely available. Hence, identifying potential risk factors for adverse surgical results after open lumbar spine surgery is very important to anticipate complications and establish preventive actions during this approach. Therefore, additional studies addressing the relationship between obesity and surgical outcomes of open lumbar decompression and fusion are needed. Notably, the most significant increases in the incidence of obesity occur in low-income regions, where a rise in the number of persons with overweight and Grade I-II, followed by Grade III obesity has been registered[6]. However, little literature exists on lumbar spine surgery from developing countries, where open approaches to the degenerative lumbar spinal stenosis are still the standard operative management. Here, we compared the perioperative results of patients with Grade I-II obesity and non-obese individuals subjected to elective surgery for lumbar spine degeneration from Mexico, where more than two-thirds of the population are overweight[7]. Our results demonstrate that, in our population, obesity does not increase the surgical complexity of open lumbar spine surgery, since perioperative outcomes did not differ between obese and non-obese patients. However, our study does not provide concluding evidence about the impact of obesity on the effectiveness of lumbar decompression and fusion in the long-term.

Materials and methods

Study population

We conducted a cohort study in consecutive non-Caucasian Mexican patients with degenerative lumbar spinal stenosis subjected to elective surgery at the Neurosurgery Department of the Centro Especializado en Neurocirugía y Neurociencias México in Mexico City during the period between 2016 and 2021. Individuals older than 18 years with moderate-to-severe manifestations of lumbar spinal degeneration who failed conservative therapy with non-steroidal anti-inflammatory drugs (NSAID) and physical rehabilitation for at least 3 months were eligible for the study. Patients with toracolumbar tandem spinal stenosis, fractures, tumors, movement disorders, or any other non-degenerative etiology of lumbar spinal stenosis were ineligible. Furthermore, individuals with incomplete medical records or those unavailable to be followed were excluded from the following analyses. All patients provided written informed consent to

participate in the investigation according to the Declaration of Helsinki for Human Research. The study was conducted under the Mexican Constitution law NOM-012-SSA3-2012, which establishes the criteria for executing clinical investigations in humans.

Procedures

All patients were clinically assessed by a neurosurgeon and an orthopedist specialized in spine surgery, who determined the surgical plan based on clinical findings, physical examination, and magnetic resonance imaging of the spine. Furthermore, on enrollment, participants were screened by an anesthesiologist who ordered laboratory tests, estimated the pre-operative risk in terms of the American Society of Anesthesiologists (ASA) physical status classification system, and retrieved the clinical data. The decision for lumbar spine surgery was based on the persistence of a constellation of manifestations, including intractable lumbar radiculopathy, neurogenic claudication, intractable low back pain, cauda equina syndrome, severe lumbar spondylolisthesis with instability, and abnormal findings in the electromyography and evoked potentials of the lower limbs.

The same surgical team carried out surgical procedures under general anesthesia. The standard surgery for the lumbar spine was the open transforaminal lumbar interbody fusion (TLIF) with interbody fusion cages (ROI-T®, LDR Medical, ATX, USA) and bilateral pedicle screw fixation. In addition, posterior instrumentation, placement of interspinous spacers (InSWing™ Interspinous Spacer, Orthofix US LLC, USA), laminectomy, and/or hemilaminectomy were used alone or as complementary procedures according to pre-operative or perioperative findings. All patients received the same standard post-operative management based on analgesia with NSAIDs, steroids, antineuritics, selective serotonin reuptake inhibitors, benzodiazepines, and/or opioids, antibiotic prophylaxis, early mobilization after 24 h of surgery, and rehabilitation during hospitalization and for at least 3 months after discharge.

Data collection

Microsoft Excel (MS Excel 365) was used for data collection. On admission, the clinical and demographic characteristics of study participants were retrieved by direct interview, physical examination, and revision of their medical records. These data included age, gender, anthropometrics, comorbidities, presence of concomitant degenerative cervical spine stenosis, history of previous non-spinal surgeries, symptoms, pre-operative radiological findings, spinal segments radiologically involved, ASA category, and initial laboratory test results. Initial laboratory tests were defined as the first test results available (typically within 24 h of admission) and included white blood cell counts, glucose, kidney function, and lipid panel. During operations, a spine surgery fellow registered the specific surgical procedures performed on the patients, the operative time, and EBL. Furthermore, patients were closely monitored during convalescence, and data on in-hospital medications administered, time of hospitalization, and post-operative systemic and neurological complications were retrieved. After discharge, patients were radiologically followed for at least 6 months to evaluate the postoperative fusion, alignment, stability, and the incidence of pseudoarthrosis, hardware failure, interbody material migration, screw misplacement, or breech.

Statistical analyses

Descriptive statistics were used to characterize the study population clinically. Frequencies and proportions were calculated for categorical data. Medians and interquartile ranges were used for continuous variables since they did not show normal distribution in the Shapiro-Wilks test. Patients were grouped according to their obesity status, defined as a BMI $\geq$ 30 kg/m^2. Differences in categorical variables between groups were assessed by the Fisher's exact or Chi-square test. For comparisons of continuous variables, we used the Wilcoxon sum-rank test. Linear regression analyses using Spearman rank correlation coefficients were used to determine correlations between BMI, EBL, surgery time, and LOS after the operation. The study's primary outcomes were significant bleeding, prolonged surgery, and extended hospital stay after lumbar decompression and fusion. For this purpose, patients with EBL, surgery time, and LOS above the third quartile were considered as having the primary outcomes. The association of BMI and obesity with surgical results was evaluated by logistic regression models. All analyses were conducted using GraphPad Prism 8 (La Jolla, CA, USA) and R Statistical Software (Foundation for Statistical Computing, Vienna, Austria). Specific analysis tests are also mentioned in the tables. Two-tailed $p \leq 0.05$ were considered significant.

Table 1. Participant characteristics

Characteristics	Overall, n = 53 (%)	Obese, n = 18 (%)	Non-obese, n = 35 (%)	p-value
Age, years	51.0 (42.0, 64.0)	52.5 (49.0, 64.0)	51.0 (39.0, 60.5)	0.3
Male gender	22 (42)	6 (33)	16 (46)	0.4
BMI, kg/m^2	27.3 (24.7,30.4)	33.2 (30.7, 34.2)	25.4 (23.9, 27.1)	< 0.001
Depression	18 (34)	5 (28)	13 (37)	0.5
Alcoholism	18 (34)	4 (22)	14 (40)	0.2
Anxiety	17 (32)	4 (22)	13 (37)	0.3
Hypertension	13 (25)	5 (28)	8 (23)	0.7
Smoking	11 (21)	3 (17)	8 (23)	0.7
Diabetes	7 (13)	3 (17)	4 (11)	0.7
Previous surgery*	36 (68)	13 (72)	23 (66)	0.6

*History of non-spinal surgical interventions under spinal or general anesthesia. The data are displayed as median (IQR); n (%). The differences between groups were calculated using the Wilcoxon rank-sum test, Pearson's Chi-squared test, or Fisher's exact test, as appropriate.
BMI: body mass index.

Results

Participant characteristics

Our cohort included 53 patients subjected to lumbar spine surgery, 22 males and 31 females, with a median age of 51. Of these, 18 were obese (BMI ≥ 30 kg/m^2), and 35 were non-obese. Although the study was open for all individuals who met the inclusion criteria independently of their obesity status, the final cohort included only two patients with BMI > 35 kg/m^2 but without a comorbid cardiovascular/metabolic condition. Hence, the following analysis results are intended to be most representative of or applicable to individuals with Grade I-II obesity. The demographic characteristics of both groups were comparable, as shown in table 1. The median BMI in obese and non-obese patients was 33 kg/m^2 and 25 kg/m^2, respectively. The most frequent comorbidities in the overall study population included depression (18/53), alcohol intake (18/53), anxiety (17/53), and hypertension (13/53). Up to two-thirds of enrolled individuals reported at least one previous non-spinal surgical intervention under spinal or general anesthesia.

As illustrated in table 2, both study groups showed similar clinical manifestations. The most frequent symptom of lumbar spine degeneration was radicular pain, followed by paresthesia and reduced muscle strength of the lower limbs. In general, patients had degenerative alterations in a median of two lumbar segments, with about 90% and 75% showing L5-S1 and L4-L5 abnormalities in radiological studies, respectively. The most frequent degenerative changes observed in the study participants included stenosis in the lateral recess and neural foramen leading to radiculopathy (92%), central canal stenosis secondary to disc herniations (89%), and a significant reduction in the lumbar canal anteroposterior diameter (49%). Initial laboratory test results showed no differences between obese and non-obese patients, except for a significant increase in platelet counts among obese individuals. However, most patients' parameters were within normal ranges (Table 3).

Surgical results

All patients showed similar pre-operative ASA categories and received similar surgical interventions, although interspinous spacers were more common among non-obese individuals (Table 4). Similarly, study participants received similar medical interventions during hospitalization (Table S1). The median EBL was 300 mL in the overall cohort, 300 mL in obese patients, and 250 mL in non-obese individuals. Despite this, the difference between groups did not reach statistical significance (Fig. 1, left panel). Furthermore, no significant correlation was found between BMI and estimated bleeding during surgery (Fig. 2, left panel). The median duration of surgical procedures was 3 h, 3.2 h in obese patients, and 3 h in non-obese individuals ($p < 0.05$; Fig. 1, middle panel) but there was no direct correlation between

Table 2. Clinical manifestations and radiological findings

Findings	Overall, n = 53 (%)	Obese, n = 18 (%)	Non-obese, n = 35 (%)	p-value
Symptom onset	2.0 (0.0, 11.0)	1.0 (0.0, 8.0)	2.5 (0.0, 11.5)	> 0.9
Radicular pain	50 (94)	18 (100)	32 (91)	0.5
Paresthesia	35 (66)	10 (56)	25 (71)	0.2
Reduced muscle strength	24 (45)	8 (44)	16 (46)	> 0.9
Sensory impairment	8 (15)	1 (5.6)	7 (20)	0.2
Hypoesthesia	6 (11)	2 (11)	4 (11)	> 0.9
Plegia	2 (3.8)	0 (0)	2 (5.7)	0.5
Tremor	1 (1.9)	0 (0)	1 (2.9)	> 0.9
Lumbar segments, n	2.0 (1.0, 2.0)	2.0 (2.0, 2.0)	2.0 (1.0, 2.0)	0.8
L5-S1	47 (89)	16 (89)	31 (89)	> 0.9
L4-L5	40 (75)	14 (78)	26 (74)	> 0.9
L3-L4	6 (11)	1 (5.6)	5 (14)	0.7
L1-L2	1 (1.9)	1 (5.6)	0 (0)	0.3
L2-L3	0 (0)	0 (0)	0 (0)	--
Radiculopathy	49 (92)	16 (89)	33 (94)	0.6
Herniation	47 (89)	15 (83)	32 (91)	0.4
Lumbar stenosis	26 (49)	8 (44)	18 (51)	0.6
CLTSS	14 (26)	7 (39)	7 (20)	0.2
Lystesis	14 (26)	2 (11)	12 (34)	0.10
LFH	9 (17)	3 (17)	6 (17)	> 0.9

The data are displayed as median (IQR); n (%). The differences between groups were calculated using the Wilcoxon rank-sum test, Pearson's Chi-squared test, or Fisher's exact test, as appropriate.
CLTSS: cervico-lumbar tandem spinal stenosis; LFH: ligamentum flavum hypertrophy.

BMI and operative time (Fig. 2, middle panel). Regarding LOS after open lumbar spine surgery, enrolled patients stayed a median of 5 days in the hospital, without significant differences between obese and non-obese participants (6 days vs. 5 days, p = 0.3; Fig. 1, right panel). Similarly, there was no significant correlation between BMI and hospital stay (Fig. 2, right panel).

After dichotomizing the values of EBL, surgery time, and post-operative LOS above or below the third quartile, no differences were observed between obese and non-obese groups in the incidence of significant bleeding (> 400 mL), prolonged surgery (> 4 h), and extended stay after surgery (> 7 days; Table 4). Using logistic regression models adjusted for covariates (age, gender), obesity was not significantly associated with the incidence of significant perioperative bleeding, prolonged surgery, and extended stay. Interestingly, the individual variable BMI was not associated with significant bleeding and extended stay but showed a significant odds ratio value for prolonged surgery (Table 5). Finally, obese and non-obese patients showed similar rates of post-operative complications, as shown in table S2.

Discussion

Overweighted patients impose several challenges on spine surgeons. Accordingly, obesity may affect several aspects of the diagnosis and surgical management of lumbar degeneration, including the interference with pre-operative radiological images of the spine, the difficulty of intubation for general anesthesia, the complex positioning for incision, and the increased operative risk associated with comorbidities of obese individuals like diabetes and hypertension[8]. Despite this, there is

Table 3. Laboratory parameters

Test results	Overall (n = 53)	Obese (n = 18)	Non-obese (n = 35)	p-value
WBC, 10^9/L	7.2 (6.15, 8.5)	7.2 (5.4, 8.5)	7.4 (6.47, 8.35)	0.4
Neutrophils, 10^9/L	59.0 (54.0, 69.5)	54.5 (53.0, 61.1)	62.6 (54.8, 70.8)	0.10
Lymphocytes, 10^9/L	31.0 (24.5, 36.0)	32.2 (30.0, 36.5)	29.0 (21.6, 33.0)	0.15
Hb, g/dL	14.3 (12.8, 15.9)	13.6 (12.7, 15.1)	14.9 (13.6, 15.9)	0.2
Htc, %	43.1 (39.5, 47.2)	42.9 (38.4, 44.2)	43.9 (39.8, 47.8)	0.6
Platelets, 10^9/L	241.5 (214.0, 295.2)	283.0 (226.0, 322.0)	234.0 (195.5, 270.5)	0.035
Glucose, mg/dL	97.5 (89.8, 108.4)	97.5 (85.5, 102.5)	98.0 (91.0, 110.0)	0.4
Urea, mg/dL	28.8 (24.5, 37.6)	26.5 (18.0, 39.2)	30.4 (27.0, 35.9)	0.2
Cr, mg/dL	0.8 (0.7, 0.9)	0.7 (0.6, 1.0)	0.8 (0.7, 0.9)	0.5
Uric acid, mg/dL	4.8 (4.3, 6.2)	5.3 (4.6, 6.2)	4.7 (4.3, 6.3)	0.8
Cholesterol, mg/dL	184.2 (148.2, 220.8)	182.0 (146.0, 204.8)	189.3 (166.2, 238.2)	0.2
Triglycerids, mg/dL	184.0 (115.0, 237.0)	134.0 (104.0, 185.0)	202.5 (135.8, 250.8)	0.051

The data are displayed as median (IQR). The differences between groups were calculated using the Wilcoxon rank sum test.
ASD: adjacent segment degeneration; Cr: creatinine; Hb: hemoglobin; Htc: hematocrit; ICU: intensive care unit; LOS: length of stay; WBC: white blood cells.

Table 4. Surgical procedures and outcomes

Interventions	Overall, n = 53 (%)	Obese, n = 18 (%)	Non-obese, n = 35 (%)	p-value
ASA	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (1.5, 3.0)	0.7
TLIF	53 (100)	18 (100)	35 (100)	> 0.9
Interspinous spacer	36 (68)	9 (50)	27 (77)	0.045
Discectomy	35 (66)	9 (50)	26 (74)	0.077
Posterior instrumentation	32 (60)	14 (78)	18 (51)	0.063
Interbody fusion cage	30 (57)	8 (44)	22 (63)	0.2
Hemilaminectomy	11 (21)	4 (22)	7 (20)	> 0.9
Laminectomy	9 (17)	2 (11)	7 (20)	0.7
Laminotomy	1 (1.9)	1 (5.6)	0 (0)	0.3
Estimated bleeding, mL	300.0 (200.0, 400.0)	300.0 (212.5, 600.0)	250.0 (100.0, 400.0)	0.069
Surgery time, h	3.0 (2.0, 4.0)	3.2 (3.0, 4.0)	3.0 (2.0, 3.0)	0.037
LOS	5.0 (3.0, 7.0)	6.0 (3.0, 10.0)	5.0 (3.0, 7.0)	0.3
Significant bleeding	17 (32)	7 (39)	10 (29)	0.4
Long surgery	14 (26)	7 (39)	7 (20)	0.2
Long stay	17 (32)	7 (39)	10 (29)	0.4

The data are displayed as median (IQR); n (%). The differences between groups were calculated using the Wilcoxon rank sum test, Pearson's Chi-squared test, or Fisher's exact test, as appropriate.
ASA: the American Society of Anesthesiologists Health Status classification system; LOS: length of stay after surgery; TLIF: transforaminal lumbar interbody fusion.

controversy about the actual impact of obesity on the surgical complexity of lumbar spine surgery, as it is believed that the recommendation for weight-loss before the procedure is not directed to reduce the peri-operative morbidity but pre-operative challenges and the long-term outcomes. However, the relationship

Table 5. Logistic regression analysis

Variable	Significant bleeding			Prolonged surgery			Long hospital stay		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Obesity	1.6	0.5, 5.30	0.45	2.55	0.72, 9.20	0.15	1.59	0.47, 5.30	0.45
BMI	1.09	0.96, 1.25	0.19	1.17	1.02, 1.37	0.028	1.04	0.91, 1.18	0.59

BMI: body mass index; CI: confidence interval; OR: odds ratio.

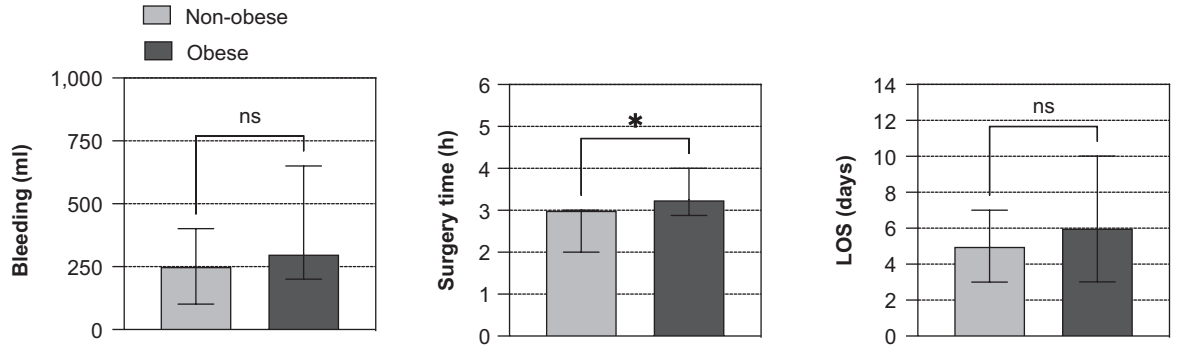

Figure 1. *Comparison of perioperative outcomes between obese and non-obese participants. The bars display medians with interquartile ranges. Differences between groups were analyzed using the Wilcoxon rank sum test. LOS: length of stay; *p < 0.05; ns: non-significant.*

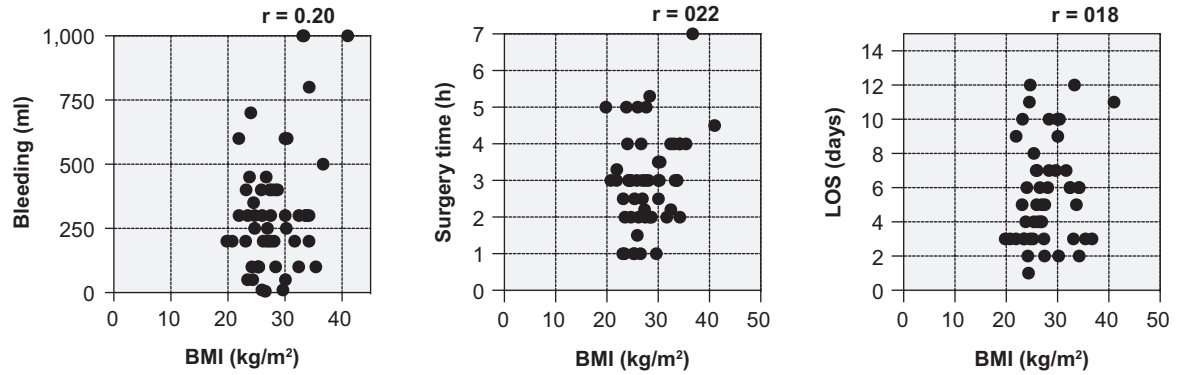

Figure 2. *Correlation between body mass index (BMI) and perioperative outcomes of lumbar decompression. The graphs show correlations between individual patient BMI and estimated blood loss calculated using the Spearman correlation coefficient (r).*

between obesity and perioperative outcomes during elective lumbar spine surgery is still a matter of debate that warrants further research.

Although several investigations have been conducted to clarify whether obesity impacts surgical results like the EBL, operative time, LOS, and functionality after lumbar spine surgery, the observations are frequently contradictory[9-11]. A possible explanation for this lack of agreement is the great methodological heterogeneity between existing studies, including the mixture of minimally invasive and open surgical approaches to the lumbar spine used for obese individuals[9-14]. Another source of heterogeneity is the distinct BMI thresholds used by different groups to define obesity, as illustrated in a recent meta-analysis of more than 23,000 patients subjected to lumbar decompression[4]. In this report, researchers identified several definitions for obesity used for comparisons of operative outcomes: BMI $\geq$ 25 kg/m^2, BMI $\geq$ 30 kg/m^2, BMI $\geq$ 35 kg/m^2, or BMI $\geq$ 95th percentile as per height and age. Interestingly, the meta-analysis also showed that up to 31% of individuals with lumbar

degeneration requiring surgical intervention were obese, as defined by a BMI ≥ 30 kg/m^2, which reflects that spine surgeons are increasingly in the situation of providing care to obese patients with lumbar spine degeneration[4].

An additional factor to be considered when analyzing evidence about the role of obesity in lumbar spine surgery is that most investigations on this matter have been carried out in developed countries with Caucasian populations where obesity is not a major public health threat. Conversely, little is known about the surgical and functional outcomes of obese patients subjected to lumbar spine surgery from developing countries where minimally invasive approaches are not always available. For this reason, the relevance of our study is that we compared the perioperative outcomes of obese and non-obese Mexican patients subjected to elective open lumbar spine surgery from a region with one of the highest burdens of obesity globally, where the prevalence of degenerative alterations of the lumbar spine is expected to further increase in the following decades due to the current trends of obesity even among children[15].

Our results indicate no differences in the EBL, duration of surgery, and LOS after surgery for degenerative lumbar spinal degeneration between patients with Grade I-II obesity and non-obese individuals, indicating that the complexity of lumbar spine surgery is not impacted by the excessive body mass of obese individuals. These observations contrast with the findings of Goyal et al.[4], who showed that obese patients have a significantly higher EBL and duration of surgery than non-obese individuals based on the results of 12 studies with 6751 participants. However, the mean differences between groups estimated by these researchers were minimal. For instance, the mean difference in blood loss between obese and non-obese patients was about 46 mL, which agrees with what we observed in our study: 300 mL vs. 250 mL of EBL. Furthermore, the mean difference in operative time observed in the meta-analysis was 17 min, whereas, in our cohort, we found a difference of 12 min between obese and non-obese participants. In contrast, Shamji et al. found that in 244 170 patients who underwent lumbar spine fusion, the transfusion requirements, wound complications, and postoperative infections were higher among those morbidly obese[16].

Overall, the differences in our study and others are barely significant in terms of statistics and may not be clinically meaningful in all subgroups of obese patients, affecting principally those with morbid obesity. Together, these data suggest that non-morbidly obese patients might not more prone to perioperative complications during lumbar spine surgery as compared to individuals with morbid obesity, reinforcing the idea of the "obesity paradox" in the general surgical population[17]. This fact does not mean that obese patients would not benefit from weight loss because they could improve several other aspects of their health, like controlling comorbidities and preventing metabolic and cardiovascular long-term complications, especially in those with BMI > 40 kg/m^2. For instance, it has been proven in different studies that weight loss before surgery may reduce preoperative manifestations such as pain and disk herniation[18]. Furthermore, in a recent investigation by Jain D and colleagues, they found that bariatric surgery in morbidly obese patients performed before elective lumbar spine surgery reduces the incidence of post-operative complications, including urinary tract infection, acute renal failure, infections, and LOS[19].

Furthermore, it is clear that an obese patient would have a worse surgical outcome in the long-term than someone without overweight, at least in the case of the morbidly obese population. However, this assumption might not be true to non-morbidly obese patients and then, the recommendation of weight loss as a condition required before spine surgery for those patients without morbid obesity must be well supported by rigorous evidence since this intervention may carry significant efforts and economic burden[20,21], especially when bariatric surgery is used before lumbar spinal decompression[19]. Hence, based on our results, surgical treatment of lumbar spine degeneration should not be denied based on patients' weight in the group of people with Grade I-II obesity, which is a widespread practice among spine surgeons. Instead, obese patients who are candidates for surgery should receive surgery for lumbar spinal degeneration with equal priority to non-obese individuals and be counseled to lose weight during their preparation for surgery, convalescence, and follow-up to prevent other long-term post-operative complications and improve the effectiveness of the intervention. These statements apply only for those without morbid obesity, since current literature indicates that in people with more severe disease there is a clear increment in the surgical risk and a benefit from weight-loss before surgery[5], as well as from the use of minimally-invasive approaches[22].

An interesting finding of our study is that, when using BMI as an independent variable, we found a significant association with the operative time, suggesting

that the threshold of BMI that is clinically relevant to determine surgical results after lumbar spine surgery is different from the cut-off used to define overweight or obesity. Similarly, Shamji et al. found that the BMI by itself correlated with higher requirements of blood transfusions after elective lumbar spine surgery[16]. Hence, as body mass increases, a critical point should be reached at which a more extensive dissection is required to gain access through the adipose tissue, thus determining a longer approach duration, which also carries the risk of a prolonged time of bleeding. Furthermore, the increased body mass might make the surgical corridor deeper, hindering the visibility of the surgical field. Although the exact significant BMI threshold leading to operative complications of lumbar spine surgery is not well defined, some studies have shown that in patients with BMI $\geq$ 35 kg/m^2, there is an incidence of prolonged surgery and wound infection[23].

The assumption that most complications of obese patients subjected to lumbar spine surgery are related to the extension of the approach and wound has led several groups to propose that minimally invasive surgery (MIS) is better to equalize surgical results of obese and non-obese groups, especially for those with morbid disease. Concurrently, several studies have shown that minimally invasive procedures like MIS-TLIF offer better outcomes than open TLIF for obese patients due to the smaller wound size and limited invasiveness to access the lumbar spine[12,14]. These findings were also corroborated in the meta-analysis by Goyal et al.[4] In this context, our study provides additional evidence showing that the outcomes after open TLIF for lumbar spine surgery are not impacted by grade I-II obesity. Hence, our results suggest that open TLIF is still a good option for non-morbidly obese patients with lumbar spine degeneration. In the case of individuals with morbid obesity, we acknowledge that our experience and the results of our study are not enough to make a conclusion about their postoperative risk. Hence, our results do not favor the use of open versus minimally invasive surgery for lumbar spine decompression and fusion.

This study has several limitations to be considered when interpreting the results, including its retrospective nature and single-center design. Furthermore, the relatively limited sample size of the study did not allow us to investigate the effect of obesity on post-operative surgical complications and long-term functional outcomes. There are several studies addressing this aspect available in the literature[24-27], which also need to be interpreted with caution due to the heterogeneity of the populations analyzed regarding the degree of overweight considered as obesity and the proportion of enrolled participants with morbid obesity. Furthermore, the study did not include enough individuals with extreme BMI to analyze the impact of morbid obesity on the perioperative lumbar spine surgery results. Future prospective studies using larger numbers of patients are required to confirm our findings.

Conclusion

The perioperative outcomes of patients with mild-to-moderate obesity are comparable to the results of non-obese individuals after lumbar spine surgery, with no clinically significant differences in post-operative EBL, operative time, and LOS between groups. Hence, lumbar spine surgery should not be denied to individuals with degenerative lumbar spinal disorders and Grade I-II obesity. The weight loss recommendation should not conditionate the spine surgery but instead promote integrative management to reduce long-term adverse post-operative outcomes, as well as metabolic and cardiovascular consequences of obesity. This assumption does not apply to the morbid obese patients, which constitutes a separate risk group with proved propensity to perioperative and post-operative adverse outcomes who require special diagnostic and therapeutic strategies to reduce perioperative and post-operative morbidity.

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Conflicts of interest

The authors declare that they do not have conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

Supplementary data

Supplementary data are available at DOI: 10.24875/CIRUE.M23000613. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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ORIGINAL ARTICLE

Pre-incisional local infiltration with levobupivacaine in laparoscopic cholecystectomy: a randomized and clinical trial

Infiltración local preincisional con levobupivacaína en colecistectomía laparoscópica: ensayo clínico aleatorizado

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Abstract

Objective: *Laparoscopic cholecystectomy (LC), despite its minimally invasive nature, requires effective control of postoperative pain. The use of local anesthetics (LA) has been studied, but the level of evidence is low, and there is little information on important parameters such as health-related quality of life (HRQoL) or return to work. The objective of the study was to evaluate the efficacy of 0.50% levobupivacaine infiltration of incisional sites in reducing POP after LC.* **Methods:** *This was a prospective, randomized, double-blind study. Patients undergoing elective LC were randomized into two groups: no infiltration (control group) and port infiltration (intervention group). POP intensity (numerical rating scale, NRS), need for rescue with opioid drugs, PONV incidence, HRQoL, and return to work data, among others, were studied.* **Results:** *Two hundred and twelve patients were randomized and analyzed: 105 (control group) and 107 (intervention group). A significant difference was observed in the NRS values (control group mean NRS score: 3.41 ± 1.82 vs. 2.56 ± 1.96) ($p < 0.05$) and in the incidence of PONV (31.4% vs. 19.6%) ($p = 0.049$).* **Conclusions:** *Levobupivacaine infiltration is safe and effective in reducing POP, although this does not lead to a shorter hospital stay and does not influence HRQoL, return to work, or overall patient satisfaction.*

Keywords: *Local anesthesia. Levobupivacaine. Laparoscopic cholecystectomy. Pain. Randomized clinical trial.*

Resumen

Objetivo: *la colecistectomía laparoscópica (CL), a pesar de su carácter mínimamente invasivo, requiere un control efectivo del dolor postoperatorio (POP). El uso de anestésicos locales (AL) ha sido estudiado pero el nivel de evidencia es bajo y existe poca información acerca de parámetros relevantes como la calidad de vida relacionada con la salud (CVRS) o la reincorporación laboral. El objetivo de este estudio es analizar la eficacia de la infiltración de los sitios incisionales con levobupivacaína 0,50% en la reducción del dolor postoperatorio tras la CL.* **Material y métodos:** *estudio prospectivo, aleatorizado y doble ciego. Pacientes sometidos a CL programada fueron aleatorizados en dos grupos: sin infiltración (grupo control) y con infiltración preincisional (grupo intervención). La intensidad del dolor (escala de puntuación numérica, NRS), la necesidad de rescates con opioides, la incidencia de náuseas o vómitos postoperatorios (NVPO) y datos de CVRS o reincorporación laboral, entre otros, fueron recogidos.* **Resultados:** *212 pacientes fueron aleatorizados y analizados: 105 en el grupo control y 107 en el grupo de intervención. Se observó una diferencia estadísticamente significativa en la intensidad del dolor (puntuación media NRS: 3.41 ± 1.82 vs. 2.56 ± 1.96) ($p < 0.05$) y en la incidencia de NVPO (31.4% vs. 19.6%) ($p = 0.049$).*

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Conclusiones: *La infiltración con levobupivacaína es segura y efectiva en la reducción del dolor postoperatorio, aunque esto no conlleva una menor estancia hospitalaria y no influye en los resultados de CVRS, reincorporación laboral o satisfacción del paciente.*

Palabras clave: *Anestesia local. Levobupivacaína. Colecistectomía laparoscópica. Dolor. Ensayo clínico aleatorizado.*

Introduction

Laparoscopic cholecystectomy (LC) is one of the most performed surgical procedures in the world, with over 300,000 patients in the USA every year[1] and about 80,000 in Spain[2]. Most patients are adults (mainly women) with symptomatic cholelithiasis, and it can be performed as an inpatient surgery or a day-case surgery. Despite the minimally invasive nature of the laparoscopic approach, it is not a POP-free procedure. Pain may have different origins: visceral pain, parietal pain, and irritation secondary to residual pneumoperitoneum[3]. POP is especially important in the first 24 h and is related to a greater use of opioid analgesics, which can present certain unwanted side effects, mainly PONV. In this way, POP can interfere with the first steps of recovery (oral tolerance, ambulation, etc.)[4]. Trying to prevent and minimize POP is not only mandatory to avoid patient discomfort and suffering but may also allow earlier hospital discharge and perhaps a better recovery after hospital discharge as well.

There are previous studies focusing on the use of LA both at surgical incision sites and intraperitoneally. However, although results point to a reduction in POP, the level of evidence is very low, and there is little information on important parameters such as HRQoL or return to work[5].

The aim of this study is to improve the existing scientific evidence about the use of levobupivacaine in the incisional sites of LC, focusing on POP, use of opioid drugs, incidence of PONV, and patient recovery, including the mentioned parameters as HRQOL and return to work.

Materials and methods

Before approval by the Ethics and Research Committee, a prospective, randomized, and double-blind study was conducted. It conformed to CONSORT guidelines for reporting parallel group randomized trials and was registered at ClinicalTrials.gov under code NCT04697329.

The inclusion criteria were patients over 18 years old scheduled for elective LC. American Society of Anesthesiologists (ASA) 1, 2, and 3 patients were included. The exclusion criteria were: cognitive impairment, previous adverse reactions to LA, coronary heart disease, and accompanying chronic pain disorders. Patients underwent inpatient surgery with at least an overnight stay at the hospital. All the operations were performed by surgeons experienced in laparoscopy.

A simple randomization was performed for each patient, which determined their assignment to a control group and an intervention group. In the latter, the LA was administered in the operating room immediately before skin incisions, already under general anesthesia. 20 ml of a 5 mg/ml levobupivacaine solution was administered to the incision sites, infiltrating skin, fascia, and preperitoneal space.

Surgery was performed laparoscopically, first placing a Hasson-type trocar at the umbilical level using the open technique, followed by an 11-mm epigastric trocar and two 5-mm trocars in the right midclavicular and midaxillary lines. Intra-abdominal pressure was maintained at 12 mmHg.

The fascia of the umbilical orifice was sutured with an absorbable braided thread (polyglycolic acid), and the skin of the four incisions was closed with staples.

Post-operative routine analgesia was metamizole 1 g IV every 6 h and paracetamol 1 g IV every 6 h. Morphine chloride, 3 mg IV every 3 h, was also administered at the patient's request, always according to the criteria, and under the supervision of the nursing staff. After hospital discharge, patients received a protocol for the administration of different non-opioid analgesics, usually 575 mg metamizole every 8 h, alternating with 1 g paracetamol every 8 h.

Follow-up with each patient was carried out from the surgical intervention until the moment of hospital discharge. In addition, 1 month after the intervention, data were collected in a face-to-face hospital review and by telephone review.

The first primary outcome was pain intensity using a numerical rating scale (NRS), ranging from zero to ten, where 0 represents "no pain" and 10 represents "the most intense pain imaginable". Pain was rated at 4, 8, 12, and 24 h after surgery. Two other primary outcomes were analyzed: the need for rescue with opioid drugs and the presence of PONV. Secondary

Table 1. Demographic data

n	Global	Control	Intervention	p - value
	212	105	107	
Mean age (year)	54.7 ± 15.2	53.9 ± 14.9	55.4 ± 15.5	0.482
Gender (n [%])	M: 72 (34.0%)/ F: 140 (66.0%)	M: 39 (37.1%)/ F: 66 (62.9%)	M: 33 (30.8%)/ F: 74 (69.2%)	0.333
ASA 1 (n [%])	31 (14.6%)	19 (18.1%)	12 (11.2%)	
ASA 2 (n [%])	162 (76.4%)	81 (77.1%)	81 (75.7%)	0.054
ASA 3 (n [%])	19 (9.0%)	5 (4.8%)	14 (13.1%)	
Mean BMI (kg/m^2)	27.9 ± 4.7	27.4 ± 4.5	28.3 ± 4.8	0.157
Active employment status (n [%])	106 (50.0%)	52 (49.5%)	54 (50.5%)	0.891
Previous open abdominal surgery (n [%])	79 (37.3%)	37 (35.2%)	42 (39.3%)	0.546
Symptomatic cholelithiasis (n [%])	199 (93.9%)	99 (94.3%)	100 (93.5%)	0.802
Gallbladder polyps (n [%])	13 (6.1%)	6 (5.7%)	7 (6.5%)	
Previous acute pancreatitis (n [%])	26 (12.3%)	8 (7.6%)	18 (16.8%)	0.041*
Previous acute cholecystitis (n [%])	25 (11.8%)	11 (10.5%)	14 (13.1%)	0.556
Previous acute colangitis (n [%])	8 (3.8%)	6 (5.7%)	2 (1.9%)	0.142
Previous ERCP (n (%)]	15 (7.1%)	7 (6.7%)	8 (7.5%)	0.818

*p < 0.05 was considered statistically significant.
ASA: American Society of Anesthesiologists; BMI: body mass index; ERCP: endoscopic retrograde cholangiopancreatography.

outcomes were oral intake initiation time, time to ambulation, and length of hospital stay. In addition, different intraoperative and post-operative parameters were recorded. HRQoL data related to the first days after hospital discharge were collected using the EuroQol-5D-3L questionnaire. This quiz includes five parameters (dimensions) scored from 1 to 3: mobility, self-care, usual activities (e.g., work, study, housework, family or leisure activities), pain or discomfort, and anxiety or depression. The following parameters were also analyzed 1 month after LC: development of hematoma or surgical site infection (SSI), number of days of analgesic intake, return to work, oral tolerance, and patient satisfaction.

Table 2. Intraoperative parameters

IO parameter	Global	Control	Intervention	p-value*
Mean operative time (min)	48.5 ± 16.7	46.4 ± 15.7	50.5 ± 17.4	0.102
Cholecystitis (n (%))	43 (20.3%)	21 (20.0%)	22 (20.6%)	0.919
Bile spillage (n (%))	60 (28.3%)	28 (26.7%)	32 (29.9%)	0.601
Dose of fentanyl (mcg/kg)	3.33 ± 1.46	3.40 ± 1.47	3.26 ± 1.46	0.519

*p < 0.05 was considered statistically significant.

Statistical analysis

The sample size was calculated with a 95% confidence level, a statistical power of 95%, and a loss to follow-up of 1%. A sample of 210 patients was considered necessary. Patients, nurse staff, and data collectors were blinded.

Data are expressed as the percentage of patients or mean ± standard deviation. Statistically significant differences were those with $p < 0.05$. Numerical data were compared by the *t* test or Mann–Whitney U test. Nominal variables were analyzed using Chi-square tests. The effect of the intervention was evaluated with the odds ratio (OR) and its confidence interval (CI) adjusted for the different covariates with a backstep logistic regression model, thus controlling possible confounding factors. Statistical analysis was performed with the IBM SPSS Statistics v.22 program (IBM Corp., Armonk, NY, USA).

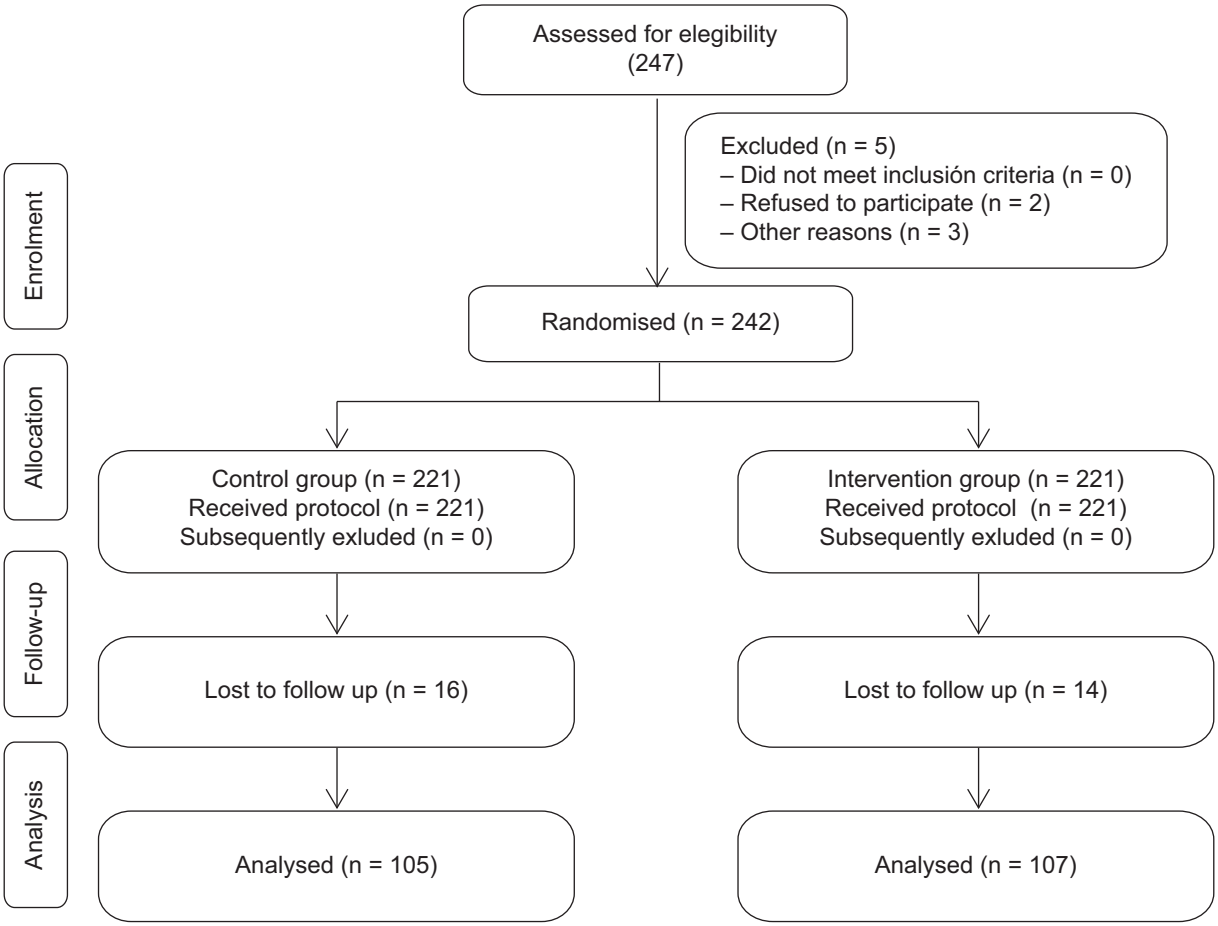

Figure 1. *Consort flow chart.*

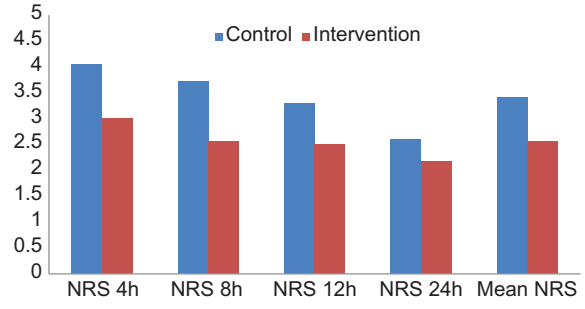

Figure 2. *NRS score.*
NRS: numeric rate scale.
Note: 4, 8, 12, and 24 h after surgery.

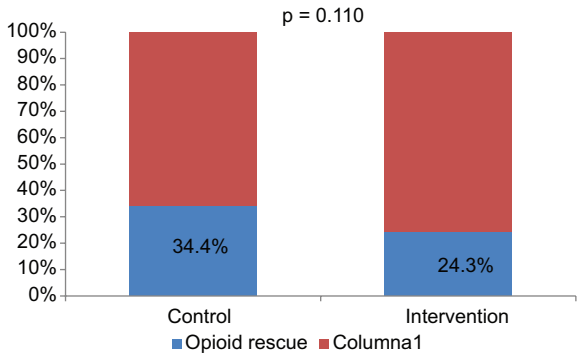

Figure 3. *Need for opioid rescue.*

Results

A total of 242 patients were enrolled and randomized from December 2020 to May 2022. The patient flow chart is shown in figure 1 (Consort Diagram). 30 patients were lost to follow-up, and 212 patients were finally analyzed. The main causes of loss of follow-up were drain placement (12 patients), open surgery conversion (nine patients), reintervention (three patients), and lack of collaboration (two patients).

Of the 212 patients analyzed, 105 underwent surgery without local infiltration (control group), while LA was administered to 107 patients (intervention group). There were no significant differences between both

Table 3. Inhospital postoperative parameters

Postoperative parameter	Global	Control	Intervention	p-value
NRS 4 h	3.52 ± 2.58	4.05 ± 2.45	3.01 ± 2.61	0.001*
NRS 8 h	3.14 ± 2.35	3.72 ± 2.34	2.56 ± 2.24	< 0.001*
NRS 12 h	2.89 ± 2.00	3.29 ± 1.86	2.50 ± 2.05	0.001*
NRS 24 h	2.39 ± 1.16	2.60 ± 1.53	2.18 ± 1.71	0.014*
Mean NRS	2.98 ± 1.93	3.41 ± 1.82	2.56 ± 1.96	< 0.001*
Opioid rescue (n [%])	62 (29.2%)	36 (34.3%)	26 (24.3%)	0.110
Nausea/vomiting (n [%])	54 (25.5%)	33 (31.4%)	21 (19.6%)	0.049*
Antiemetics rescue (n [%])	45 (21.2%)	23 (21.9%)	22 (20.6%)	0.811
Mean systolic blood pressure (mm Hg)	131.3 ± 18.1	130.9 ± 18.3	131.7 ± 18.0	0.667
Mean diastolic blood pressure (mm Hg)	74.2 ± 9.7	74.9 ± 9.2	73.5 ± 10.01	0.460
Mean heart rate (bpm)	72.5 ± 10.9	73.3 ± 11.4	71.7 ± 10.4	0.161
Mean PACU length of stay (min)	210.6 ± 127.0	205.6 ± 123.5	215.4 ± 132.64	0.665
Shoulder pain (n [%])	44 (20.8%)	25 (23.8%)	19 (17.8%)	0.277
Mean oral intake initiation time (h)	9.6 ± 4.8	9.7 ± 4.6	9.4 ± 5.0	0.425
Mean ambulation initiation time (h)	13.9 ± 5.0	13.9 ± 5.1	13.8 ± 5.0	0.828
Mean discharge time (h)	26.0 ± 8.7	26.6 ± 9.7	25.3 ± 7.8	0.603
Mean second night stay	12 (5.7%)	6 (5.7%)	6 (5.6%)	0.973

*p < 0.05 was considered statistically significant.
NRS: numeric rate scale; PACU: post-anesthesia care unit.

Table 4. Multivariate analysis of risk factors for pain intensity ≥ 3

Risk factor	OR	95% CI	p value
LA infiltration	0.34	0.10-0.65	0.001*
Bile spillage	1.79	0.87-3.67	0.111
Cholecystitis	1.17	0.51-2.66	0.708
Dose of fentanyl < 3 mcg/kg	0.56	0.27-1.13	0.106

*p < 0.05 was considered statistically significant.
OR: odds ratio; CI: confidence interval; LA: local anesthetic

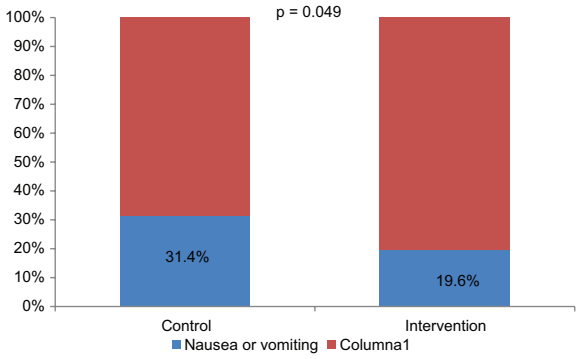

Figure 4. *Nausea/vomiting.*

groups except for previous episodes of acute pancreatitis (p = 0.041). The characteristics of the patients are shown in table 1. There were no allergic reactions or toxicity in the group of patients with port infiltration (PI).

Intraoperative parameters recorded are shown in table 2. There were no statistically significant differences in the operative time, presence of cholecystitis, bile spillage, or dose of opioid (fentanyl).

Parameters recorded in the post-operative period, both in the post-anesthesia care unit (PACU) and in the hospitalization ward, are shown in table 3. Intervention group patients showed lower NRS values than those in the control group, both at 4 h (3.01 ± 2.61 vs. 4.05 ± 2.45) and in the successive measurements at 8 h (2.56 ± 2.24 vs. 3.72 ± 2.34), 12 h (2.50 ± 2.05 vs. 3.29 ± 1.86) and 24 h (2.18 ± 1.71 vs. 2.60 ± 1.53). The mean NRS score was 2.56 ± 1.96 in the intervention group and 3.41 ± 1.82 in the control group (Fig. 2).

Table 5. Data collected 1 month after the intervention

Parameter	Global	Control	Intervention	p-value*
Mean of analgesic intake (days)	4.0 ± 5.46	3.8 ± 5.4	4.1 ± 5.5	0.544
Hematoma (n [%])	54 (25.5%)	26 (24.8%)	28 (26.2%)	0.814
Surgical Site Infection (n [%])	14 (6.6%)	7 (6.7%)	7 (6.5%)	0.971
Return to work (n [%])	27/106 (25.5%)	15/52 (28.8%)	12/54 (22.2%)	0.434
Full oral tolerance (n [%])	96 (45.3%)	46 (43.8%)	50 (46.7%)	0.669
Quite/very satisfied (n [%])	201 (94.8%)	99 (94.3%)	102 (95.3%)	0.733

*p < 0.05 was considered statistically significant.

Table 6. EuroQol-5D questionnaire

EuroQol dimension	Global	Control	Intervention	p-value
Mobility				
No problems in walking about	133 (62.7%)	65 (61.9%)	68 (63.6%)	
Some problems	74 (34.9%)	39 (37.1%)	35 (32.7%)	0.403
Confined to bed	5 (2.4%)	1 (1.0%)	4 (3.7%)	
Self-care				
No problems	153 (72.2%)	76 (72.4%)	77 (72.0%)	
Some problems	53 (25.0%)	26 (24.8%)	27 (25.2%)	0.997
Unable to wash/dress	6 (2.8%)	3 (2.9%)	3 (2.8%)	
Usual activities				
No problems	150 (70.8%)	76 (72.4%)	74 (69.2%)	
Some problems	59 (27.8%)	27 (25.7%)	32 (29.9%)	0.654
Unable	3 (1.4%)	2 (1.9%)	1 (0.9%)	
Pain/discomfort				
No pain/disconfort	157 (74.1%)	78 (74.3%)	79 (73.8%)	
Moderate	51 (24.1%)	25 (23.8%)	26 (24.3%)	1.000
Extreme	4 (1.9%)	2 (1.9%)	2 (1.9%)	
Anxiety/depression				
Not anxious/depressed	201 (94.8%)	99 (94.3%)	102 (95.3%)	
Moderately	10 (4.7%)	5 (4.8%)	5 (4.7%)	0.873
Extremely	1 (0.5%)	1 (1.0%)	0 (0.0%)	

These differences were statistically significant, with values $p < 0.05$.

The need for rescue with opioid drugs among patients with levobupivacaine infiltration was lower than that of patients in the control group (24.3% vs. 34.3%), without reaching a statistically significant difference ($p = 0.110$) (Fig. 3). The incidence of PONV did show a significant difference between both groups (control group: 31.4%/ intervention group: 19.6%; $p = 0.049$) (Fig. 4). This statistically significant difference was not observed among rescues with antiemetic drugs (control group: 21.9%; intervention group: 20.6%; $p = 0.881$). The values of systolic blood pressure, diastolic blood pressure, heart rate (HR), and length of stay in PACU did not show significant differences. There were also no significant differences in oral intake initiation time, time to ambulation, or time to hospital discharge. Patients in the control group did not require a second night in the hospital more often than patients in the intervention group (5.7% vs. 5.6%, $p = 0.973$).

In the multivariate analysis (Table 4), we studied the risk factors for a NRS score ≥ 3 that were statistically significant after the univariate analysis (PI with LA) and those that were considered of interest even though they did not reach statistical significance (bile spillage, cholecystitis, and a dose of fentanyl < 3 mcg/kg). Only LA infiltration showed statistical significance, with an odds ratio (OR) = 0.34 ($p = 0.001$).

Regarding the data collected 1 month after the intervention, shown in table 5, we did not observe differences in the incidence of hematoma or SSI, as well as in the number of days of analgesic intake or full oral tolerance. Rates of return to work were not statistically different either. Global patient satisfaction did not show differences between the two groups. HRQoL data (EuroQol-5D-3L questionnaire) are shown in table 6.

Discussion

Since the laparoscopic approach has definitely spread in performing cholecystectomy, different studies have tried to bring scientific evidence about the use of LA in order to reduce postoperative pain. These works are based on the use of LA either intraperitoneally[6-10], either at the incision sites[11-13] or using both routes of administration[14-17], some at the beginning of the intervention and others at the end of it. The most frequently used drug has been bupivacaine; fewer studies have used other anesthetics such as levobupivacaine or ropivacaine[14,18].

Various systematic reviews and meta-analyses pool and analyze the existing literature[5,19,20]. Loizides et al. concluded that there is a very low level of scientific evidence in favor of infiltration of incisional sites, with a reduction in POP in patients with low anesthetic risk and little clinical relevance derived from it. In addition, they recommend that future studies should have a lower risk of bias and include results about return to work and HRQoL.

These conclusions and recommendations have been taken into account when designing this study.

Our results show, with statistically significant differences, lower NRS values and lower PONV incidence in patients with PI. Although the need for rescue with opioid drugs among patients with PI was also lower, differences did not reach statistical significance. From our perspective, this is attributable to the fact that not all patients with high NRS values received opioid rescue, and some patients with low NRS values did. This is so because opioid rescue administration depends on the criteria of the responsible nursing staff, and the NRS value is not a single or rigid parameter that determines the administration.

The times of oral intake initiation, ambulation, and hospital discharge were similar, so when LC is performed in an inpatient surgery program with a protocol that significantly delays the onset of oral tolerance and ambulation (remember that our patients began to tolerate liquids more than 9 h after surgery and to ambulate almost 14 h after it), PI does not imply significant differences in these parameters. Instead, in a day-case surgery program, when recovery times need to be notably shorter, patients with more pain or PONV would probably show statistically significant longer recovery times compared to the rest of the patients.

We have also focused on clinical outcomes after hospital discharge. To compare recovery immediately after hospital discharge, we used the HRQoL data provided by the EuroQol-5D-3L questionnaire. We decided to use this questionnaire not only because of its simplicity and speed of completion but also because the dimensions it includes fit well with the nature of this part of the study, that is, to compare postoperative recovery (especially at a physical level) between the two groups of patients.

Our results confirm that 24 h after the LC, the evolution is independent of the use of LA. In addition to the absence of differences between the two groups, we would point out the good results collected, with up to 48.6% of patients scoring 1 on the 5 dimensions of the questionnaire and only 13 patients scoring 3 on any of them.

One month after LC, we studied the rate of return to work without finding differences between the two groups. We must highlight that of the 212 patients analyzed, only 106 (50.0%) had an active employment status at the time of the operation, 52 in the control group and 54 in the intervention group, which may limit the validity of the findings.

We would also include, as a limitation of the study, the absence of recording of intraoperative anesthetic parameters that could point to a contribution of the PI to better hemodynamic behavior.

Conclusions

Our results are in line with other studies showing that preoperative infiltration of LC incision sites with 0.50% levobupivacaine is safe and reduces POP, the need for rescue with opioid drugs, and the incidence of PONV. The rest of the parameters studied do not show significant differences, highlighting oral intake initiation time, time to ambulation, and hospital discharge time. Outside of an outpatient cholecystectomy program, these results do not translate into earlier hospital discharge.

On the other hand, the recovery of the patient once at home is independent of the use or not of the LA, showing the same need for analgesics intake and similar data on HRQoL, return to work, or global satisfaction.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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ORIGINAL ARTICLE

Clinical and urodynamics outcomes in pediatric primary bladder diverticula: a comparative study

Resultados clínicos y urodinámicos en divertículos vesicales primarios pediátricos: un estudio comparativo

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Abstract

Objective: *This study aimed to compare the effects of bladder diverticula smaller than 30 (SD) mm and larger than 30 mm (LD) on bladder functions and urodynamics.* **Materials and methods:** *Our retrospective analysis involved a cohort of 40 pediatric patients diagnosed with primary bladder diverticula.* **Results:** *The predicted mean bladder capacity (MBC) was 197.7 ± 95.8 mL, whereas the observed MBC was lower at an average of 170.1 ± 79.6 mL. This indicates that the observed MBC was 88.2 ± 12.9% of the predicted value (percentage). The mean diverticula diameter recorded was 33 ± 19.5 mm, and the diverticula to MBC ratio were calculated to be 0.25 ± 0.18. The distribution of urinary tract infections (UTIs) differed significantly between the groups ($p < 0.001$). Upper UT dilatation was significantly more common in the LD group (60%, n = 12) than in the SD group (15%, n = 3) ($p = 0.003$). The mean detrusor pressure (P[detrusor]) was significantly higher in the LD group (137.2 ± 24.1 cm H_2O) than in the SD group (63.9 ± 5.8 cm H_2O) ($p = 0.001$). In addition, the mean peak flow rate (Q_{max}) was significantly higher in the SD group (20.7 ± 7.9 mL/s) compared to the LD group (12.7 ± 3.8 mL/s) ($p < 0.001$).* **Conclusion:** *Bladder diverticula size is a significant factor in the clinical presentation and management of primary bladder diverticula in pediatric patients.*

Keywords: *Bladder. Diverticula. Vesicoureteral reflux. Urodynamic. Urinary tract infections.*

Resumen

Objetivo: *Este estudio tuvo como objetivo comparar los efectos de los divertículos vesicales menores 30 mm (SD), mayores 30 mm (LD) en las funciones y urodinámica de vejiga.* **Materiales y métodos:** *Nuestro análisis retrospectivo involucró una cohorte de 40 pacientes pediátricos diagnosticados con divertículos vesicales primarios.* **Resultados:** *Capacidad vesical media predicha (MBC) fue de 197.7 ± 95.8 mL, mientras que MBC observada fue menor con promedio de 170.1 ± 79.6 mL. Esto indica que MBC observada fue del 88.2 ± 12.9% del valor predicho (porcentaje). Diámetro medio de divertículos registrados fue de 33 ± 19.5 mm, y se calculó que relación entre los divertículos y la MBC era de 0.25 ± 0.18. Distribución de infecciones del tracto urinario (ITU) difirió significativamente entre grupos ($p < 0.001$). Dilatación del tracto urinario superior (UT) fue significativamente más común en grupo LD (60%, n = 12) que en grupo SD (15%, n = 3) ($p = 0.003$). Presión media del detrusor (P[detrusor]) fue significativamente mayor en grupo LD (137.2 ± 24.1 cm H_2O) que en grupo SD (63.9 ± 5.8 cm H_2O) ($p = 0.001$). Además, tasa de flujo máximo promedio (Q_{max}) fue significativamente mayor en grupo SD (20.7 ± 7.9 mL/seg) en comparación con grupo LD (12.7±3.8 mL/seg) ($p < 0.001$).* **Conclusiones:** *Tamaño de divertículos vesicales es factor significativo en presentación clínica, manejo de divertículos vesicales primarios en pacientes pediátricos.*

Palabras clave: *Vejiga. Divertículos. Reflujo vesicoureteral. Urodinámica. Infecciones del tracto urinario.*

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Introduction

About 1.7% of children are born with bladder diverticula, which are sac-like protrusions from the bladder wall. Diverticula of the bladder can be present at birth (primary bladder diverticula) or develop later in life (secondary bladder diverticula)[1,2]. Paraureteral diverticula, also known as Hutch diverticula, share a common etiology in which a defect in Waldeyer's fascial sheath plays a pivotal role in their development[3].

Hutch diverticula cause significant vesicoureteral reflux because they distort the ureterovesical junction[4,5]. Primary congenital diverticula have been linked to the connective tissue disorders known as Ehlers–Danlos types IV, V, and IX, which are said to cause the diverticula to rupture spontaneously[6,7]. Interestingly, a high prevalence of primary bladder diverticula has been linked to Menkes' kinky hair disease, a rare X-linked recessive disorder of copper metabolism[6,7].

Various genitourinary complications, including infections and voiding dysfunction, have been linked to bladder diverticula, which are primarily diagnosed through voiding cystourethrograms[8]. The main problem is that it is not known whether or not surgical intervention affects the frequency of associated infections or voiding dysfunction, and there are no established guidelines for the repair of primary pediatric bladder diverticula[8,9]. By discussing experiences with primary bladder diverticula in children, with an emphasis on the urinary tract infections (UTI) and voiding dysfunction that often accompany them.

This study aimed to compare the effects of bladder diverticula smaller than 30 (SD) mm and larger than 30 mm (LD) on bladder functions and urodynamics.

Materials and methods

Patients and groups

Our retrospective analysis involved a cohort of 40 pediatric patients diagnosed with primary bladder diverticula. All patients were selected from our hospital's patient database from the period between January 2020 and April 2023. The inclusion criteria encompassed patients aged < 18 years who had a confirmed diagnosis of primary bladder diverticula. Patients with secondary bladder diverticula or those with other significant genitourinary abnormalities were excluded from this study.

The following patient data were collected: patient age at the time of diagnosis, gender, the number of UTIs experienced, the presence of upper UT dilatation, renal impairment, vesicoureteral reflux, post-micturition residue (PMR), and whether the patient underwent surgery. Moreover, diverticula diameter, predicted mean bladder capacity (MBC), observed MBC, the percentage of predicted MBC, diverticula to MBC ratio, mean detrusor pressure (P[detrusor]), and mean peak flow rate (Q_{max}) were documented.

Patients were divided into two groups based on the size of their diverticula, with one group comprising those with diverticula < 30 mm in diameter, and the other with diverticula > 30 mm.

The diverticula diameter was determined through ultrasound examination. Predicted MBC and observed MBC were assessed through voiding cystourethrograms, which were also used to diagnose bladder diverticula and vesicoureteral reflux. PMR was evaluated through post-void ultrasound. The pressure-flow study was utilized to measure P(detrusor) and Q_{max}.

This study was conducted following the ethical standards of the Declaration of Helsinki, and it was approved by the Institutional Review Board of our hospital. Given the retrospective nature of the study (KAEK/2023.05.193), the requirement for individual informed consent was waived.

Statistical analysis

Data were analyzed using SPSS software (version 26.0). Continuous variables were presented as mean ± standard deviation and categorical variables as frequency and percentage. The independent *t*-test was used for the comparison of continuous variables between two groups, and the Chi-square test was utilized for categorical variables. A $p < 0.05$ was considered statistically significant.

Results

The study encompassed 40 patients with a mean age of 5.8 ± 3.8 years. The cohort consisted predominantly of males, making up 80% of the total patients (n = 32). The predicted MBC was 197.7 ± 95.8 mL, whereas the observed MBC was lower at an average of 170.1 ± 79.6 mL. This indicates that the observed MBC was 88.2 ± 12.9% of the predicted value (percentage). The mean diverticula diameter recorded was 33 ± 19.5 mm, and the diverticula to MBC ratio were calculated to be 0.25 ± 0.18. Half of the patients

(n = 20) had diverticula > 30 mm in diameter. The distribution of UTIs among patients was as follows: 7.5% of patients had no UTIs (n = 3), 42.5% had one UTI (n = 17), 17.5% had two UTIs (n = 7), 22.5% had three UTIs (n = 9), and 10% had four or more UTIs (n = 4). Further clinical observations revealed that 37.5% of patients (n = 15) had upper UT dilatation. Renal impairment was found in 7.5% of patients (n = 3), whereas 25% of the patients (n = 10) exhibited vesicoureteral reflux. Positive PMR was observed in 30% of patients (n = 12). The mean detrusor pressure (P[detrusor]) was 100.6 ± 40.9 cm H_2O, and the mean peak flow rate (Q_{max}) was found to be 16.7 ± 65.6 mL/s. Among the patient group, 27.5% (n = 11) underwent surgery as part of their treatment pathway (Table 1).

The study participants were divided into two equal groups, based on the size of their diverticula. Twenty patients (50%) had diverticula of < 30 mm, whereas the other 20 (50%) had diverticula larger than 30 mm. The mean age of patients in the smaller diverticula group was 5.3 ± 3.7 years, compared to 6.3 ± 3.9 years in the larger diverticula group (p = 0.439). In terms of gender, males made up 70% (n = 14) and 90% (n = 18) of the smaller and larger diverticula groups, respectively, although this difference was not statistically significant (p = 0.235). The predicted MBC was 183 ± 91.2 mL in the smaller diverticula group and 212.5 ± 100.3 mL in the larger group (p = 0.337). The observed MBC was 176.9 ± 87.1 mL in the smaller diverticula group, slightly higher than the 163.2 ± 72.9 mL in the larger group (p = 0.539). The observed MBC as a percentage of the predicted MBC was significantly higher in the smaller diverticula group 98.04 ± 8.7 than in the larger diverticula group 78.4 ± 8.01 (p < 0.002). The distribution of UTIs differed significantly between the two groups (p < 0.001). In terms of clinical observations, upper UT dilatation was significantly more common in the larger diverticula group (60%, n = 12) than in the smaller group (15%, n = 3) (p = 0.003). The rate of renal impairment was similar in both groups (p = 1.000). Vesicoureteral reflux and positive PMR were found exclusively in the larger diverticula group (50%, n = 10, and 60%, n = 12, respectively), with significant differences observed (p < 0.001 for both). The mean detrusor pressure (P[detrusor]) was significantly higher in the larger diverticula group (137.2 ± 24.1 cm H_2O) than in the smaller group (63.9 ± 5.8 cm H_2O) (p = 0.001). In addition, the mean peak flow rate (Q_{max}) was significantly higher in the smaller diverticula group (20.7 ± 7.9 mL/s) compared to the larger group (12.7 ± 3.8 mL/s) (p < 0.001). Finally, surgery was more prevalent in the larger diverticula group, with 55% of these patients (n = 11) undergoing surgery, compared to none in the smaller diverticula group (p < 0.001) (Table 2).

Table 1. Patients demographic

Variables	n (or mean)	% (or SD)
Age (year)*	5.8	3.8
Gender (M)	32	80
Predicted MBC (mL)*	197.7	95.8
Observed MBC (mL)*	170.1	79.6
Percentage of predicted MBC (%)*	88.2	12.9
Diverticula diameter (mm)*	33	19.5
Diverticula to MBC ratio*	0.25	0.18
Diverticula > 30 mm	20	50
Total UTI (n)		
Never	3	7.50
1 time	17	42.50
2 times	7	17.50
3 times	9	22.50
4 and more	4	10
Upper UT dilatation	15	37.50
Renal impairment	3	7.50
Vesicoureteral reflux	10	25
PMR (yes)	12	30
P (detrusor) cm H_2O*	100.6	40.9
Q_{max} (mL/s)*	16.7	5.6
Surgery	11	27.50

*mean/SD (standard deviation).
MBC: mean bladder capacity; PMR: post-micturition residue.

Discussion

Our study provides valuable insights into the clinical management and outcomes of pediatric patients diagnosed with primary bladder diverticula. It is notable that primary bladder diverticula are rare and generally associated with significant genitourinary complications including infections and voiding dysfunction[1,2,8].

The main finding of this study is the substantial differences observed between patients with smaller and larger diverticula. We found that those with larger diverticula (> 30 mm) experienced significantly more UTIs, higher instances of upper UT dilatation, greater

Table 2. Comparison of diverticula diameters

Variables	< 30 mm (n = 20) (%)	> 30 mm (n = 20) (%)	p-value
Age (year)*	5.3 ± 3.7	6.3 ± 3.9	0.439
Gender (M)	14 (70)	18 (90)	0.235
Predicted MBC (mL)*	183 ± 91.2	212.5 ± 100.3	0.337
Observed MBC (mL)*	176.9 ± 87.1	163.2 ± 72.9	0.539
Percentage of predicted MBC (%)*	98.04 ± 8.7	78.4 ± 8.01	< 0.002
Total UTI (n)			< 0.001
Never	3 (15)	0 (0)	
1 time	16 (80)	1 (5)	
2 times	1 (5)	6 (30)	
3 times	0 (0)	9 (45)	
4 and more	0 (0)	4 (20)	
Upper UT dilatation	3 (15)	12 (60)	0.003
Renal impairment	1 (5)	2 (10)	1.000
Vesicoureteral reflux	0 (0)	10 (50)	< 0.001
PMR (yes)	0 (0)	12 (60)	< 0.001
P (detrusor) cm H_2O*	63.9 ± 5.8	137.2 ± 24.1	0.001
Qmax (mL/s)*	20.7 ± 7.9	12.7 ± 3.8	< 0.001
Surgery	0 (0)	11 (55)	< 0.001

*mean/SD: Standard deviation; T-test; other items Chi-square test.
MBC: mean bladder capacity; PMR: post-micturition residue; UTI: urinary tract infection.

vesicoureteral reflux, higher PMR, increased detrusor pressure, lower peak flow rates, and were more likely to undergo surgery than those with smaller diverticula (< 30 mm). These findings emphasize the clinical importance of diverticula size in the presentation and management of the condition[10].

The association between bladder diverticula size and UTIs is particularly noteworthy. As our data suggest, UTIs are significantly more frequent in patients with larger diverticula. This is consistent with previous literature suggesting that urinary stasis within the diverticula facilitates bacterial growth, leading to an increased susceptibility to UTIs[2,8]. Moreover, it is well-established that UTIs are a common complication of bladder diverticula, particularly in children[2,10].

Our findings also demonstrated that patients with larger diverticula had significantly higher rates of upper UT dilatation and vesicoureteral reflux. Previous research has indicated that larger bladder diverticula can cause bladder outlet obstruction, which leads to increased intravesical pressure and can contribute to the development of upper UT dilatation and vesicoureteral reflux[5,10,11]. This further underscores the importance of bladder diverticula size in clinical outcomes.

The need for surgical intervention was another significant difference between the two groups. The larger diverticula group had a higher incidence of surgery compared to those with smaller diverticula. Surgery was more commonly needed in patients with larger bladder diverticula due to an increased likelihood of complications[11,12].

One limitation of our study is its retrospective nature, which may introduce selection bias. In addition, our sample size was relatively small, which might limit the generalizability of our findings. Despite these limitations, our study provides important information that could guide clinicians in the management of pediatric patients with primary bladder diverticula.

Conclusion

Our study suggests that bladder diverticula size is a significant factor in the clinical presentation and management of primary bladder diverticula in

pediatric patients. These findings highlight the need for further studies to establish clear guidelines for the management of this condition, particularly regarding the optimal time for surgical intervention.

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Conflicts of interest

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Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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ORIGINAL ARTICLE

Pentafecta evaluation in robot-assisted radical prostatectomy by risk group

Evaluación de pentafecta en prostatectomia radical asistida por robot por grupo de riesgo

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Abstract

Objetivo: *Radical prostatectomy is a therapeutic option in organ-confined prostate cancer. As the development of robotic systems progresses, the approach with this technology has begun to impact the functional and oncological outcomes of urological patients. The objective is to report the rate of pentafecta in patients undergoing robot-assisted radical prostatectomy (RARP) stratified by risk groups.* **Method:** *Retrospective, observational, descriptive study from 2013 to 2020 that included 112 patients undergoing RARP.* **Results:** *A rate of pentafecta at 12 months of follow-up of 35.7% (n = 40) was obtained. In the subanalysis by risk groups, at 1-year follow-up, was obtained an index of 43% (n = 26), 26% (n = 9) and 22% (n = 4) in low-, intermediate-, and high-risk patients, respectively.* **Conclusions:** *Prostatectomy showed functional and oncological results similar to those reported in the literature with robotic approach, regardless of the risk group for prostate cancer.*

Keywords: *Prostate cancer. Robotic surgery. Urology.*

Resumen

Objetivo: *La prostatectomía radical es la alternativa terapéutica de elección en el cáncer de próstata confinado al órgano. Conforme avanza el desarrollo de los sistemas robóticos, el abordaje con esta tecnología ha comenzado a impactar en los desenlaces funcionales y oncológicos de los pacientes urológicos. El objetivo es reportar el índice de pentafecta en pacientes sometidos a prostatectomía radical asistida por robot (PRRA) estratificados por grupos de riesgo.* **Método:** *Estudio retrospectivo, observacional, descriptivo, de 2013 a 2020, que incluyó 112 pacientes sometidos a PRAR.* **Resultados:** *Se obtuvo un índice de pentafecta a 12 meses de seguimiento del 35.7% (n = 40). En el subanálisis por grupos de riesgo, al año de seguimiento, se obtuvieron unos índices del 43% (n = 26), el 26% (n = 9) y el 22% (n = 4) en los pacientes de bajo, intermedio y alto riesgo, respectivamente.* **Conclusiones:** *La prostatectomía demostró resultados funcionales y oncológicos similares a lo reportado en la literatura con abordaje robótico independientemente del grupo de riesgo del cáncer de próstata.*

Palabras clave: *Cáncer de Próstata. Cirugía robótica. Urología.*

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Introduction

Prostate cancer is the second most common oncological disease among men older than 50 years and the sixth leading cause of mortality in this population group, becoming a serious problem of public health worldwide[1,2].

The clinical spectrum of the disease is diverse. In its initial stages, when the disease is confined to the prostate gland, there are multiple treatment modalities, with radical prostatectomy (surgical removal) offering the best rates of cancer-specific survival and disease-free survival[3-5].

Radical prostatectomy as a therapeutic option for managing prostate cancer can be performed using open, laparoscopic, or robot-assisted approaches, being oncological outcomes very similar. However, there are significant differences in terms of functional outcomes and perioperative complications that favor robot-assisted surgery, making it a safer, more effective alternative with better satisfaction rates reflected in the patients' quality of life[6,7].

The introduction of robotic systems in the field of urology has allowed for the optimization of the management of patients with prostate cancer, thanks not only to the optical system that provides 3D vision and the ergonomics it provides to the surgeon but also to the freedom of movement that the identification and preservation of anatomical structures provides allowing nerve preservation and helping us preserve erectile function and urinary continence without sacrificing oncological control[8].

The beginning of the 21st century started a technological revolution in our discipline, and robotic systems have continued to advance since their inception. However, their safety and efficacy profile still needs to be evaluated, which is why various groups have investigated parameters to achieve this.

Regarding prostate cancer and robot-assisted surgery, in 2003, Salomon et al.[9] developed the first concept they called "trifecta," to evaluate the efficacy profile of robot-assisted radical prostatectomy (RARP), which included: 1) postoperative biochemical control, 2) urinary continence, and 3) preserved erectile function.

The trifecta concept has some limitations that do not allow for adequate evaluation of the overall results of RARP. For example, it does not consider perioperative complications, meaning that a patient could require a transfusion during RARP and still meet the operational definition.

Therefore, in 2011, Patel et al.[10] redefined the objectives of RARP in prostate cancer and added the absence of perioperative complications and negative surgical margins to revolutionize the concepts of safety, efficacy, and oncological control. Since then, oncological, and functional outcomes of patients diagnosed with prostate cancer undergoing radical prostatectomy, regardless of the approach, are reported using the "pentafecta" concept, which includes the following:

- Perioperative complications: reported according to the standardized Clavien-Dindo classification system[11] as minor (grades I and II), or major (grades III, IV, and V) complications.
- Negative surgical margins: absence of neoplastic cells in the surgical bed. It is the most important independent predictor of biochemical and local recurrence, and metastasis. According to the scientific medical literature currently available, it is inversely proportional to the learning curve and the number of cases performed each year per hospital center.
- Urinary continence: defined as the ability to avoid involuntary urinary leaks after removal of the transurethral catheter. Evaluation can be subjective, based on the need to use protectors to remain dry, or with validated tools such as the International Consultation Questionnaire Urinary Incontinence Short Form (ICIQ-UISF).
- Erectile function: the ability to achieve and maintain an erection with erotic stimulation that allows for satisfactory sexual intercourse for the patient and his partner. It is evaluated using standardized questionnaires, such as the International Index of Erectile Function (IIEF-5), or the Sexual Health Inventory for Men (SHIM).
- Biochemical control: defined as an increased prostate-specific antigen (PSA) > 0.2 ng/mL in 2 consecutive measurements after RARP.

In the last decade, various groups have tried to demonstrate the safety and efficacy profile of RARP with various associated technique variants (anterior, posterior, lateral, nerve-sparing, etc.) based on the pentafecta concept, making robot-assisted surgery the best option to achieve oncological control and optimize the quality of life of patients with prostate cancer[6,12-14].

The population diagnosed with prostate cancer in Mexico differs from reality in other parts of the world. Although sometimes prostate cancer is found in the prostate gland, there is a high risk for regional or

systemic metastatic activity, as well as more aggressive cellular components[15]. Added to the limited accessibility to robot-assisted surgery systems, reports on functional and oncological outcomes are scarce and incomplete, which limits the acceptance of the utility of RARP among the urological community.

In the Mexican scientific medical literature, there are only 2 partial reports of pentafecta. In the first report, from a hospital in the south of Mexico City, a rate of complications of 29% has been reported, with rates of positive surgical margins and urinary continence (3 months) of 63% and 57%, respectively; biochemical control and erectile function post-RARP were not reported, making the overall evaluation of pentafecta virtually impossible[15]. The second report from a Mexican naval hospital reported rates of positive surgical margins, urinary incontinence, erectile dysfunction, and biochemical complications of 45.8%, 91%, 53%, and 14.6%, respectively; perioperative complications were not reported, also making the evaluation of pentafecta impossible[16].

The objective of our research is to report the oncological and functional outcomes, and perioperative complications, of patients with organ-confined prostate cancer undergoing RARP stratified by risk groups.

Method

This was a retrospective, observational, descriptive study conducted from 2013 from 2020, using clinical data from the health records of patients diagnosed with clinically localized prostate cancer undergoing RARP. Inclusion criteria were a diagnosis of clinically localized prostate cancer, initial treatment with RARP, and a 12-month clinical and biochemical control. Exclusion criteria were metastatic prostate cancer, therapies prior to RARP, inability for intraoperative nerve preservation, and need for adjuvant treatment to RARP. A descriptive study was conducted, obtaining simple frequencies and measures of central tendency.

Results

A total of 112 patients undergoing RARP from 2013 through 2020 were included. Their mean age was 63 years, with an initial PSA of 13.3 ng/mL. A total of 93% (n = 104) were in clinical stage T1. The mean surgical time was 199 minutes, and the conversion rate was 0%. The mean intraoperative bleeding was 357 mL, and the blood transfusion rate was 6% (n = 7). The rate of complications was 10.7%, all being Clavien-Dindo I-II (n = 12). Bilateral nerve preservation was performed in 70% of patients (n = 79) and unilateral nerve preservation in 19% (n = 22). The mean length of stay was 3.1 days, and the duration of transurethral catheterization, 5.6 days. All clinical and surgical characteristics are shown in table 1.

Pathology reports documented positive surgical margins in 22.3% (n = 25). Immediate biochemical control was achieved in 88.4% (n = 99); subsequently, 89.3% (n = 100) at 3 months, 90.2% (n = 101) at 6 months, and 80.4% (n = 90) at 12 months.

Continence rates were 96.4% (n = 108) immediately after transurethral catheter removal, 95.5% (n = 107) at 3 months, 98.2% (n = 110) at 6 months, and 99.1% (n = 111) at 12 months. Erectile function was present in 61.5% (n = 69) at 3, 6, and 12 months.

Overall, pentafecta rates in patients undergoing RARP were 39% (n = 44) at 3 and 6 months, and 35.7% (n = 40) at 12 months. Functional and oncological outcomes at 3, 6, and 12 months are shown in table 2.

In low-risk patients, unilateral nerve preservation was achieved in 18% (n = 11) and bilateral nerve preservation in 68% (n = 41); in intermediate-risk patients, unilateral nerve preservation was achieved in 24% (n = 8) and bilateral nerve preservation in 74% (n = 25); and in high-risk patients, unilateral nerve preservation was achieved in 28% (n = 5) and bilateral nerve preservation in 61% (n = 11).

Finally, in the subgroup analysis by risk groups, pentafecta was achieved in 43% (n = 26) of low-risk patients, 26% (n = 9) of intermediate-risk patients, and 22% (n = 4) of high-risk patients at the 12-month follow-up (Table 3).

Discussion

We presented the results of the first cohort of Mexican patients undergoing RARP for prostate cancer and the pentafecta rates achieved through this approach. At the 12-month follow-up, the rates of continence, erectile function, and biochemical control were 99.1%, 61.5%, and 80.4%, respectively. The complication-free rate was 89.3%, and the positive surgical margins-free rate was 77.7%. Our 12-month pentafecta rate was 35.7%.

Overall, our results are debatable compared to what has been previously reported in the scientific medical literature. We have sufficient follow-up to compare the outcomes of prostate cancer patients. Individually

Table 1. Clinical and procedural characteristics of patients undergoing robot-assisted radical prostatectomy for prostate cancer.

Age	**63 years**		
Initial PSA, mean	13.3 ng/mL		
Gleason score (biopsy), n (%)	ISUP 1 (G 6): 61 (54.4%)	ISUP 2-3 (G 7): 35 (31.2%)	ISUP 4-5 (G 8, 9, 10): 16 (14.4%)
Clinical state, n (%)	≤ T2: 109 (97.3%)	≥ T3: 3 (2.7%)	
Risk (D'Amico), n (%)	Low: 60 (53%)	Intermediate: 34 (30%)	High: 18 (16%)
Surgical time, mean	199 minutes		
Bleeding, mean	357 mL		
Blood transfusion, n (%)	7 (6%)		
Conversion to open surgery, n (%)	0 (0%)		
Complications (Clavien-Dindo), n (%)	I-II: 12 (10.7%)	III-IV: 0 (0%)	V: 0 (0%)
Positive surgical margins, n (%)	25 (22.3%)		
Pathological state, n (%)	pT2: 85 (75.8%)	pT3: 27 (24.1%)	pT4: 0 (0%)
Length of stay, mean	3.1 days		
Duración de sonda transuretral, media	5.6 days		

ISUP, International Society of Urological Pathology; PSA, prostate specific antigen.

Table 2. Functional and oncological outcomes in our series

	Immediate	**3 months**	**6 months**	**12 months**
Erectile function, n (%)	69 (61.5%)	69 (61.5%)	69 (61.5%)	69 (61.5%)
Continence, n (%)	108 (96.4%)	107 (95.5%)	110 (98.2%)	111 (99.1%)
Biochemical control (PSA), n (%)	99 (88.4%)	100 (89.3%)	101 (90.2%)	90 (80.4%)
Pentafecta, n (%)	47 (42%)	44 (39.3%)	44 (39.3%)	40 (35.7%)

PSA, prostate specific antigen.

Table 3. Pentafecta results by risk groups of prostate cancer

Low risk (n = 60)		**Intermediate risk (n = 34)**	**High risk (n = 18)**	**Total (n = 112)**
Pentafecta, n (%)	26 (43%)	9 (26%9)	4 (22%4)	39 (35%39)
Complications, n (%)	8 (13%)	4 (12%)	0 (0%)	12 (11%)
Negative surgical margins, n (%)	50 (83%)	22 (65%)	15 (83%)	87 (77.6%)
Biochemical control, n (%)	54 (90%)	25 (74%)	11 (61%)	90 (80.4%)
Erectile function, n (%)	42 (70%)	20 (59%)	7 (39%)	69 (61.5%)
Continence, n (%)	59 (98%)	34 (100%)	18 (100%)	111 (99%)

speaking, strictly regarding continence, our results are superior to those of the series by Patel et al.[10] (96%), Ou et al.[12] (98%), and Ihsan-Tasci et al.[6] (96%). Regarding the rates of complication and the oncological outcomes reported (positive surgical margins and biochemical recurrence-free rates), our results are within the average of the series provided by Anastasis et al.[9], and Gárate et al.[13]. However, in terms of erectile function,

Table 4. Pentafecta report of patients undergoing robot-assisted prostatectomy worldwide

Authors	n	Clinical state (%) (T1/T2)	Low/ Intermediate/ High risk (%)	Follow-up (months)	Continence (%)	Erectile function (%)	Biochemical relapse-free rate (%)	Complication-free rate (%)	Negative surgical margins (%)	Pentafecta (%)
Patel et al.[10]	332	92.7/7.3	67.2/28.9/3.9	12	96.4	89.8	96.4	93.4	90.7	70.8
Anastasis et al.[9]	136	-	-	12	90.4	66.2	95.6	85.3	84.6	45.6
Gárate et al.[13]	100	-	54.3/31.3/14.3	12	87.5	59.5	87.5	81.1	79.2	-
Ou et al.[12]	230	58.7/41.3	-	28	98.3	86.1	92.6	93.9	77	60.4
Ihsan-Tasci et al.[6]	334	-	59/32.9/8.1	12	96.7	74.5	96.7	94	89.3	-
Soto et al.[16]	48	12.5/70	52/29/19	6	91.3	53.5	85.4	67.9	54.2	-
Herrera et al.[15]	35	-	12/16/4	12	100	57	94.3	79	78	-
Corona et al.	112	93/4/2	53/30/16	12	99.1	61.5	80.4	89.3	77.7	35.7

we presented worse results (61.5%) compared to those reported by Patel et al.[10] (89%), Ou et al.[12] (86%), and Ihsan-Tasci et al.[6] (74%). This can be explained by the proportion of patients in our series with some degree of pre-existing erectile dysfunction, pre-existing comorbidities (diabetes mellitus, hypertension, arteriosclerosis, etc.), elevated initial PSA levels, and unfavorable conditions (Gleason score, digital rectal examination, risk group, etc.).

Overall, the pentafecta rate presented in our series is lower than the most important international series reported (Patel et al.[10], 70.8%), but it is the only series in Mexico presenting individual and combined functional and oncological outcomes, which is very relevant. Table 4 illustrates the main reports in the scientific medical literature currently available on pentafecta in RARP.

In our setting, there are reports of isolated functional and oncological outcomes in the last 5 years of patients undergoing RARP. Comparatively, our results are individually better (continence, erectile function, biochemical control, complications, and surgical margins) than those reported by Soto et al.[16] and Herrera et al.[15], and we are the only ones reporting the pentafecta rate.

Finally, our study has some important limitations. The first one being its retrospective design; secondly, the high prevalence of comorbidity in our series; and thirdly, the relatively short follow-up, which we propose to extend to confirm the oncological results and achieve a positive impact on disease-free survival and cancer-specific survival through adequate biochemical control. However, we perform an analysis by risk groups, which is inversely proportional to a higher risk of positive surgical margins to achieve nerve preservation, which gives us in-depth information on each of these areas, exposing the risk of preservation despite the robotic haptic system. Additionally, we have an objective evaluation of functional outcomes, as it was performed using standardized surveys (SHIM for erectile function and the PAD test validated by Ahlering et al.[17]); strengths of our research that minimize the relativity of functional results.

Conclusions

Our study presents an overall pentafecta rate in patients undergoing RARP of 35.7%, a rate that can be optimized over time through better patient selection, disease identification at earlier stages, and exceptional technical development during nerve preservation.

Standardization of outcomes in the context of robotic surgery is crucial to consolidate this approach as the one of choice, as functional and oncological outcomes are promising in the short and medium term in expert hands.

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Conflicts of interest

None declared.

Ethical disclosures

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

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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ORIGINAL ARTICLE

The value of endoscopic duodenal papilloplasty with titanium clip in improving post-operative complications of choledocholithiasis

El valor de la papiloplastia duodenal endoscópica con clip de titanio en la mejora de las complicaciones postoperatorias de la coledocolitiasis

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Abstract

Objective: *To investigate the value of endoscopic duodenal papillary sphincterotomy combined with balloon dilatation in the treatment of duodenal papilloplasty with titanium clip after choledocholithiasis in post-operative complications.* **Materials and methods:** *One hundred and twenty-five patients (69 males and 56 females) with a median age of 65 (32-81) years were included. The treatment plan was randomly divided into Group A (n = 59) and Group B (n = 66) according to the random number table. Patients in Group A were treated with endoscopic sphincterotomy (EST) combined with endoscopic papillary large balloon dilation (EPLBD), followed by a titanium clip for duodenal papilloplasty and then indwelling nasobiliary drainage, whereas those in Group B were treated with EST combined EPLBD to remove stones and then indwelling nasobiliary drainage.* **Results:** *In patients with choledocholithiasis or with anatomical changes that make stone extraction difficult, this prospective study attempted to perform duodenal papilloplasty with titanium clips after EST and EPLBD lithotripsy to compare and observe post-operative papillary healing, biliary reflux, and complication rates.* **Conclusions:** *The use of endoscopic duodenal papilloplasty with a titanium clip can improve biliary reflux after lithotripsy and reduce the incidence of post-operative cholangitis complications.*

Keywords: *Titanium clip. Plastic surgery of duodenal papilla. Common bile duct stones. Complication. Cholangitis. Biliary tract reflux.*

Resumen

Objetivo: *Investigar el valor de la esfinterotomía papilar duodenal endoscópica combinada con dilatación con balón en el tratamiento de la papiloplastia duodenal con clip de titanio después de coledocolitiasis en complicaciones postoperatorias.* **Materiales y métodos:** *Se incluyeron un total de 125 pacientes (69 hombres y 56 mujeres) con una mediana de edad de 65 (32-81) años. Los pacientes del Grupo A se trataron con esfinterotomía endoscópica (EST) combinada con dilatación papilar endoscópica con balón grande (EPLBD), seguida de clip de titanio para papiloplastia duodenal y luego drenaje nasobiliar permanente, mientras que los del Grupo B se trataron con EPLBD combinado con EST para eliminar cálculos y luego drenaje nasobiliar permanente.* **Resultados:** *En pacientes con coledocolitiasis o con cambios anatómicos que dificultan la extracción de cálculos, este estudio prospectivo intentó realizar papiloplastia duodenal con clips de titanio después de litotricia EST y EPLBD para comparar y observar la cicatrización papilar postoperatoria, el reflujo biliar y las tasas de complicaciones.*

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Conclusión: *El uso de papiloplastia duodenal endoscópica con clips de titanio puede mejorar el reflujo biliar después de la litotricia y reducir la incidencia de complicaciones de colangitis postoperatorias.*

Palabras clave: *Clip de titanio. Cirugía plástica de la papila duodenal. Cálculos del conducto biliar común. Complicación. Colangitis. Reflujo del tracto biliar.*

Introduction

Endoscopic sphincterotomy (EST) is an important endoscopic treatment modality based on the diagnostic endoscopic retrograde cholangiopancreatography (ERCP) technique and is widely used for the treatment of choledocholithiasis[1], and its clinical safety and efficacy are widely recognized[2,3]. However, EST requires a full or partial incision of the sphincter of Oddi, which damages its structure and function to a certain extent, and post-operative complications such as cholangitis, pancreatitis, and bleeding can occur[4]. The endoscopic papillary balloon dilation (EPBD) procedure allows for greater preservation of Oddi sphincter function. Many studies[5,6] have shown that EST combined with endoscopic papillary large balloon dilation (EPLBD) is effective in the treatment of choledocholithiasis and has the advantage of preserving papillary sphincter function to a greater extent and reducing the incidence of complications. However, post-operative complications, such as enterobiliary reflux, pancreaticobiliary reflux, infection, and bleeding were still present in patients who underwent EST combined with EPLBD for choledocholithiasis. Therefore, how to effectively improve the function of the sphincter of Oddi and further reduce the incidence of post-operative complications still needs to be studied and discussed in depth. In this study, we used EST combined with EPLBD lithotripsy to treat choledocholithiasis and applied titanium clips to perform duodenal papilloplasty to observe the success rate of lithotripsy, post-operative papilla healing, X-ray dilute barium to detect biliary reflux, and analyze the incidence and extent of complications such as cholangitis, pancreatitis, bleeding, and perforation in patients.

Materials and methods

General information

Patients who underwent ERCP lithotripsy at the Second Hospital of Nanjing Medical University and the Second Hospital of Xuzhou Medical University Gastrointestinal Endoscopy Center from June 2015 to June 2020 were screened. A total of 125 patients were included, 69 men and 56 women, with a median age of 65 (32-81) years. Among them, 27 had combined gallbladder stones and 38 had combined parapapillary diverticula. The inclusion criteria were as follows: (1) Pre-operative diagnosis of choledocholithiasis by computed tomography (CT) or magnetic resonance cholangiopancreatography (MRCP); (2) stone diameter ≥ 1.4 cm. The exclusion criteria were as follows: (1) Combination of intrahepatic bile duct stones; (2) upper gastrointestinal stenosis or lower common bile duct stenosis; (3) combination of acute cholangitis; (4) poor cardiopulmonary function unable to tolerate ERCP procedure; (5) severe allergy to iodine contrast agent or multiple drugs; (6) previous history of combined ERCP operation; (7) previous history of combined PTCD operation; (8) significant abnormalities in coagulation function; (9) combination of other contraindications to endoscopic treatment. The criteria of surgeons were as follows[7]: (1) Experienced with 4-5 years of experience and at least 200 ERCP procedures per year; (2) standard ERCP conforming to normal anatomy with ≥ 95% successful intubation rate. This study was approved by the Hospital Ethics Committee of The Second Affiliated Hospital of Xuzhou Medical University, this study was registered in the Chinese Clinical Trial Registry (ChiCTR) under number ChiCTR1900027465, and the patients or their family members signed an informed consent form.

Instruments and materials

Olympus TJF-260V electronic duodenoscope and STO725 contrast catheter were used. The contrast agent was Hengrui iodofol (50 mL). GEC 9900Elite X-ray machine, barium, 14 mm*40 mm dilatation balloon (balloon length 40 mm, maximum diameter after filling 14 mm), 16 mm*60 mm dilatation balloon (balloon length 60 mm, maximum diameter after filling 16 mm), 18 mm*60 mm dilatation balloon (balloon length 60 mm, maximum diameter after filling 18 mm), stent, and titanium clip (Angelus) were used.

Treatments and groups

Pre-operative preparation: Patients underwent a complete blood routine test, coagulation function

test, hepatitis immunity test, virus test, and ECG. An imaging scan (CT/MRCP) was also performed to further clarify the patient's condition. Anticoagulation and antiplatelet drugs were discontinued 1 week before surgery. Patients fasted 6-8 h before surgery.

Grouping: Patients who met the selection criteria were randomly divided into two groups: Group A and Group B, using the random number table method by numbering them according to the order of the time they were admitted.

Group A (study group): Duodenal papilloplasty was applied. Patients were placed in the left lateral position and were monitored for ECG, blood pressure, pulse rate, and oxygen saturation.

After sedation with diazepam and pethidine hydrochloride, enter the scope to find the papilla in the descending duodenum, selective intubation and contrast (iophorol) under the guidance of a zebra guidewire, confirm successful intubation, then place the guidewire and perform duodenal papillotomy. The papillary sphincter was dilated with a combined large balloon, followed by lithotripsy basket or balloon extraction, re-imaging to confirm the removal of the stone, leaving the guidewire in place, and then applying a titanium clip to close the incised duodenal papilla along the edge of the incision for shaping. According to the size and location of the incision, combined with the surrounding tissue damage, bleeding, and other conditions to determine the number of titanium clips applied. A nasobiliary tube was routinely placed for drainage, the drainage of the nasobiliary tube after surgery was observed, the amount of bile drained, and the color and properties of the drainage fluid were recorded. The nasobiliary drainage time was about 3-5 days. When the patient's clinical symptoms improved, the relevant indexes were normal, and no obvious stone shadow was observed on the imaging, the drainage tube was then removed. Patients fasted for 24 h after surgery and were observed for clinical symptoms and vital signs. Blood routine test and blood amylase analysis were performed at 3 h after surgery. Blood routine, blood amylase, bilirubin, transaminase, and C-reactive protein were measured at 24 h after surgery.

Group B (control group): After the stone was removed by EST combined with EPLBD, a nasobiliary drain was routinely left in place. After surgery, the nasobiliary drainage was observed, the amount of bile drained, and the color and properties of the drainage fluid were observed. The drainage tube was then removed according to the condition of the patient. Patients fasted for 24 h after surgery. The observation index and examination were the same as those in Group A.

Data collection

- Blood routine test, analysis of blood amylase, C-reactive protein, and liver function were performed before, 3 h after surgery, and 24 h after surgery.
- The clinical symptoms included abdominal pain, bloating, nausea, vomiting, black stool, fever, jaundice, itchy skin, etc.
- The success rate of lithotripsy, number of days in hospital, and cost.
- The incidence and extent of intraoperative (bleeding) and post-operative complications (bleeding, perforation, biliary ductitis, pancreatitis, and stone recurrence) at 1 week, 1 month, and 12 months.
- Post-operative follow-up 1 week, 1 month, and 1 year, X-ray detection of titanium clip detachment
- Post-operative follow-up at 1 week, 1 month, and 1 year, X-ray dilute barium meal to detect gas and barium reflux to the biliary tract, which assisted in determining post-operative changes in duodenal papillary sphincter function.
- Endoscopy 1 month and 1 year after surgery to observe the healing of the post-operative duodenal papilla incision and the length of the opening.

Complications

- Gastrointestinal bleeding: intraoperative bleeding refers to active bleeding seen intraoperatively under the endoscope, with a large amount that cannot be stopped by itself and requires the application of electrocoagulation, titanium clips, or drugs to stop bleeding; post-operative bleeding refers to bleeding that occurs hours to weeks after the operation and can be as late as more than 2 weeks after the operation, and the patient can be accompanied by blood in the stool, black stool, vomiting blood. and other manifestations of gastrointestinal bleeding, which can be accompanied by a progressive decrease in hemoglobin, or confirmed by endoscopy.
- Post-operative cholangitis: clinical signs and symptoms of new or worsening abdominal

pain, fever, jaundice, systemic toxic symptoms or infectious shock, combined with abnormal liver function, elevated bilirubin, bile duct dilatation, and other tests, and excluding cholecystitis and other infections.

– Post-operative pancreatitis: new or worsening abdominal pain with more than 3-fold elevation of serum amylase, or higher than the upper limit of normal for 24 h, supported by imaging.
– Cholecystitis: fever, abdominal pain, elevated inflammatory markers, and imaging suggestive of an enlarged gallbladder or with effusion of the gallbladder fossa.
– Gastrointestinal perforation: imaging reveals the presence of free gas or subcutaneous emphysema under the diaphragm or retroperitoneum.

Follow-up

Outpatient or telephone follow-up was used, with a follow-up period of 12 months.

Statistical analysis

SPSS 16.0 statistical software was used for data analysis. Data were expressed as median or mean ± standard deviation. The t-test was used for measurement data. The χ^2 test was used for count data. $p < 0.05$ was considered a statistically significant difference.

Results

General information

The differences in age, stone size, number, white blood cell count, total bilirubin, C-reactive protein, and operation time for stone extraction between the two groups were not statistically significant ($p > 0.05$) (Table 1).

Lithotripsy success rate

The success rates of lithotripsy in Group A and Group B were 88.14% (52/59) and 86.36% (57/66), respectively, with no statistically significant difference ($p > 0.05$). For patients in both groups who were unsuccessful in stone extraction, biliary stenting or surgical transfer was performed according to the wishes of the patients and their families after communication about their conditions, with no statistically significant differences ($p > 0.05$).

Symptom remission rate

Patients showed better symptom relief within 1 week postoperatively. The symptom remission rates of abdominal pain, bloating, nausea, and vomiting in both groups (86.44% [51/59] in Group A vs. 81.82% [54/66] in Group B) were not statistically significant ($p > 0.05$); the symptom remission rates of jaundice in both groups (83.05% [49/59] in Group A vs. 81.82% [54/66] in Group B) were not statistically significant ($p > 0.05$).

Hospitalization time and cost

The hospitalization costs of patients in Group A and Group B were 21,576.59 ± 2217.76 and 22016.29 ± 2552.57 (CNY), respectively. The hospitalization cost of Group A was slightly lower than that of Group B, the difference was not statistically significant ($p > 0.05$). The hospitalization time of patients in Groups A and B was 6.5 days and 7.6 days, respectively, and the difference was not statistically significant ($p > 0.05$).

X-ray detection of titanium clip detachment at 1 week, 1 month, and 1 year after surgery

In Group A, 59 patients with a total of 120 titanium clips were applied, 51 patients (with a total of 103 clips) were X-rayed 1 week after surgery, and 7.77% (8/103 clips) were dislodged. A total of 45 patients (with a total of 89 clips) were X-rayed 1 month after surgery and 80.90% (72/89 clips) were dislodged; 22 patients (with a total of 45 clips) were X-rayed 1 year after surgery in 22 patients (45 titanium clips), all titanium clips were dislodged.

Biliary gas/barium reflux detected by X-ray dilute barium meal at 1 week, 1 month, and 1 year after surgery

At 1 week, 1 month, and 1 year postoperatively, Group A showed gas reflux of 15.69% (8/51), 8.89% (4/45), and 4.55% (1/22) and barium reflux of 5.88% (3/51), 2.22% (1/45), and 0% (0/22), respectively; Group B showed gas reflux of 19.23% (10/52), 17.78% (8/45), and 13.64% (3/22) and barium reflux of 13.46% (7/52), 13.33% (6/45), and 9.09% (2/22), respectively, during the same period. The incidence of gas and barium reflux in Group B was higher than that in Group A in the same post-operative period.

Table 1. General data of two patients

Groups	n	Gender (male/ female)	Medium age (range, years)	Stone diameter (mm)	Number of stones (n)	Diverticulum (n)	Gallbladder stones (n)	TBIL (umol/L)	WBC (10^9/L)	CRP (mg/L)	Operation time (min)
Group A	59	32/27	66 (36-81)	18 (14-30)	3.15 ± 1.57	18	14	125.57 ± 61.79	9.57 ± 5.98	56.57 ± 30.59	30.55 ± 17.69
Group B	66	37/29	63 (32-79)	16 (14-28)	3.03 ± 1.05	20	13	113.61 ± 59.57	9.29 ± 5.77	54.42 ± 31.57	30.67 ± 19.65
p-value		0.838	0.319	0.257	0.375	0.980	0.584	0.451	0.395	0.417	0.597

TBIL: total bilirubin; WBC: white blood cell count; CRP: C-reactive protein.

Table 2. Comparison of the incidence of post-operative complications between the two groups of patients

Groups	n	Early complications (within 1 month)					Long-term complications (12 months of follow-up)			
		Cholangitis	Hyperamylasemia	Pancreatitis (mild)	Intraoperative bleeding	Post-operative bleeding	Cholangitis	Cholangitis	Pancreatitis	Stone recurrence
Group A	59	0 (0%)	8 (13.56%)	2 (3.39%)	7 (11.86%)	0 (0%)	0 (0%)	1 (1.69%)	0 (0%)	7 (11.86%)
Group B	66	6 (9.09%)	11 (16.67%)	3 (4.55%)	9 (13.64%)	3 (4.55%)	1 (1.52%)	0 (0%)	1 (1.52%)	12 (18.18%)
p-value		0.029	0.629	1.000	0.767	0.246	1.000	0.472	1.000	0.326

Duodenoscopy at 1 month or 1 year after surgery

In Group A, the healing of the duodenal papilla incision was observed at 1-month and 1-year post-operative review, and the post-operative incision was healed, and the opening was not narrower than before. In Group B, the length of the duodenal papilla incision was observed to be slightly shorter than after surgery, the post-operative incision was slightly shortened, and the opening was larger than before. In Group B, the improvement of the incision length and opening was not obvious at 1-year post-operative review.

Comparison of post-operative complications

– Early complications: 0 cases (0%) of cholangitis, 8 cases (13.56%) of hyperamylasemia, 2 cases (3.39%) of mild pancreatitis, 7 cases (11.86%) of intraoperative bleeding and 0 cases (0%) of post-operative bleeding in Group A; 6 cases (9.09%) of cholangitis, including three cases of combined parapapillary diverticulum, in Group B. Post-operative patients presented with elevated body temperature and abdominal pain, combined with examination. In Group B, 6 cases (9.09%) had post-operative cholangitis, of which three cases had combined parapapillary diverticulum, postoperative temperature rise, and abdominal pain, combined with the examination, and the symptoms improved after treatment with intravenous application of sensitive antibiotics and unobstructed drainage; 11 cases (16.67%) had hyperamylasemia, 3 cases (4.55%) had mild pancreatitis, 9 cases (13.64%) had intraoperative bleeding, and 3 cases (4.55%) had post-operative bleeding, all of which improved after conservative medical treatment without complications such as perforation and severe pancreatitis.

The incidence of post-operative cholangitis complications in Group A was lower than that in Group B, and the difference was statistically significant ($p < 0.05$); the incidence of post-operative bleeding complications in Group A was lower than that in Group B, but the difference was not statistically significant ($p > 0.05$);

Figure 1. *Endoscopic sphincterotomy combined with endoscopic papillary large balloon dilation for stone removal.*

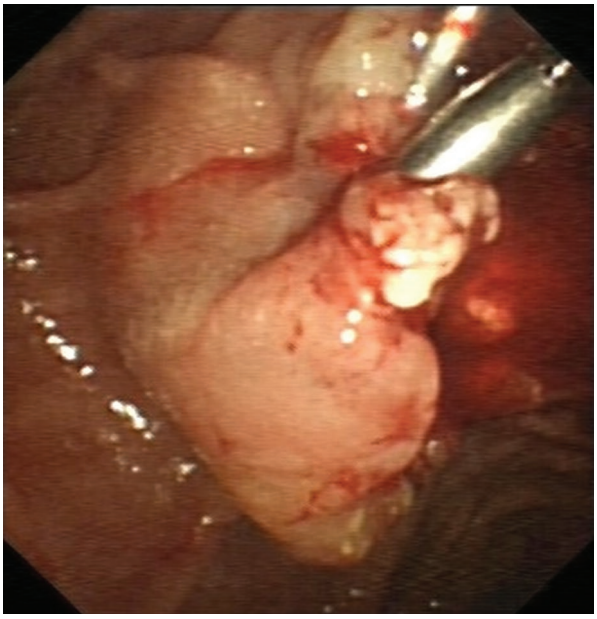

Figure 2. *Titanium clip for duodenal papilloplasty.*

the differences in the incidence of post-operative hyperamylasemia and pancreatitis (mild) in both groups were not statistically significant ($p > 0.05$), and the differences in the incidence of intraoperative bleeding complications in both groups were not statistically ($p > 0.05$) (Table 2).

– Long-term complications: 1 case (1.69 %) of biliary tract infection (cholecystitis); 0 cases (0%) of pancreatitis; 7 cases (11.86%) of stone recurrence, including 6 patients with combined gallbladder stones in Group A. 1 case (1.52%) of biliary tract infection (cholangitis) and 1 case (1.52%) of pancreatitis in Group B, all of which improved after conservative medical treatment; 12 cases (18.18%) of stone recurrence and eight of them were combined with gallbladder stones. Three patients in Group B had recurrent post-operative post-prandial abdominal pain with nausea and vomiting, which was diagnosed as bile reflux gastritis by gastroscopy. The differences in the incidence of post-operative biliary tract infection, pancreatitis, and stone recurrence between the two groups were not statistically significant ($p > 0.05$) (Table 2).

Discussion

With the development of medical technology, EST has become the main treatment option for common bile duct stones, but EST requires incision of the sphincter of Oddi, which damages its structure and function to a certain extent, and a variety of post-operative complications can occur. Compared with EST, EPBD can preserve the function of the Oddi sphincter to a greater extent and reduce the risk of complications such as bleeding[8]. However, it was reported that EPBD is more suitable for the application of smaller-diameter stones[9,10]. Previous studies[5,6] have shown the efficacy of EST combined with EPLBD in large-diameter common bile duct stones. However, as the balloon diameter increases in EPLBD, the sphincter of Oddi expands further and the deformability of the muscle fibers exceeds the load, which also causes complications of papillary dysfunction. Both papillary sphincterotomy and balloon dilation disrupt the function of the Oddi sphincter to varying degrees, and how to effectively improve the function of the Oddi sphincter after surgery and reduce the complication rate is the focus of this study. In patients with choledocholithiasis or with anatomical changes that make stone extraction difficult, this prospective study attempted to perform duodenal papilloplasty with titanium clips after EST and EPLBD lithotripsy to compare and observe post-operative papillary healing, biliary reflux, and complication rates.

The sphincter of Oddi usually surrounds the jugular abdomen of the common bile duct and the end of the pancreaticobiliary duct to maintain the pressure in the bile duct and pancreatic duct. After ERCP, the pressure gradient between the sphincter

of Oddi and the bile duct duodenum decreases or disappears, triggering the risk of enterobiliary reflux and pancreaticobiliary reflux, and the degree of reflux is influenced by the length of the incision and the function of the papilla. A previous study[11] has shown a strong relationship between reflux and cholangitis, biliary bacterial colonization/infection, and recurrence of biliary stones. In this study, through post-operative follow-up duodenoscopy and X-ray dilute barium examination, it was found that without statistical difference in incision length, the duodenal papilloplasty group had better incision healing than the control group, and the incidence of gas and barium biliary reflux was significantly decreased, analyzing that the application of titanium clip duodenal papilloplasty could reduce biliary reflux to some extent, and the possible mechanism was that duodenal papilloplasty could improve the coordinated movement of pylorus and duodenum to some extent.

The incidence of cholangitis, a common complication after EST, has been reported to be about 1-5%[12,13], mostly caused by reflux, poor drainage, and other factors. Stone diameter, number of stones, advanced age, combined gallbladder stones, and anatomical changes are also important risk factors for cholangitis after lithotripsy. With the increase of these factors, the incidence of biliary tract infection complications can reach 10.5%[14]. Therefore, effective prevention and treatment is also a key research direction for gastrointestinal endoscopists. The results of this study showed that no acute cholangitis occurred in the group with titanium clips for papilloplasty after surgery, and the incidence of cholangitis was reduced compared with the control group, with statistically significant differences. In this study, we compared two groups of patients who received ERCP again for the recurrence of stones and found that the incisions in the papilloplasty group had healed without significant stenosis and were well drained; the incisions in the control group were relatively larger compared to the papilloplasty group. These findings showed that duodenal papilloplasty promoted the healing of Oddi sphincter incision, improved the function of muscle fibers, promoted the recovery of its anti-reflux barrier function, effectively reduced post-operative biliary reflux, and reduced the incidence of post-operative cholangitis to a certain extent, suggesting that papilloplasty may have important application value in reducing the incidence of cholangitis after choledocholithiasis extraction of large stones.

Post-operative complications of cholangitis not only prolong the course of the disease, but also increase the pain, increase the economic burden, and the need for timely application of antibacterial drugs to control the disease; in recent years, with the widespread use of antibacterial drugs, bacterial resistance, and adverse reactions are increasing. The incidence of cholangitis in the control group in this study was slightly higher than the literature average and was analyzed in relation to factors such as large stone diameter, some combined gallbladder stones, and advanced age. No complications of acute cholangitis occurred in the study group after surgery, which not only effectively shortened the number of days of hospitalization, reduced the patients' pain, and promoted their early recovery, but also reduced the adverse drug reactions and the occurrence of secondary infections to a certain extent.

The smaller the incision, the lower the efficiency of the stone extraction operation and the success rate of stone extraction, but the larger the incision, the higher the risk of complications such as bleeding and perforation, for EST surgery for large bile duct stones. In this study, no patients with post-operative bleeding or perforation were seen in the duodenal papilloplasty group, suggesting that the use of titanium clips for duodenal papilloplasty can not only ensure the degree of papillary expansion but also reduce the risk of bleeding and perforation to a certain extent. We also found that when titanium clips are applied to perform papilloplasty, the clips can mostly fall off on their own after the wound heals, and even if the clips do not fall off for a long time in some patients, there are no obvious clinical symptoms and no special treatment is needed.

Previous studies[15,16] have shown that biliary tract infection, sphincter of Oddi dysfunction, cholestasis, abnormal bile composition, diverticula, and gallbladder stones are all high-risk factors for the recurrence of distant stones. Both EST and EPLBD can cause post-operative enterobiliary reflux, pancreaticobiliary reflux, or bacterial contamination of bile to some extent, increasing the risk of recurrent bile duct stones, reflux cholangitis, and even bile duct cancer.

Compared to EST, balloon dilation has the function of protecting the sphincter of Oddi and has some advantages in preventing stone recurrence[17]. In this study, the incision healing was better in the titanium-clamped duodenal papilloplasty group, and the post-operative stone recurrence rate was relatively slightly lower, but the difference in the post-operative stone recurrence rate between the two groups was not statistically significant.

The application of titanium clips for papilloplasty can restore the integrity of the sphincter structure to some extent, reduce the biliopancreatic duct complications secondary to sphincter function damage, reduce the incidence of bile duct reflux and cholangitis, and prevent stone recurrence to some extent.

Conclusion

The application of titanium clips for duodenal papilloplasty can promote papilla healing, reduce post-operative bile duct reflux and the incidence of post-operative cholangitis complications to a certain extent, and did not increase the recurrence rate of post-operative stones. The present study was limited by a small sample with a maximum follow-up of 1 year, and further validation in more prospective controlled studies is still needed for our analysis of whether there is an advantage in the rate of distant stone recurrence.

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Conflicts of interest

All authors have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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ORIGINAL ARTICLE

Review and analysis of the results of kidney transplantation programs in Mexico

Revisión y análisis de los resultados de los programas de trasplante renal en México

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Abstract

Objective: *To know, analyze and compare kidney transplant programs; considering the survival of recipients at 1 and 5 years, from hospitals in Mexico.* **Method:** *A systematic review was carried out whose search focused on the survival of kidney trans- plant recipients. All publications found in PubMed and Google from 1963 to 2021 were included. The expectation-maximization algorithm was applied, proposing a mixture of normals, and hierarchical grouping to establish if there is any type of pattern and determine if there is a difference between the percentages. of survival at 1 and 5 years between the groups formed.* **Results:** *Eight hospitals that published the survival of kidney transplant recipients were found. Survival rates ranged, at 1 year, from 94.7% to 100%, and at 5 years, from 85% to 96.2%. The methods used for their comparison indicated that there is a difference between survival at 1 and 5 years.* **Conclusions:** *In Mexico there is little information on the results of kidney trans- plant programs, and the information found shows great heterogeneity in said programs. Some strategies and actions are proposed to improve survival underreporting.*

Keywords: *Kidney transplant. Survival. Mexico.*

Resumen

Objetivo: *Conocer, analizar y comparar los programas de trasplante renal, considerando la supervivencia de los receptores a 1 y 5 años, en los hospitales en México.* **Método:** *Se realizó una revisión sistemática cuya búsqueda se centró en la supervivencia de los receptores de trasplante renal. Se incluyeron todas las publicaciones encontradas en PubMed y Google de 1963 a 2021. Se aplicó el algoritmo de expectation-maximization, proponiendo una mezcla de normales, y agrupamiento je- rárquico para establecer si hay algún tipo de patrón y determinar si hay diferencia entre los porcentajes de supervivencia a 1 y 5 años entre los grupos formados.* **Resultados:** *Se encontraron ocho hospitales que publicaron la supervivencia de los receptores de trasplante renal. Los rangos de las tasas de supervivencia fueron, a 1 año, del 94.7% al 100%, y a los 5 años, del 85% al 96.2%. Los métodos empleados para su comparación indican que hay diferencia entre la supervivencia a 1 y 5 años.* **Conclusiones:** *En México se tiene poca información sobre los resultados de los programas de trasplante renal, y la información encontrada muestra gran heterogeneidad en dichos programas. Se proponen algunas estrategias y acciones para mejorar el subregistro de supervivencia.*

Palabras clave: *Trasplante Renal. Supervivencia. México.*

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Introduction

In Mexico, the first kidney transplant was performed in 1963 at the Mexican Social Security Institute (IMSS)[1]. Since then, a total of 273 kidney transplant centers have been established, although only 122 of them are currently active. Currently, Mexico has a kidney transplant rate of 15.2 per million population (PMP), with a total of 58 668 kidney transplants performed from 1963 through 2021[2]. As of October 7th, 2022, there is a waiting list for kidney transplants of 15 411 individuals[3]. The National Transplant Registry was established back in 1984, and since 2000, a decentralized body under the Federal Public Administration, the CENATRA (National Transplant Center), has been responsible for regulating, coordinating, supporting, and promoting actions related to organ and tissue transplantation in Mexico[4]. Although CENATRA designed a form back in 2015 for tracking transplant patients, only the 1-year follow-up data of 953 kidney transplant recipients has been reported until 2016, with a survival rate of only 33%[5] of these patients. Subsequently, the National Transplant Registry Information System (SIRNT) was created, and from the second half of 2019, modules for reporting recipient and post-transplant graft survival were implemented in the SIRNT, which allowed for establishing information reporting obtained from monitoring their transplant recipient patients. However, as of February 3rd, 2022, only 1402 kidney transplant recipients had, at least, 1 survival report out of a total of 15 218 patients operated on from 2016 through 2021, representing information available for only 9.2% of patients transplanted during that time[2].

In general, all centers performing transplants consider the number of transplants performed as the main indicator of success. However, we should not dismiss that the only way to objectively know clinical success, and what kind of thing will eventually have an impact on the patients and their family, is the survival of the transplant recipient and the survival of the kidney graft; unfortunately, this information is not available from official sources, which is why we conducted this study to understand, analyze, and compare kidney transplant programs in hospitals in Mexico, considering the survival of kidney transplant recipients at 1 and 5 years.

Method

We conducted a systematic review on the survival of kidney transplant recipients in hospitals located in Mexico. All publications found in PubMed and Google up to December 2021 were included. Studies that did not report the 1 and 5-year survival of kidney transplant recipients or did not use the Kaplan-Meier estimator of the survival function as a non-parametric analysis technique were excluded.

Data analysis was performed using R statistical software[6]. The analysis conducted was exploratory due to the lack of necessary individual data for estimating survival functions, as well as the variance of these estimates via the Kaplan-Meier estimator. Two clustering techniques were used to analyze reported estimate values. The first technique was used to analyze the change between the reported values for year 1 and 5. This involved considering a mix of normal distributions for these differences. The second technique was hierarchical clustering[7].

Results

We found a total of 8 (6.5%) out of 122 hospitals active in kidney transplantation in Mexico that reported on the survival of kidney transplant recipients within their programs, with an overall 6545 kidney transplant recipients across these 8 hospitals. The mean number of transplants performed per hospital included in this study was 818, with a standard deviation (SD) of ± 677 and a range of 83 up to 1940 transplants performed. The mean period reported by these 8 hospitals was 17 years (SD, ± 13), ranging from 7 up to 24 years. The 1- and 5-year survival of patients reported in each of the 8 hospitals is shown in table 1.

The data analyzed are estimate values, according to the Kaplan-Meier method, of the survival function for 2 different time periods (1 and 5 years) reported in the publications included in this study[8-15]. We should mention that supplementary data was not found in the articles from which specific data for estimating the Kaplan-Meier survival function, such as patients at risk in each timeframe and censored patients, could be extracted. Therefore, the log-rank test—the most common technique for comparing survival curves—cannot be used. The log-rank test is, in fact, a chi-square technique that compares an observed parameter (sample survival curves) and an expected one (bringing all values into a single sample). The goal is to verify that each of these samples allows us to deduce that the differences between them are statistically significant or, on the contrary, can be attributed to chance.

Table 1. Survival of kidney transplant recipients per hospital

Hospital	No. of patients analyzed	Cumulative rate of patients currently alive		Period considered (years of follow-up)
		1 year	5 years	
UMA134 Unidad Médica de Alta Especialidad No. 134 del IMSS[8]	1940	100%	87%	1987-2011 (24 years)
CMN Centro Médico Nacional Siglo XXI[9]	1544	95%	91.8%	1991-2010 (19 years)
INCMNSZ Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán[10]	1000	94.9%	86.8%	1967-2011 (45 years)
HRAEB Hospital Regional de Alta Especialidad del Bajío[11]	837	95.4%	88.1%	2008-2016 (8 years)
IMT Instituto Mexicano de Trasplantes[12]	754	98.8%	96.2%	1999-2012 (13 years)
INCICH Instituto Nacional de Cardiología Ignacio Chávez[13]	292	95%	85%	2000-2007 (7 years)
HRAEV Hospital Regional de Alta Especialidad de Veracruz[14]	95	94.7%	85.2%	2006-2016 (10 years)
HUNL Hospital Universitario José E. González, Nuevo León[15]	83	98.8%	85.9%	2003-2011 (8 years)
Total	6545			

Therefore, as an alternative, we used an exploratory analysis of the reported estimate values for 1 and 5 years, as illustrated in figure 1. We should mention that these 2 values can be considered a rough approximation to the estimate survival function.

Based on the slope, we can see there are hospitals for which the values reported have similar variations; for example, the case of UMA134 and HUANL, or INCICH and HRAEB. To study the aforementioned, the slope of the line connecting the estimates is calculated. Considering that the point estimators of the survival function are asymptotically normal[16], and that the slope is a linear transformation of 2 of these, a mixed model of Gaussian distributions[7] is suggested to group hospitals based on their slope.

Figure 2 illustrates the density function adjusted using the expectation-maximization algorithm employing the library[17]. As we can see, in the case of the middle group, the estimate variance is large. With this, no pattern related to the number of participants in the study or the years in which it was conducted can be seen.

Therefore, hierarchical clustering was performed[7], which consists of forming groups among data based on the distance between them. Figure 3 illustrates the values of these data. This image can be considered an estimate of the position of hospitals based on their estimate survival function.

The size of the name in figure 3 is given by the following formula:

$$\frac{ns}{1000} + 0.05$$

where ns is the number of participants involved in the study. As we can see, although the number of study participants is similar across different hospitals, the value of estimates differs significantly. At least 3 types of records can be distinguished: those with high estimate values for both 1 and 5 years, those with high values for 1 year and low values for 5 years, and those with low values for both 1 and 5 years.

To study the existence of the mentioned groups, the hierarchical data clustering technique was used. This technique involves considering the progressive formation of groups, taking the distance between them as the criterion for union. The result obtained when using this technique is shown in figure 4. Since HRAEV and INCICH are the closest, these hospitals are grouped first. Subsequently, the HRAEB-INCMNSZ group is formed. The last group of 2 elements to form is HUANL-UMA134. Since the closest groups

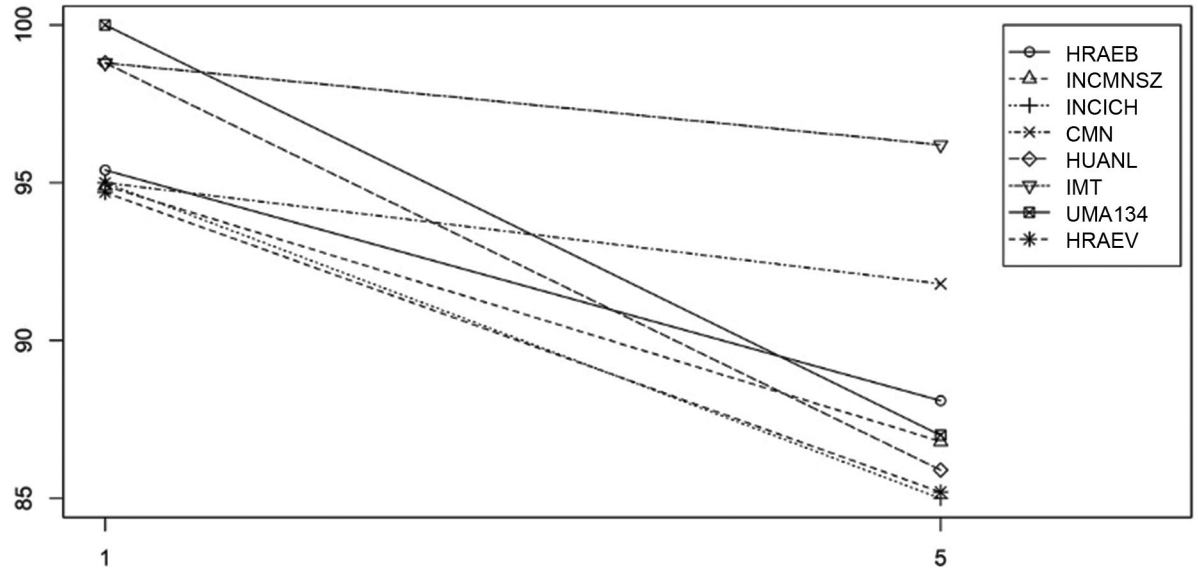

Figure 1. *Estimated values reported for 1 and 5 years.*

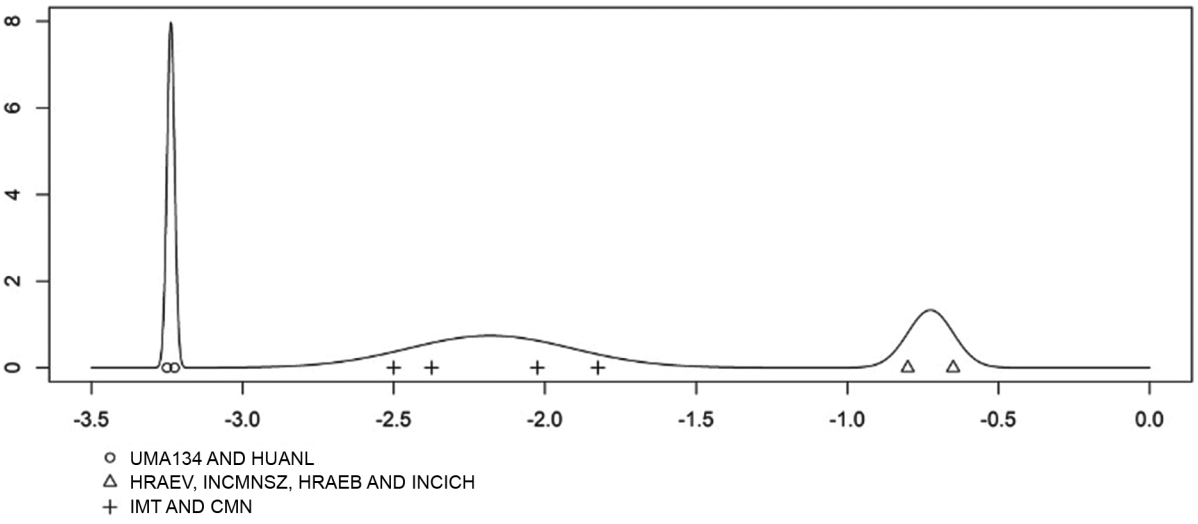

Figure 2. *Density adjusted using the expectation-maximization algorithm.*

are HRAEB-INCMNSZ and HRAEV-INCICH, the HRAEB-INCMNSZ-HRAEV-INCICH group is formed. Similarly, the other groups are formed by joining the closest ones.

Again, we should mention that the values of the variables associated with conducting the study do not seem to reveal any kind of pattern. This could be an indicator that there is, indeed, a real difference between the survival rates at 1 and 5 years among the formed groups. However, in the absence of complete data for the patients considered, a standard hypothesis test to study the difference between the reported values could not be performed.

Discussion

The results found in the 8 articles published on survival in kidney transplant recipients in hospitals located in Mexico included in this study[8-15] show a great heterogeneity in the activity of kidney transplant programs, with a mean number of transplants per hospital of 818, a standard deviation of ± 677, and a range of

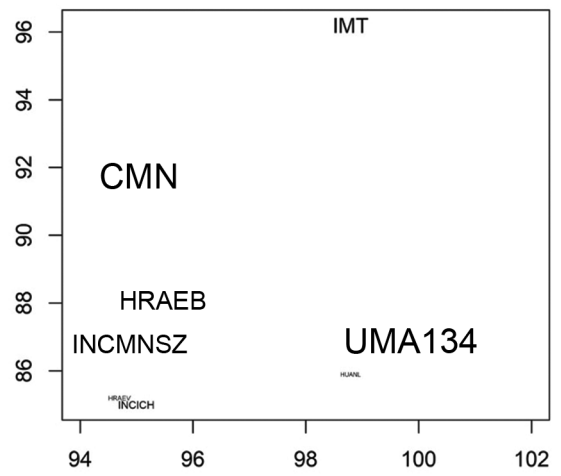

Figure 3. *Position of hospitals based on their estimated survival function.*

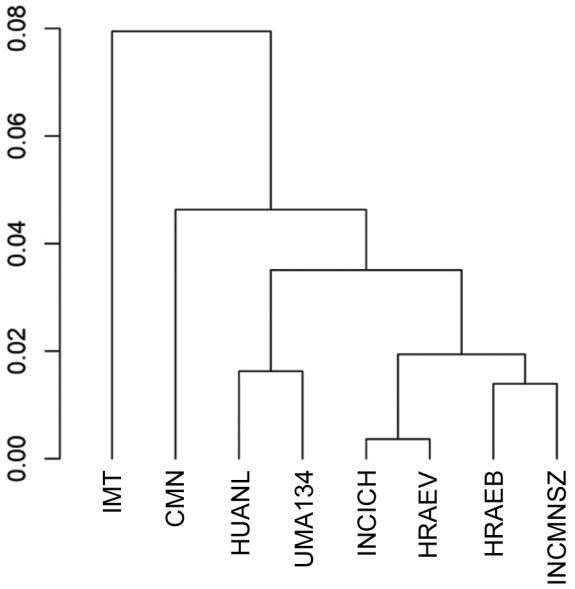

Figure 4. *Hierarchical clustering.*

83 to 1940, as well as in the periods considered in each publication, with a mean 17 years, a standard deviation of ± 13, and a range of 7 to 24 years. All hospitals included in this study reported the survival of kidney transplant recipients from 1967 through 2016, when the cumulative number of transplant recipients in Mexico was 46 495. Therefore, this study only shows the survival of 14.07% (6545 recipients out of 46 495), and if we added the number of kidney transplant recipients reported by the SIRNT from 2016 through 2021 (1402 recipients), we would unfortunately have follow-up data for only 13.54% (7947 recipients out of 58 668).

The ranges of survival rates for kidney transplant recipients in the hospitals included in this study went from 94.7% to 100% (at 1 year), and from 85% to 96.2% (at 5 years), which at first glance shows differences. However, it is necessary to conduct a survival analysis and use a statistical comparison technique.

Survival analysis is an inferential technique whose essential aim is to model the time elapsed until a certain event occurs[18]. In the case of kidney transplants, this event, when talking about the survival of recipients, is death.

In survival analysis, the sample consists of following a series of individuals from the beginning of the study until the end of it, and in a situation like this, it is common for some of these individuals who enter the study to disappear. It is also possible that, when an individual enters the study, it ends before the event we are trying to detect even occurs. Although these are 2 isolated events, in practice, they are the same. In statistics, these individuals are referred to as "censored"[18].

A censored data point represents an individual who disappears. We had this patient but he/she has been lost before the event we are analyzing even occurs, either because the patient has been lost from the study or because the study has ended, and the event never occurred. A censored data point is not a data point that does not provide information. In fact, it does, but partially. Disregarding it outright would be wasting information, and that, in statistics, is not good[18].

Since the Kaplan-Meier estimator of the survival function is based on the times at which patients' deaths occurred and all those patients who were in the study at that time, this involves the number of censored patients (those who are lost to follow-up). Therefore, this type of data certainly needs to be reported, as with them it is possible to calculate the standard errors in the estimates, which in turn allows for a deeper statistical analysis; it is even advisable to construct confidence intervals for the estimate survival function[19].

The most common technique for comparing survival curves is the log-rank test. This is, in fact, a chi-square technique where a comparison is drawn between an observed parameter (the sample survival curves) and an expected one (bringing together all the values into a single sample)[19]. Since the publications found in this study on the survival of kidney transplant recipients do not provide the number of censored

patients, or have complete databases, this comparison with the log-rank test cannot be drawn. Therefore, we used 2 clustering techniques to analyze the reported estimated values, finding differences in survival across different hospitals. However, we should mention that no standard tests have become available to measure the statistical significance of these differences when applying clustering techniques, as it is currently a topic of research in statistics[20].

Finding differences in the survival of kidney transplant recipients in the hospitals included in this study has important implications: 1) the possibility of knowing the effectiveness of kidney transplantation in each of the hospitals to improve their results, and 2) the possibility of knowing the evolution of kidney transplant programs to support their development and strengthen them.

The inefficiency and ineffectiveness of the SIRNT are exposed since after 2 and a half years, there were only 1402 kidney transplant recipients available, with, at least, 1 survival report, out of a total of 15 218 transplanted patients from 2016 through 2021, that is, we had post-kidney transplant information from only 9.2% of the patients from that period[2], with the limitation of not being able to construct survival curves with that information. This should encourage government and institutional authorities to keep a record not only from the traditional perspective of the number of transplants performed but also from the responsibility of keeping a follow-up of kidney transplant recipients to estimate their survival and evaluate the results of kidney transplant programs.

Underregistration of survival among renal transplant recipients can be attributed to several factors, among which the following are the primary ones:

- Lack of a legal framework mandating the reporting of kidney transplant recipient survival.
- A fragmented health care system (including the Ministry of Health, IMSS, ISSSTE, PEMEX, SEDENA, and state health services) lacking intercommunication.
- Health care service collapse, leading to patients being transplanted in tertiary care centers and then being transferred to second-level hospitals for follow-up 1 year after transplantion.
- This overload also makes patients in need for a renal transplant have to migrate between sectors, seeking faster transplantation and returning to their original health insurance provider for immunosuppressant drugs.

Knowing these factors, we can propose the following strategies and actions to improve the registration of renal transplant recipient survival:

- Establishing a legal framework mandating the registration and reporting of renal transplant recipient survival:
  - Adding to the General Health Act, “Article 338.- The National Transplant Center shall be responsible for the National Transplant Registry, which shall integrate and keep updated the following information,” an additional section that could state “VI. The survival of organ transplant recipients”.
  - Amending the Regulations of the General Health Act on Transplants, “Article 33.- The Internal Transplant Committees, in addition to those provided for by the Law, shall have the following functions:. XI Evaluate the results of the Transplant Programs available at the Health Establishment,” it would need to be more specific too: “XI Evaluate the results of the Transplant Programs available at the Health Establishment, through the number of transplants performed, morbidity, mortality, and the survival of transplant recipients”.
  - Adding to the Regulations of the General Health Act on Transplants, “Article 62. The integration, management, and updating of information from the National Transplant Registry, in addition to complying with the provisions established by the Federal Law on Transparency and Access to Government Public Information, shall be subject to the following:”, an additional section that could state: “The health authority of the Health Establishment where a transplant will be performed must record the survival of organ transplant recipients”.
- To improve communication between different health services, and taking advantage of the infrastructure of CENATRA, namely the SIRNT, both transplanting centers and hospitals providing follow-up care should have access to the database of all kidney transplant recipients in Mexico. This way, the patient, even if changing sectors or hospitals, would have their follow-up and specifically their survival recorded.

Conclusions

The information gathered on renal transplant programs in hospitals located in Mexico demonstrates

significant heterogeneity, both in the number of transplants performed per hospital and in recipient survival. To comprehensively assess the results of renal transplant programs in Mexico, it is important to include not only the number of transplants performed per hospital but also recipient and graft survival. However, in Mexico, there is limited information on the follow-up of renal transplant recipients: only 13.54% of the total accumulated. This needs strategies and actions to understand the survival of a greater number of recipients, as it is a useful tool for evaluating the effectiveness of various renal transplant programs. Such strategies and actions would include: 1) establishing a legal framework mandating the reporting of transplant recipient survival, and 2) improving intercommunication among centers using the SIRNT.

When analyzing the data, this study identified differences in reported survivals, but due to incomplete databases and the number of censored patients, the differences found may not be as reliable as if the log-rank test had been applied.

Funding

None declared.

Conflicts of interest

None declared.

Ethical disclosures

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

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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ORIGINAL ARTICLE

Colorectal endometriosis. A proposal of complementary classification and surgical management in stages

Endometriosis colorrectal. Una propuesta de clasificación complementaria y de manejo quirúrgico por etapas

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Abstract

Objective: *To organize the experience and international knowledge in the surgical management and staging of colorectal endometriosis, with a management proposal in stages.* **Method:** *An extensive non-systematic review of the literature was carried to organize the disease in stages (limited, intermediate and advanced) according to a scoring system, which considers the characteristics of the endometrioma, the personal history and surgical findings. We tested the proposed staging in a retrospective group of patients.* **Results:** *From January 2017 to April 2023, we collected 19 patients with a confirmed diagnosis of colorectal endometriosis, treated laparoscopically, by the same group of surgeons, in whom we found a strong correlation between the stage of the disease and the presence of complications that required reinterventions.* **Conclusions:** *We suggest a sequence of colorectal surgical management in stages according to the staging of the disease and we hope that this work will be followed by joint efforts to test it prospectively in order to compare results between hospital centers and make planned decisions.*

Keywords: *Colorectal endometriosis. Intestinal endometriosis. Deep endometriosis.*

Resumen

Objetivo: *Organizar la experiencia y el conocimiento internacional en el manejo quirúrgico y la estadificación de la endometriosis colorrectal, con una propuesta de manejo por etapas.* **Método:** *Se realizó una revisión amplia no sistemática de la literatura para organizar la enfermedad en etapas (limitada, intermedia y avanzada) de acuerdo con un sistema de puntuación que considera las características del endometrioma, los antecedentes personales y los hallazgos en la cirugía. La estatificación propuesta se probó en un grupo retrospectivo de pacientes.* **Resultados:** *De enero de 2017 a abril de 2023 recopilamos 19 pacientes con diagnóstico confirmado de endometriosis colorrectal, tratadas por vía laparoscópica, por el mismo grupo de cirujanos, en las que encontramos una fuerte correlación entre el estadio de la enfermedad y la presencia de complicaciones que requirieron reintervenciones.* **Conclusiones:** *Sugerimos una secuencia de manejo quirúrgico colorrectal en etapas de acuerdo con la estadificación de la enfermedad y esperamos que el presente trabajo sea seguido de esfuerzos compartidos por probarla de manera prospectiva para poder comparar resultados entre centros hospitalarios y tomar decisiones planificadas.*

Palabras clave: *Endometriosis colorrectal. Endometriosis intestinal. Endometriosis profunda.*

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Introduction

Endometriosis is a chronic inflammatory disease caused by endometrial tissue growing outside the uterus. It is estimated to affect 2% to 10% of the female population overall, rising up to 50% in women with infertility, affecting, at least, 190 million reproductive-age women and some beyond menopause[1].

A prevalence of 8% to 12% has been estimated for colorectal endometriosis, with almost 90% of all intestinal lesions being found in the rectum and sigmoid colon[2].

The main symptoms of endometriosis include chronic pelvic pain related to the menstrual cycle and infertility. When the condition affects the intestines, additional symptoms such as abdominal bloating, changes to bowel habits (constipation or diarrhea), passage of mucus with bowel movements, rectal bleeding, urgency to defecate, and feeling of incomplete evacuation may occur, often worsening with the menstrual cycle. Additionally, endometriotic nodules can cause narrowing of the intestinal lumen leading to obstructive symptoms, and eventually to reduced quality of life affecting not only women with endometriosis but also their partners and families[3,4].

Medical treatment of deep endometriosis involving the colorectum is an option for many women, with symptomatic relief probabilities ranging from 70% to 80%[5] and increased overall pregnancy rates from 42% up to 80%[3]. However, there is a group of patients who will require surgical management, including those who have not responded favorably to medical management, those with contraindications or intolerance to hormonal therapy, those with intestinal obstructive symptoms, and couples seeking natural conception or preferring surgery[6].

Two distinct approaches have been described in the management of colorectal endometriosis, with different rates of complications, long-term side effects, and recurrences:

- A radical approach with segmental colorectal resection and anastomosis.
- A more conservative approach involving local transmural and non-transmural resections, with reconstructions using manual or mechanical sutures[5,6].

The balance between the conservative or the radical approach regarding complications and recurrence rates has led to a debate among different surgical schools, with no current consensus on the standard surgical technique[5].

We believe that the problem arises when discussing colorectal endometriosis as a uniform condition without recognizing the significant differences in treating limited vs advanced disease. Currently, there is no standardized classification to design staged therapies that can be compared among different working groups regarding cure outcomes, morbidity/mortality, and recurrence.

Therefore, we decided to develop a staging classification for colorectal endometriosis, considering the cumulative global experience in its management, including the treating surgeon's criteria for choosing the extent and type of surgery, associated complications, disease recurrence rates, and need for reinterventions. We retrospectively tested this classification on a group of patients treated at Instituto Nacional de Perinatología, Mexico City, Mexico from 2017 through 2023.

Method

The group of authors, including 6 national and 1 international member of various backgrounds (gynecologists, urogynecologists, reproductive biologists, colorectal surgeons, and general surgeons), all experienced in advanced pelvic surgery, both laparoscopic and open, worked collaboratively, both in-person and online, to conduct a non-systematic review of the literature. This review included the clinical practice guidelines from the European Society of Human Reproduction and Embryology (ESHRE)[7], the German guidelines from 2014[8], and meta-analyses, randomized and non-randomized controlled clinical trials, prospective and retrospective studies since 2006 through 2022. Overall, these sources included a total of 16 846 patients, aiming to review the factors involved in the surgeons' decisions when treating patients with colorectal endometriosis, the factors associated with intra- and postoperative complications, and the factors associated with disease recurrence.

Once these factors were identified, they were grouped into categories, being the most relevant those associated with tumor characteristics (T), with the patients' medical history (H) and with surgical factors (S), creating the acronym THS.

After defining the categories, they were categorized into 3 groups, being the first one the best clinical-surgical scenario and the third one being the worst scenario and defining an intermediate group in terms of technical difficulty, complications, and recurrences.

Each group was assigned a numerical parameter representing it, allowing for proper differentiation of each group. This resulted in defining an unclassifiable stage due to lack of data, an initial stage or THS 1, an intermediate stage of evolution or THS 2, and an advanced stage of the disease or THS 3.

Due to the nature of the disease and the difficulties in diagnosis, an initial preoperative classification (for surgical planning purposes) will be performed, which will be complemented with intraoperative findings and defined postoperatively with histopathological results (both with prognostic purposes).

The version thus obtained is retrospectively evaluated using data from electronic health records from a group of consecutive patients treated at Instituto Nacional de Perinatología from January 2017 through April 2023 (including the years of the COVID-19 pandemic, which limited non-emergency surgeries due to hospital restructuring), with a confirmed histopathological diagnosis of colorectal endometriosis.

Based on the findings made, the group provides recommendations for the staged surgical treatment of patients with colorectal endometriosis.

Table 1. Characteristics to be evaluated by the surgeon for surgical decision-making in a patient with colorectal endometriosis

Tumor (characteristics of colorectal endometrioma)	Size
	Number
	Location
	Depth of invasion
	Intestinal lumen obstruction
Background	Age
	BMI
	Caprini (thromboembolic risk classification)
	ASA (American Society of Anesthesiologists) health status classification
Surgery	History of previous surgeries for endometriosis
	Type of surgery performed in the current procedure
	Intraoperative bleeding
	Histopathological resection

ASA: American Society of Anesthesiologists; BMI: body mass index.

Results

Characteristics to be assessed by the surgeon for surgical decision-making in patients with colorectal endometriosis

After reviewing the literature on factors impacting the surgeon's decision-making on the surgical treatment of patients with colorectal endometriosis, factors associated with intra- and postoperative complications, and factors associated with disease recurrence, we stay with the following elements as the characteristics that should be evaluated: those that are endometrioma-dependent, those dependent on the patients' past medical history, and those dependent on surgery (Table 1):

- Tumor or endometrioma: size, number, location, depth of invasion of colorectal wall, and presence or absence of intestinal lumen obstruction.
- Patient history: age, body mass index, thromboembolic risk, and health status.
- Surgery: previous surgeries for endometriosis, type of current surgery, intraoperative bleeding, and histopathological examination of resected material.

Once the characteristics to be considered by the surgeon in decision-making were defined and grouped, a table was created to score their importance in 3 categories, from 0 to 3, based on the importance of each characteristic and its specific weight in decision-making process (Table 2).

Regarding the characteristics of the endometrioma or tumor, we considered as the most favorable scenarios the presence of only 1 lesion, size < 3 cm, location above the rectum, depth of invasion not exceeding the serosa, and no evidence of colorectal lumen obstruction. Conversely, the least favorable characteristics include endometrioma or tumor size > 3 cm, presence of 3 or more lesions, lower rectum location, involving the full thickness of the wall, and causing some form of colorectal lumen obstruction.

Regarding the patient's past medical history, the most favorable scenarios are said to be age younger than 40 years, a body mass index (BMI) under 34, low-to-moderate thromboembolic risk, and a healthy-to-stable and controlled comorbidity status (American Society of Anesthesiologists [ASA] I-II). Conversely, the least favorable scenarios include age older than

Table 2. Auxiliary table for scoring characteristics based on their importance for decision-making in the treatment of a patient with colorectal endometriosis

Item	0 points	1 point	3 points
Tumor	Size: < 3 cm	No scoring	Size: > 3 cm
	Number: 1	Number: 2	Number: > 3
	Location: above rectum	Location: rectosigmoid junction	Location: lower rectum
	Depth: serosal	Depth: muscular	Depth: full thickness
	Obstruction: no	No scoring	Intestinal lumen obstruction: yes
History	Age: < 40 years	Age: > 40	No scoring
	BMI: < 34	BMI: > 35	
	Caprini: low, medium	Caprini: high or very high	
	ASA: I-II	ASA: > III	
Surgery	Previous surgeries for endometriosis: no	Previous surgeries for endometriosis: yes	No scoring
	Current surgery: nodules resection	Current surgery: includes hysterectomy	Current surgery: includes urinary tract opening or extrapelvic involvement
	Hemorrhage: < 500 mL	No scoring	Hemorrhage: > 500 mL
	Pathology: complete resection	Pathology: residual endometriosis	No scoring

ASA: American Society of Anesthesiologists; BMI: body mass index.

40 years, BMI > 35, high-to-very high thromboembolic risk, and ASA > III health status. The patient's pats medical history was scored from 0 to 1 point as it was considered by the surgeons to be of lesser importance in intraoperative decision-making vs tumor characteristics or surgical factors.

Regarding surgical factors, the most favorable scenario is when the patient has no history of previous surgeries for endometriosis, only undergoing resection of endometriotic nodules in the current surgery, with intraoperative bleeding of < 500 mL, and pathology reporting complete resection of the endometrioma margins. In contrast, the least favorable scenario includes a history of previous surgeries for endometriosis, current surgery involving opening the genital or urinary tracts or with extrapelvic involvement, intraoperative bleeding > 500 mL, and residual endometriosis on the histopathological examination.

Having defined the importance of these characteristics and grouped them for scoring, patients were categorized into 4 stages. The first stage including those for whom sufficient information was not available for classification, while the remaining stages include those with limited, intermediate, and advanced disease (Table 3).

Table 3. Stage categorization of patients with colorectal endometriosis

Stage	Meaning	Score
U	Unclassifiable	Missing data for classification purposes
THS 1	Limited	0-2
THS 2	Intermediate	3-4
THS 3	Advanced	> 5

Retrospective assessment of patients treated with a confirmed diagnosis of colorectal endometriosis

From January 2017 through April 2023, we collected data from 19 patients diagnosed with colorectal endometriosis, treated laparoscopically by the same group of lead surgeons (Table 4).

According to the Enzian classification, 17 of our patients were considered to have C1 colorectal involvement, 1 patient had C2 involvement, and another one, C3 involvement. When categorized based on the THS system, patients fell into THS 1 (8 patients), THS 2 (6 patients), and THS 3 (5 patients) (Table 5).

Table 4. Retrospective evaluation of patients treated at Instituto Nacional de Perinatología with a confirmed diagnosis of colorectal endometriosis

Patient	THS score	THS stage	Enzian classification*	Surgical management	Complications and observations
1	4	2	C1	LNTR	No
2	4	2	C1	LNTR	No
3	4	2	C1	LNTR	No
4	1	1	C1	LNTR	No
5	6	3	C1	SRA	No
6	4	2	C1	LNTR	No
7	0	1	C1	LNTR	No
8	8	3	C1	LNTR	Yes†
9	4	2	C1	LNTR	No
10	4	2	C1	LNTR	No
11	2	1	C1	LNTR	No
12	5	3	C1	LNTR	Yes‡
13	4	2	C1	LNTR	No
14	4	2	C1	LNTR	No
15	1	1	C2	LNTR	Yes§
16	12	3	C3	SRA	Yes¶
17	2	1	C1	LNTR	No
18	6	3	C1	LNTR	Yes**
19	2	1	C1	LNTR	No

LNTR: local non-transmural resection; SRA: segmental resection with anastomosis.
*Only Enzian stage is considered for colorectal involvement.
†Intestinal perforation as a complication not detected intraoperatively, requiring intestinal resection and emergency stoma in a 2nd surgical act.
‡Surgical wound infection. Six colorectal nodules, each 1 cm in size, were resected during a 6-hour surgery.
§Surgical drainage of pelvic hematoma via laparoscopy.
¶3rd degree burn due to equipment use, requiring escharotomy and double interpositional flap.
**Intraoperative hemorrhage (1800 mL) and 6-hour surgical time.

Regarding the type of surgical management used, 17 patients underwent local non-transmural resection (LNTR), and 2 patients underwent segmental resection with colo-colo segmental resection with anastomosis (SRA) without protective stoma.

We encountered complications in 5 patients, accounting for 26% of the sample, with 74% of the patients progressing uneventfully.

Among patients treated with SRA, 1 progressed uneventfully, while another one suffered a third-degree burn due to equipment use, which required escharotomy and a double interpositional flap in a 2nd surgical act.

Among the patients operated on with LNTR, we had 4 cases with complications: 1 had an intraoperative undetected intestinal perforation, which required intestinal resection and emergency stoma in a 2nd surgical act, 1 had a surgical wound infection, 1 required surgical laparoscopial drainage of a pelvic hematoma, and finally, 1 experienced intraoperative bleeding (1800 mL) and a 6-hour surgical procedural time.

Four out of the 5 patients with complications had advanced colorectal disease with THS 3, which accounted for 80% of the sample. Additionally, we observed that a THS 3 level positively correlated with the presence or absence of surgical complications, 80% and 93% sensitivity and specificity rates, respectively (Table 6).

Discussion

Endometriosis is a condition estimated to affect 190 million reproductive-aged women worldwide, with

Table 5. Distribution of patients based on colorectal endometriosis damage

Enzian		THS	
Stage	**Patients**	**Stage**	**Patients**
C1	17	1	8
C2	1	2	6
C3	1	3	5

Table 6. 2 × 2 table for the sensitivity and specificity of THS 3 and surgical complications

	Current complication	Absent complication
Present THS 3	4	1
Abent THS 3	1	13

Sensitivity: 80%.
Specificity: 93%.

a prevalence of colorectal involvement of 8% up to 12%, accounting for approximately 19 million women in this age group[2]. Colorectal complications in patients with endometriosis are challenging for the medical team, requiring the availability of special resources including human expertise (experienced pelvic surgeon, urologist, and general or colorectal surgeon) and material resources (advanced laparoscopic equipment and instrumentation with intestinal endographe).

Therefore, preoperative management planning is crucial, based on the patient's clinical presentation, including bimanual, rectal, and speculum examination, supported by diagnostic aids such as transvaginal ultrasound and occasionally magnetic resonance imaging with rectal and vaginal contrast[9].

Currently, the most widely used classification for endometriosis is the Enzian classification, which specifically considers only the size of the lesion (C1 = 1 cm, C2 = 1-2 cm, and C3 > 3 cm)[10]. However, upon analyzing the international literature for this study on 16 846 patients, we found that the surgical management decision-making process for the surgeon involves other factors besides the size of the nodule, such as the number and depth of lesions, the presence or absence of intestinal lumen obstruction, the opening of genital, urinary, and digestive tracts in the same surgical act, intraoperative blood loss, history of previous surgeries for endometriosis, the patient's overall health status, specific surgical risk, and the possibility of clinically relevant disease recurrence. Therefore, we decided to include these factors in a classification system we coined THS (tumor or endometrioma characteristics, the patients' medical history and observations during surgery)

We categorized our patients into 3 stages of disease (limited, intermediate, and advanced) and tested the staging classification in a group of patients retrospectively treated at Instituto Nacional Perinatología from January 2017 through April 2023. We found a strong correlation within our group between high THS scale values (advanced colorectal endometriotic disease) and the presence of complications requiring subsequent surgical management. Based on this correlation, we suggest a staged surgical management scheme:

- For all stages:
  - Management in centers experienced in the management of endometriosis.
  - Preoperative definition of Enzian and THS stage as accurately as possible based on experience and available institutional resources (physical and bimanual vaginal examination with speculoscopy and transvaginal ultrasound, supplemented, if necessary, with magnetic resonance imaging with rectal and vaginal contrast).
  - Appropriate informed consent. Do not operate if the patient does not agree and is not aware of the benefits and risks of the procedure, or if the risks due to comorbidities outweigh the expected benefits.
  - Availability of complete human team (gynecological, general, urological, and colorectal surgeons) and technical equipment to address unforeseen events (staplers, blood products, etc.)
  - Preoperative intestinal preparation.
- THS 1 stage (limited): local non-transmural extirpations or resections.
- THS 2 stage (intermediate): transmural discoid resection. No more than 2 in segments < 10 cm.
- THS 3 stage (advanced): segmental colon resection with anastomosis, preferably without a stoma.

We believe that the present study contributes to a staged surgical management plan for patients with colorectal endometriosis, in addition to serving as a basis for comparing results between centers and opening new avenues for prospective research.

Conclusions

Colorectal endometriosis is a common condition that requires a planned and comprehensive approach to reduce complications from overtreatment or suboptimal management, which should be based on a good preoperative diagnosis including comprehensive physical examination, bimanual examination, digital rectal examination, and speculoscopy, complemented by transvaginal ultrasound and sometimes magnetic resonance imaging with rectal and vaginal contrast.

Currently, the most widely used classifications for endometriosis, such as Enzian, especially for colorectal involvement, only consider the size of the nodule, which we believe to be insufficient for surgical decision-making. Therefore, we propose a classification that considers a more comprehensive approach based on the patient's history, nodule characteristics, and intraoperative conditions.

In our patients, advanced endometriotic disease determined by THS classification positively correlated with the presence of complications, so we consider the present staged classification for colorectal endometriosis an approach to achieve disease staging by organizing the international experience already available in the management of these patients, allowing us to define stage-based treatments and compare results between hospitals.

Due to its limitations, this study should pave the way for prospective studies that, with appropriate statistical analysis, should allow us to refine the scale and increase its utility, to offer patients the best option for personalized surgical management and perform planned interventions with a multidisciplinary team in a single procedure.

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Conflicts of interest

None declared.

Ethical disclosures

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

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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ORIGINAL ARTICLE

Tele-rehabilitation program in patients with distal radius fracture: a controlled clinical trial

Programa de telerrehabilitación en pacientes con fractura de radio distal: ensayo clínico controlado

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Abstract

Objective: *To determine the effectiveness of tele rehabilitation versus supervised treatment in the functional recovery of patients with distal radius fracture.* **Method:** *A randomized clinical trial was conducted that included 91 patients with distal radius frac- tures grades AO23 A and AO23B, which were randomly assigned to a treatment group, the supervised rehabilitation group received for two weeks a program of 10 treatment sessions and the tele rehabilitation group received through the Moodle platform instructions to carry out the rehabilitation program. Outcome measures (functionality, active range of motion, hand grip strength, quality of life and pain) were measured at the time of admission to rehabilitation and at 1, 3 and 6 months.* **Results:** *In both treatment groups at 6 months, statistically significant intragroup differences in functionality were demon- strated, with no intergroup differences.* **Conclusions:** *At 6 months, both rehabilitation programs increase functionality, range of motion, quality of life and decrease pain, without statistically significant differences intergroup.*

Keywords: *Distal radius fracture. Tele rehabilitation. Physiotherapy. Functionality. Quality of life.*

Resumen

Objetivo: *Determinar la efectividad de la telerrehabilitación en comparación con el tratamiento supervisado en la recuperación funcional de los pacientes con fractura de radio distal.* **Método:** *Se realizó un ensayo clínico aleatorizado que incluyó 91 pacientes con fracturas de radio distal de grados AO23A y AO23B, los cuales se asignaron aleatoriamente a un grupo de rehabilitación supervisado que recibió durante 2 semanas un programa de 10 sesiones de tratamiento o un grupo de telerrehabilitación que mediante la plataforma de Moodle recibió instrucciones para realizar el programa de rehabilitación. Las medidas de resultado (funcionalidad, rango de movimiento activo, fuerza de prensión de la mano, calidad de vida y dolor) se midieron en el momento del ingreso a rehabilitación y a los 1, 3 y 6 meses.* **Resultados:** *A los 6 meses, ambos grupos de tratamiento demostraron diferencias estadísticamente significativas intragrupo en la funcionalidad, sin diferencias intergrupo.* **Conclusiones:** *A los 6 meses, ambos programas de rehabilitación aumentan la funcionalidad, el rango de movimiento y la calidad de vida, y disminuyen el dolor, sin diferencias estadísticamente significativas intergrupo.*

Palabras clave: *Fractura de radio distal. Telerrehabilitación. Fisioterapia. Funcionalidad. Calidad de vida.*

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Introduction

Distal radius fractures are among the most frequent fractures worldwide. In the United States, they are the second most common upper limb fracture, with an estimated annual incidence of 643 000[1], representing 1.5% of visits to the ER for hand and forearm fractures, following fractures of the radius and ulna[2]. In the United Kingdom, the National Health Service estimated a mean daily cost of £1375.34 per patient with surgical fixation of distal radius fracture[3]. In the United States, Medicare system estimated a cost of over $170 million for the management of these fractures[4]. After a variable period of immobilization, these patients are generally referred to rehabilitation services, increasing the cost of care. The cost of hospital physical therapy is estimated at £82.03 per day, and outpatient physical therapy at £40.70[3].

Despite several studies, it is still unclear which type of therapy has the most significant impact on wrist function recovery, range of motion, and strength[5]. Currently, studies show that home programs are as effective as supervised rehabilitation programs[6,7]; however, other studies indicate the opposite[8-10].

The COVID-19 pandemic has imposed new paradigms of care for distal radius fractures, now recommended to be treated as non-emergent and conservative. Therefore, it is necessary to establish rehabilitation strategies to continue treating patients without exposing them to the risk of infection. In this regard, the World Confederation for Physical Therapy has proposed the online practice of rehabilitation services (telemedicine)[11,12]. Therefore, the aim of this study was to determine the effectiveness of telerehabilitation compared to supervised therapy in the functional recovery of patients with distal radius fractures.

Method

Approval for the study was obtained from the regional hospital local research and ethics committee no.1 (R-2020-3201-153), and all patients agreed to participate and the publication of results.

We conducted a randomized, controlled, parallel treatment trial protocol. Using computer-generated random numbers, hidden allocation was performed (sequential and sealed envelopes filled by a person unrelated to the study), administered by the project coordinator after the patients' acceptance to enter the study. Due to the nature of the intervention, both participants and investigators alike were blinded to the intervention.

The first group received a supervised rehabilitation program and was considered the control group, receiving a 10-session program over a 2-week period, including external heat application, stretching, mobilization, strengthening, and occupational therapy focused on improving essential functions and strengthening extrinsic and intrinsic hand musculature, effectiveness in wrist mobility, and simulation of specific activities to go back to work.

Members of the second group were provided with the Moodle application on their cell phones to access the online content of the distal radius fracture rehabilitation program, where they received self-care advice and the type of exercises that should be performed. The program included hydrotherapy, mobility exercises, muscle strengthening, and activities to improve wrist and hand function, with planned objectives for 4 full weeks.

Participants in both groups received written exercise material, training, and advice on how to return to work and leisure activities. Each patient kept a weekly record of the therapy they had given administered, including the day, type, and time of their exercise development.

From November 2020 through April 2021, men and women older than 15 years with AO23 A and AO23 B type distal radius fractures were included, with prior immobilization for 6 weeks (with or without surgical fixation), with indication from the orthopedic physician to undergo rehabilitation, and who had a mobile phone and internet access.

Patients with distal radius fractures were excluded if they showed any of the following radiographic findings: > 12° tilt, > 23° radial tilt, and > 12 mm radial height. Patients with neurological problems, illiteracy, presence of pressure ulcers in the distal third of the forearm or hand that did not heal, users of orally or IV administered steroids, with preexisting arthritis or osteoarthritis of the wrist, or with a history of injury were also excluded. Participants with < 80% compliance to treatment were eliminated.

Sample size calculation

A minimum clinically important difference of 14 points was considered on the Disabilities of the Arm, Shoulder, and Hand (DASH) functionality scale, with a standard deviation of 20, a significance level of 5%,

a statistical power of 80%, and an estimated loss of 20% for sample size calculation[13]. The formula used for sample size calculation was the difference of means for 2 independent groups:

$$n = \frac{2(Z_\alpha + Z_\beta)^2 * S^2}{d^2}$$

Thus, the sample size was 44 subjects per group.

Procedures and equipment

Each patient was assigned a folio number, including their file with sociodemographic, clinical, and functional data obtained from the DASH scale. Quality of life was measured using the SF-36 survey. A commercial goniometer was used to measure the wrist range of motion, and the CAMRY electronic hand dynamometer, model EH101, was used to measure strength. For all, the arithmetic mean was calculated after 3 consecutive attempts, maintaining maximum grip strength for 4 seconds, with a 1-minute interval, as previously described[14,15]. The visual analog scale was used for pain evaluation.

Outcome assessment

All participants were assessed for function, wrist range of motion, hand grip strength, quality of life, and pain at baseline and at 4, 12, and 24 weeks.

Regarding compliance, all patients from group #1 reported attending their therapies on time and filling their record card, completing the treatment cycles. In group #2, compliance was estimated between 81% and 90%. Patients had to repeat home exercises daily, which was monitored via phone calls, an exercise diary, and an checklist.

Statistical analysis

Qualitative variables were expressed as absolute and relative frequencies, and quantitative ones as measures of central tendency and dispersion. A univariate general linear model (ANCOVA) was used for comparing quantitative variables between treatment groups, considering the study variable (functionality, quality of life, pain, range of motion arcs, and hand grip strength) as the dependent variable and the study group as the independent variable. The model was adjusted for age, sex, and type of treatment.

The paired t-test was used to analyze intra-group dependent variables at the beginning and end of follow-up. Statistical significance was established as $p < 0.05$. IBM-SPSS Software® v21 was used for statistical analysis.

Table 1. General characteristics of the study sample (n = 91)

Supervised (n = 46)	Telerehabilitation (n = 45)	Total (n = 91)	p
Age (years)*	47.17 ± 13.1	43.69 ± 13.8	45.4 ± 13.5
Female sex†	27 (58.7)	25 (55.6)	52 (57.1)
Right side affected†	45 (97.8)	43 (95.6)	88 (96.7)
Low-energy injuries†	30 (65.2)	29 (64.4)	59 (64.8)
Extension injury†	23 (50.0)	23 (51.1)	46 (50.5)
Flexion injury†	10 (21.7)	4 (8.9)	14 (15.4)
Surgical treatment†	21 (45.7)	22 (48.9)	43 (47.3)
Disability days*	90.23 ± 28.2	84.33 ± 26.4	87.3 ± 27.3

*Data are expressed as mean ± standard deviation.
†Data are expressed as n (%).

Results

A total of 110 patients with distal radius fractures were identified, 10 of whom were excluded from the study for presenting radius and ulna fractures, thus assigning 50 patients to each group. Subsequently, 7 patients were eliminated for not following treatment, and 2 for abandoning it (4 in the control group and 5 in the rehabilitation group) (Fig. 1).

The final sample consisted of 91 patients (46 in the control group and 45 in the experimental one), of whom more than 50% were women, with a mean age of 45 years. Almost 100% of the injuries were on the right side, while 65% were low- energy injuries, being forced extension the most frequent mechanism of injury. Less than 50% of fractures were treated surgically, with a mean of 87 days of disability. No statistically significant differences were found between the 2 groups (Table 1).

Type AO23 A fracture occurred in 55.5% of the supervised group vs 62.2% of the telerehabilitation group; type OA23B occurred in 43.5% of the supervised group vs 37.8% of the telerehabilitation group. No statistically significant differences were found either.

At 24 weeks, both treatment groups showed statistically significant differences in functionality, wrist range of motion, quality of life, and reduction of pain, with no inter-group differences except for hand grip strength (Tables 2 and 3).

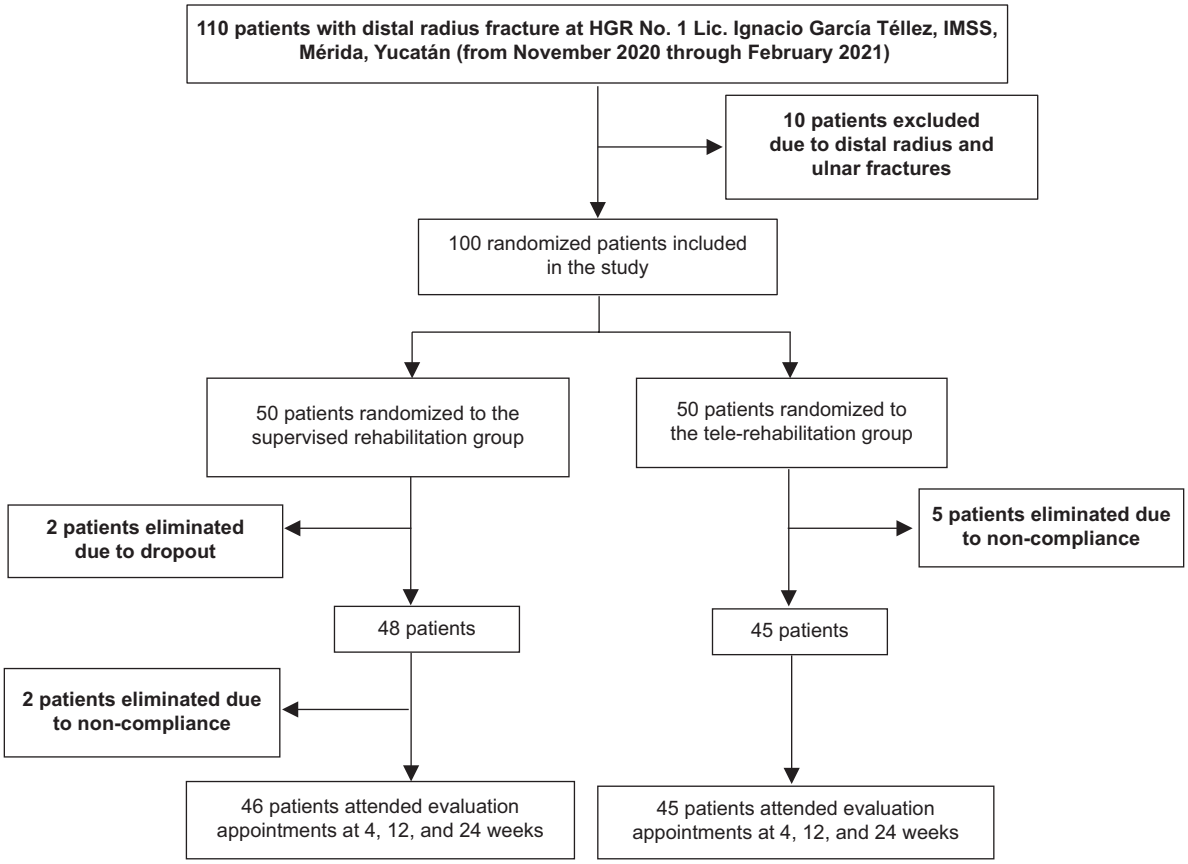

Figure 1. *Flowchart of patient selection with distal radius fracture.*

At the end of the study, 8 patients experienced residual pain (5 from the supervised therapy group and 3 from the telerehabilitation group), and 6 patients had difficulty fully closing their hand (three in the supervised therapy group and three in the telerehabilitation group).

One patient from the supervised therapy group experienced dislocation of the ulna bone after a fall from his support surface, requiring conservative treatment. On the other hand, a patient from the telerehabilitation group developed hypoesthesia in the area of the radial nerve of the affected hand, confirmed by electroneuromyography, revealing axonal sensory neuropathy of the radial nerve. There were no cases of malunion, nonunion, tendon rupture, or soft tissue infection.

Discussion

In this study, at 24 weeks, both treatment groups showed statistically significant differences in functionality, wrist range of motion, quality of life, and pain reduction, with no inter-group differences being reported; only an inter-group difference was found in hand grip strength, with better results in the telerehabilitation group from 12 weeks onwards.

The mean age the study participants was 45 years, which is similar to the mean age reported by Egund et al.[16] in the Swedish population and Handoll and Elliott[10] in the United Kingdom. A total of 57% of the patients were women, which is similar to the findings made by Handoll and Elliott[10] in the United Kingdom and Azad et al.[17] in Southern California, although lower than that described by Rundgren et al.[18] in Sweden. The most frequent injury mechanism was low energy (65%), with the hand in extension, which is consistent with the findings made by MacIntyre and Sander et al.[19] (73.1%), who demonstrated that the most common injury in adults results from low-energy trauma after sustaining a fall from their height.

The most common fracture type was AO23A, which is similar to the fracture type reported by the study conducted by Sander et al.[19], who reported a prevalence of 43.3%, being subtype A2 present in 39.6% of the patients younger than 65 years.

A total of 52% of the patients in this study received conservative treatment, which is a similar rate to that

Table 2. Active range of motion and grip strength of the hand by treatment group

Variable	Group	Evaluation time								
		Basline		4 weeks		12 weeks		24 weeks		Baseline - 24 weeks
		Mean ± SD	p	Mean ± SD	p	Mean ± SD	p	Mean ± SD	p	Intra-group p
Flexion of the wrist of the affected side (degrees)	Supervised	38.61 ± 16	0.87	50.65 ± 16	0.11	57.48 ± 13	0.57	60.48 ± 11	0.30	< 0.05*
	Telerehabilitation	38.71 ± 11.37		53.02 ± 11		56.93 ± 9		59.91 ± 8		< 0.05*
Extension of the wrist of the affected side (degrees)	Supervised	18.63 ± 22	0.74	42.26 ± 22	0.27	49.48 ± 18	0.22	53.57 ± 17	0.43	< 0.05*
	Telerehabilitation	21.69 ± 19		43.96 ± 17		49.02 ± 16		51.49 ± 15		< 0.05*
Radial deviation of the affected wrist (degrees)	Supervised	9.57 ± 10	0.58	17.13 ± 11	0.90	20.43 ± 10	0.99	21.65 ± 10	0.95	< 0.05*
	Telerehabilitation	10.36 ± 9		18.80 ± 10		20.84 ± 8		22.19 ± 8		< 0.05*
Ulnar deviation of the wrist of the affected side (degrees)	Supervised	19.13 ± 11	0.70	25.70 ± 10	0.35	29.52 ± 8	0.68	31 ± 7	0.70	< 0.05*
	Telerehabilitation	20.62 ± 9		28 ± 9		29.96 ± 7		30.88 ± 7		< 0.05*
Grip strength of the side of the affected side (kg)	Supervised	5.22 ± 4	0.0†	9.98 ± 7	0.07*	12.09 ± 7	0.00†	14.33 ± 7	0.00†	< 0.05*
	Telerehabilitation	7.08 ± 5		12.46 ± 6		15.33 ± 7		18.19 ± 8		< 0.05*

*Statistically significant differences within the group ($p < 0.05$).
†Statistically significant differences between groups ($p < 0.05$).

Table 3. Comparison of functionality, quality of life, and pain by treatment group

Variable	Supervised (Mean ± SD)	Telerehabilitation (Mean ± SD)	Inter-group p-value
DASH			
Baseline	66.40 ± 19.29	58.06 ± 21.41	0.23
4 weeks	38.48 ± 25.03	28.70 ± 19.33	0.12
12 weeks	20.57 ± 18.46	13.66 ± 11.68	0.18
24 weeks	9.93 ± 11.34	5.95 ± 6.21	0.32
Intra-group p	0.003*	< 0.001	
SF-36			
Baseline	68.3 (19.0)	69 (14.8)	0.20
4 weeks	75.5 (15.4)	74.8 (13.6)	0.37
12 weeks	77.9 (14.5)	79.8 (11.5)	0.60
24 weeks	81.5 (17.1)	82.7 (10.9)	0.20
Intra-group p	0.001*	< 0.001*	
EVA			
Baseline	4.7 ± 2.7	4.8 ± 2.8	0.43
4 weeks	2.6 ± 2.9	2.8 ± 2.7	0.97
12 weeks	1.9 ± 2.6	1.3 ± 1.9	0.13
24 weeks	0.9 ± 1.7	0.7 ± 1.1	0.75
Intra-group p	0.001*	< 0.001*	

*Statistically significant intra-group difference ($p < 0.05$).
DASH, Disabilities of the Arm, Shoulder and Hand; EVA, Visual Analog Scale; SF-36, Short Form Health Survey.

was reported by Azad et al.[17] in their study. Intra- and inter-group analyses were performed for range of motion arcs, comparing functionality at the beginning and at the end, finding statistically significant differences for all variables in the intra-group comparison, while no differences were found in the inter-group comparison except for hand grip strength. These results are similar to those reported by Wakefield and McQueen[20], who found significant improvement in joint mobility range for flexion and extension at the 6-month follow-up. There was also a statistically significant increase in hand grip strength in both groups at 12 and 24 weeks, with an absolute gain of 9 kg in the supervised therapy group and 11 kg in the telerehabilitation group, which was statistically significant; however, this difference is not valid since these variables were not homogeneous from the beginning of the study. The difference in strength reported between the beginning and the end in both groups is similar to that reported by Challis et al.[21], who described a 9.3 kg increase in a group of patients who received a statistically significant 10-week course of face-to-face physical therapy.

Different former studies suggest that home programs are more effective than supervised programs for increasing functional recovery[6,7,20,22-24]. However, other authors have not found any differences between patients who did home exercises and those who received professional follow-up care from therapists[8,9]. In our study, the supervised physical therapy group received a mean 10 sessions, which was not a factor that affected the results, as in several studies comparing the effectiveness of supervised physical therapy vs home exercises, the difference in the number of sessions between the 2 varied from 3 to 12 sessions, showing similar effectiveness[7,9,20,25,26].

The improvement in functionality was slightly higher in the home program group, although a statistically nonsignificant difference was reported. According to a study, the most critical factor in hand functionality recovery is treatment compliance[27]. Based on this, we believe patients with distal radius fractures should be encouraged to take responsibility for treatment compliance to promote functional recovery. In studies where higher functionality has been reported in home programs, researchers believe that in supervised programs, therapists may be too cautious in treating these patients, which may limit patients from doing exercises beyond the point where they become painful, resulting in slower recovery[28].

Supervised therapy should be spared for patients with poor or suboptimal fixation, and with complications after fixation with a volar locking plate, including complex regional pain syndrome and carpal tunnel syndrome[24].

Regarding quality of life, as expected, both groups had higher function and quality of life, with no inter-group differences being reported as in former studies[20,23].

Subacute complications were mainly mechanical symptoms, which is consistent with the description given by Azad et al.[17], who reported a prevalence of 2.06% of this type of complication in their population, among which residual pain and incomplete hand closure attributed to finger stiffness were stressed out, in a rate < 16% reported by Moore and Leonardi-Bee[29]. The most frequent causes of these complications are inadequate immobilization with plaster, edema, unmanageable pain, lack of patient cooperation, lack of understanding when doing the exercises, or no motivation[30]; this may persist up to 1 year after distal radius fracture[31]. However, long-term follow-up for late complications was not part of the objectives of this study.

We estimate that patients with distal radius fractures often achieve optimal strength, range of motion, and functionality within 3-6 months after sustaining the injury, regardless of whether treatment is conservative or surgical[29]. A 7-year follow-up prospective study of women older than 50 years with distal radius fractures revealed that 15% of them were more likely to have significant functional decline attributed to the musculoskeletal system's status (including bone loss), body mass index, general health status, and associated comorbidity[32].

The management of musculoskeletal conditions through real-time telerehabilitation effectively achieves a significant improvement in physical function and pain[33], which makes it a feasible option thanks to its low cost and the patient's adequate commitment to perform and complete their routine.

Most patients reported feeling comfortable with the platform. In their own words, it is easy to access, find, and understand rehabilitation therapy instructions, with clear guidance and simple visualization of videos. This study did not analyze this aspect, but it would be interesting to do so in future studies.

Study limitations

The main issues reported by our patients were technical aspects, such as accessing an internet connection, and an unstable signal in remote or hard-to-reach communities, as well as individuals with limited financial resources who could not afford internet access for long periods of time. Older adults who were afraid due to their poor technological skills overcame this barrier by having caregivers or close family members use a cellphone with internet access. Another limitation was the difference in functionality at the beginning of the study between both groups, which limited the comparison of effectiveness at the end of follow-up.

Strengths found

We consider the main strengths of the study to be its methodological design, complete patient follow-up, and sample size.

Implications for the routine clinical practice

Based on these results, we consider remote rehabilitation through digital platforms to be an effective option for improving short- and long-term functionality in patients with uncomplicated distal radius fractures. We also believe that emphasis should be placed on patient education to make sure they take responsibility and improve treatment compliance, thereby enhancing their functionality.

Conclusions

The telerehabilitation program in patients with uncomplicated distal radius fractures increased functionality, quality of life, pain, and range of motion in a similar way compared to supervised rehabilitation. Therefore, telerehabilitation in these patients is considered a feasible option to improve functionality and quality of life, with the advantages of avoiding patient travel to the rehabilitation unit, reducing costs, and preventing rehabilitation service overload.

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Conflicts of interest

None declared.

Ethical disclosures

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

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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CASE REPORT

Intestinal intussusception as a postoperative complication of gastric bypass

Intususcepción intestinal como complicación posoperatoria de bypass gástrico

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Abstract

The gold standard for bariatric surgery is the laparoscopic gastric bypass, which consists in forming a small gastric pouch and a Roux-en-Y anastomosis. We present the case of a 41-year-old female who underwent a laparoscopic gastric bypass 8 years prior to her admission to the emergency room, where she arrived complaining of severe and colicky epigastric abdominal pain. The abdominal computed tomography showed a jejuno-jejunal intussusception, for which the patient underwent urgent exploratory laparotomy with intussusception reduction. Intestinal intussusception is a possible postoperative complication of a Roux-en-Y gastric bypass.

Keywords: *Intussusception. Gastric bypass. Bariatric surgery.*

Resumen

El método de referencia en la cirugía bariátrica es el bypass gástrico laparoscópico, que consiste en la creación de una bolsa gástrica pequeña, anastomosada al tracto digestivo mediante una Y de Roux. Presentamos el caso de una mujer de 41 años con el antecedente de un bypass gástrico laparoscópico realizado 8 años antes, quien ingresó al servicio de urgencias refiriendo dolor abdominal grave. La tomografía computarizada abdominal evidenció una intususcepción a nivel de la anastomosis yeyuno-yeyuno, por lo que se realizó una laparotomía exploradora con reducción de la intususcepción. Se debe considerar la intususcepción intestinal como complicación posoperatoria de bypass gástrico.

Palabras clave: *Intususcepción. Bypass gástrico. Cirugía bariátrica.*

Introduction

Bariatric and metabolic surgery is increasingly being performed in response to the rising incidence of obesity and overweight in Mexico and worldwide, and to the growing demand from patients for such procedures. The main indications for bariatric surgery are a body mass index (BMI) ≥ 40 kg/m^2, or between 35 40 kg/m^2 and 40 kg/m^2 associated with a major comorbidity (type 2 diabetes mellitus, systemic arterial hypertension, obstructive sleep apnea syndrome, or dyslipidemia)[1].

The reference method for bariatric surgery currently is laparoscopic gastric bypass, which involves creating

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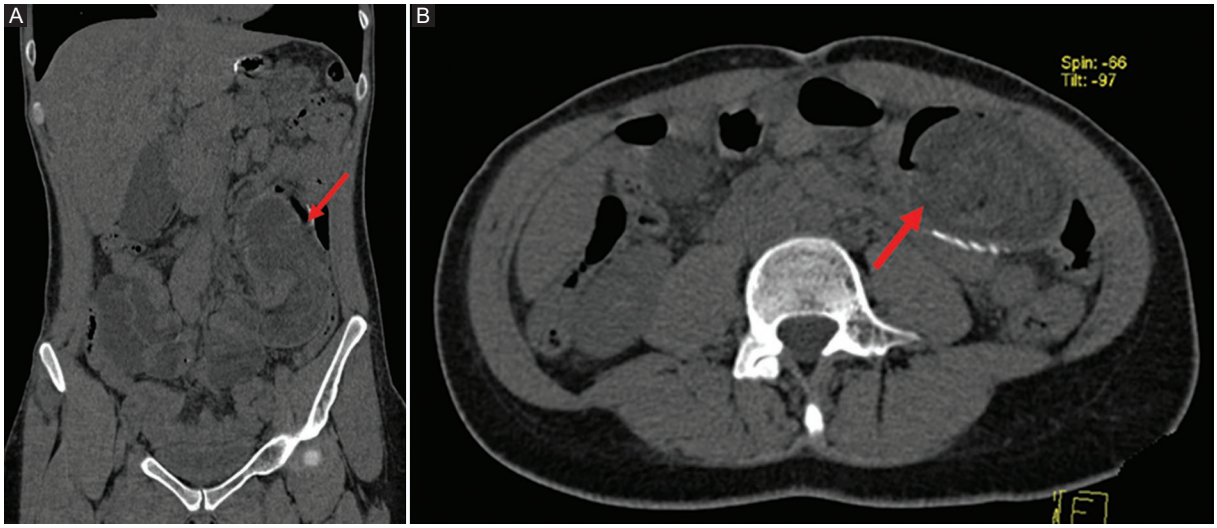

Figure 1. *Simple abdominal computed tomography. Evidence of intussusception at the level of the jejuno-jejunal anastomosis (arrow).* **A:** *coronal view.* **B:** *cross-ectional view.*

a gastric reservoir of about 30 mL in capacity, anastomosing it to the intestinal tract through a Roux-en-Y configuration. Surgeons should not forget that postoperative complications of bariatric surgery and laparoscopic gastric bypass are not trivial.

Next, we present the case of a patient who presented to the ER with an intestinal obstruction following gastric bypass surgery, as well as a review of the scientific medical literature currently available.

Case report

A 41-year-old woman with a history of laparoscopic gastric bypass surgery performed 8 years earlier presented to the ER complaining of epigastric localized abdominal pain, colicky in nature, radiating to the back, rated 7/10 on the numerical analog scale (NAS) for pain, which became exacerbated after food intake, and was alleviated after vomiting twice. This clinical presentation progressed symptomatically into NAS 10/10, which made her seek emergency care. Physical examination revealed the presence of a soft and depressible abdomen, painful to superficial and deep palpation, with increased intensity and frequency of peristalsis. As part of the diagnostic approach, laboratory tests were conducted, all of which reported normal ranges. Additionally, and a simple abdominal computed tomography (CT) (Fig. 1) revealed a jejuno-jejunal intussusception at the level of anastomosis. Consequently, emergency surgical management was decided, with exploratory laparotomy performed to reduce the intestinal intussusception by taxis and adhesion lysis (Figs. 2 and 3). Findings revealed the presence of a 20 cm intussusception of the small intestine at the jejuno-jejunal anastomosis, after which the patient had to be hospitalized for 5 days with good progress being uneventfully discharged on day 6.

Discussion

The Roux-en-Y gastric bypass is a restrictive and malabsorptive bariatric procedure developed in 1966 by Mason. Currenlty, laparoscopic gastric bypass is the bariatric procedure of choice[2,3]. The Roux-en-Y gastric bypass consists of the creation of a small gastric reservoir anastomosed to the intestinal tract through a Roux-en-Y configuration. The jejunum is, then, sectioned 60 cm to 80 cm away from the Treitz angle to form the biliopancreatic limb, followed by an antecolic gastrojejunostomy. Finally, the remaining intestinal transit is reconstructed with a jejuno-jejunal anastomosis 100 cm away from the Treitz angle, forming the alimentary limb[1].

Complications that may occur after gastric bypass include ulceration, stenosis or anastomotic leak, gastrogastric fistula, and intestinal obstruction due to adhesions or internal hernia[4]. Due to the prevalence of bariatric surgery, the number of postoperative complications has increased exponentially; however, fewer than 200 cases of postoperative intestinal intussusception have been reported in the medical literature[5].

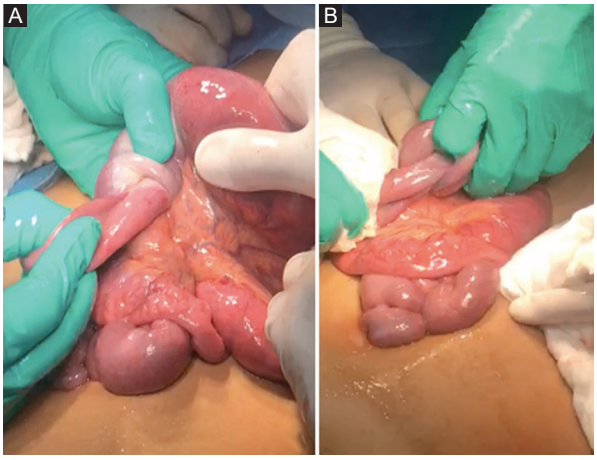

Figure 2. *Surgical procedure (exploratory laparotomy).* **A:** *intestinal intussusception at the jejuno-jejunal anastomosis.* **B:** *reduction of intussusception by taxis.*

Figure 3. *Surgical procedure: complete intestinal reduction with adequate intestinal viability.*

Although intestinal intussusception is an extremely rare complication of gastric bypass surgery, it can be a catastrophic one[6].When it occurs, it often appears at the site of the jejuno-jejunal anastomosis, with a reported incidence of 0.1% to 1% in patients undergoing gastric bypass[7]. It has been reported that lengths of the jejuno-jejunal anastomosis of more than 60 mm may be associated with a higher incidence of intussusception and other complications[8,9]. Clinical presentation will mainly include abdominal distension and inability to evacuate, along with severe acute abdominal pain occurring, approximately, 25 to 52 months after gastric bypass surgery[8-10]. The imaging modality of choice for diagnosis is a simple abdominal CT scan, which will reveal thickening and edema of the intestinal wall, proximal intestinal loop dilatation, and the target sign of a sagittal section[4,11-13].

Once high intestinal obstruction is suspected in bariatric patients, early surgical intervention is advised to prevent the vascular compromise that would cause intestinal ischemia and necrosis[7,11]. Surgical management is prioritized since endoscopy does not have direct access to the intussusception site[4]. Intraoperatively, in the presence of ischemic or irreducible intestine, resection of the jejuno-jejunal anastomosis must be performed[6,8,9]. The treatment of choice is laparotomy with reduction of the intussusception within 48 hours to ensure intestinal viability. As a good practice, experts recommend securing the reduced jejunum to adjacent tissues, such as the mesocolon, colon, or stomach, to prevent recurrence. Time and speed in diagnosis and treatment are important because when surgery is performed within the first 48 hours, mortality rate is 10%, but if performed > 48 hours, mortality rate can be up to 50%[5,11].

Conclusions

Morbid obesity surgery is currently the most effective treatment due to its short- and long-term benefits. Among the options for bariatric procedures, laparoscopic gastric bypass is the method of choice. However, it is crucial to be aware of associated complications, as well as their early diagnosis and treatment, to reduce the morbidity and mortality associated with these patients.

We reported the case of a patient with intestinal intussusception following gastric bypass, a rare but potentially fatal complication in this type of bariatric surgery. Intestinal intussusception should be considered in the differential diagnosis in the presence of a patient with signs of intestinal obstruction and a past medical history of gastric bypass.

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Conflicts of interest

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Ethical disclosures

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

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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CASE REPORT

Presentation of Wernicke encephalopathy in patient secondary to one anastomosis gastric bypass. Case report and literature review

Presentación de encefalopatía de Wernicke en paciente secundaria a bypass gástrico de una anastomosis. Reporte de caso y revisión de la literatura

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Abstract

Wernicke encephalopathy, which is caused by a thiamine deficiency, occurs in 0.8-2% of the population. Only 16% present the typical triad of this disease: nystagmus, confusion and ataxia. We present the case of a postoperative patient with a one anastomosis gastric bypass with reoperation undergoing a Roux-en-Y gastric bypass that begins with confusion and nystagmus on her third postoperative day. The diagnosis of Wernicke encephalopathy is made by imaging, and vitamin B1 is administered with total improvement of nystagmus and altered state of consciousness (lethargy, bradypsychia, bradylalia).

Keywords: *Wernicke encephalopathy. Bariatric surgery. Vitamin B1 deficiency.*

Resumen

La encefalopatía de Wernicke se produce por una deficiencia de tiamina se presenta en un 0.8-2% de la población. Solo el 16% de los casos presentan la tríada típica de esta enfermedad: nistagmo, confusión y ataxia. Presentamos el caso de una paciente operada de bypass gástrico de una anastomosis con reintervención convirtiendo a bypass gástrico en Y de Roux que en su tercer día de posoperatorio comienza con confusión y nistagmo. Se realiza por imagen el diagnóstico de encefalopatía de Wernicke se administra vitamina B1 con mejoría total del nistagmo y alteración del estado de consciencia (letargia, bradipsiquia, bradilalia).

Palabras clave: *Encefalopatía de Wernicke. Cirugía bariátrica. Deficiencia de vitamina B1.*

Introduction

Obesity is a chronic multifactorial disease involving genetic, environmental, and lifestyle aspects, which leads to an excessive accumulation of body fat[1]. The World Health Organization (WHO) considers obesity as one of the rapidly growing metabolic disorders, which is similar to data reported for diabetes[2]. In 2016, in Mexico, according to the report from the National Institute of Public Health, the combined prevalence of overweight and abdominal obesity in adults older than 20 years was 76.6[3].

The limited effectiveness of current medical therapies has led to an increase in bariatric procedures. Bariatric surgery has proven effective promoting weight loss and reducing the 10-year mortality rate in up to 23% compared to patients without obesity management[4]. Currently, the most widely performed procedures are laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass, with more than

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500 000 procedures performed each year across the world[5]. Laparoscopic one-anastomosis gastric bypass (OAGB) is an effective alternative to the management of obesity and comorbidity, with a reported surgical time in a cohort of 2410 OAGBs of 37.5 minutes and a mean length of stay of 1 day, with fewer reported complications vs other procedures, such as the Roux-en-Y gastric bypass[6]. The most common nutritional deficits in patients undergoing bariatric surgery are deficiencies in iron, vitamin B1 (thiamine), vitamin B12, calcium, vitamin D, folic acid, copper, and zinc[7]. The anatomical changes made in these procedures lead to frequent complications associated with a reduction of these nutrients, such as Wernicke's encephalopathy induced by thiamine deficiency.

This is the case of a patient who presented to the ER after undergoing OAGB surgery, with a 40-day history of oral intolerance, we reoperated, with Wernicke's encephalopathy during her hospitalization and in-hospital management.

Case report

A 42-year-old woman with a 10-year history of systemic arterial hypertension under control and morbid obesity with a body mass index of 47.5 (height, 159 cm; weight, 120 kg). Surgical history of adjustable gastric banding via supraumbilical laparotomy 8 years prior to her current condition, complicated 2 years later with a gastric perforation treated with laparotomy, adjustable band removal, and gastric repair. Forty days prior to being admitted to our hospital, she underwent OAGB via laparotomy, and 3 days after being put on a diet after surgery, she started vomiting, showing no improvement in her condition. After these events, she was referred to our hospital with clinical signs of severe dehydration, oral intolerance, and electrolyte abnormalities. A central venous catheter was placed, followed by electrolyte replacement and the administration of multivitamin serum, and parenteral nutrition, which improved her clinical conditions for 3 days. On day 4, we decided to operate on the patient performing an exploratory laparotomy, a Roux-en-Y gastric bypass, and a gastrostomy in the gastric remnant. Enteral diet via gastrostomy was started 48 hours later. On day 3, the patient was extubated, and bilateral nystagmus with altered consciousness became evident. Brain magnetic resonance imaging revealed the presence of characteristic structural changes of Wernicke's encephalopathy (Fig. 1). Supplementation with vitamin B1 was initiated with partial symptom improvement. The patient was discharged 10 days after surgery.

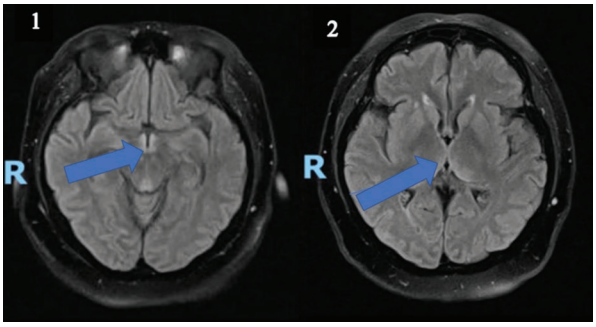

Figure 1. *The arrow in image 1 indicates thalamic hyperintensity, while the arrow in image 2 indicates basal ganglia hyperintensity. Hyperintensity can be seen on T2 and FLAIR sequences, in the anterior and lateral regions to the head of the caudate nucleus, without diffusion restriction, related to changes due to microangiopathy.*

Discussion

Wernicke's encephalopathy was first described by Carl Wernicke back in in 1881, who reported on 3 patients with the characteristic acute onset triad[8]. Wernicke's encephalopathy is an acute neuropsychiatric syndrome characterized by nystagmus with ophthalmoplegia, altered consciousness, and ataxia, although this triad is observed in only 16% of the patients[9]. Thiamine is a water-soluble vitamin that acts as a coenzyme in the metabolism of carbohydrates, lipids, and amino acids, and plays an important role in adenosine triphosphate synthesis, maintenance of myelin layers in neurons, and neurotransmitter production[1,9]. Thiamine is absorbed by the proximal small intestine. Previously, thiamine deficiency used to occur in alcoholic patients, but nowadays, it is a common finding after bariatric surgery and can result from a combination of factors such as decreased intake, frequent vomiting, and malabsorption[1,7]. Most case reports and case series in the scientific medical literature currently available on bariatric surgery report that the main precipitating factor for Wernicke's encephalopathy is vomiting[5,9]. The pathophysiology of Wernicke's encephalopathy results in increased lactate production in neurons and astrocytes, lactate accumulation, reduced pH, and focal acidosis with fragmentation in thalamic neurons, presenting apoptosis and cell death after 2 weeks of thiamine deficiency[9].

In patients with surgical changes to their GI tract for weight loss Wernicke's encephalopathy has been reported occurs in < 1%, probably with cases being underdiagnosed[10-12]. In 2008, in a review of 84 cases after bariatric surgery, Aasheim[11] described the presence of Wernicke's encephalopathy in 79 patients (94%) within the first 6 months after obesity surgery, in whom vomiting

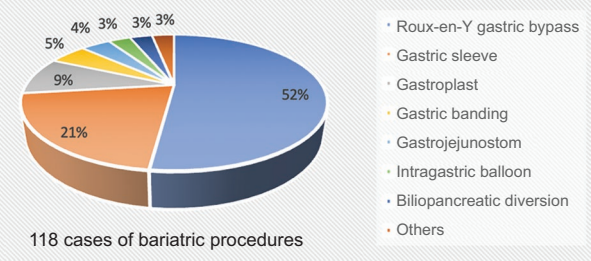

Figure 2. *Presentation of Wernicke's encephalopathy in 118 cases of different types of bariatric procedures.*

was the most important risk factor, present in 76 cases (90%), with a mean history of the disease of 21 days at the time of admission. In our case, upon admission, the patient had been vomiting for 40 days, probably the most important factor of Wernicke's encephalopathy in her postoperative period. In another systematic review on Wernicke's encephalopathy conducted in 2018, Oudman et al.[5] reported 118 cases. The procedures performed in that review are shown in Fig. 2, being Roux-en-Y gastric bypass and sleeve gastrectomy the most common ones. Vomiting was the most common predisposing factor (87.3%) for the presentation of Wernicke's encephalopathy; ataxia was reported in 100 cases (84.7%); changes to the mental status, such as delirium, confusion, and cognitive problems, in 90 (76.3%); and movement impairment, such as nystagmus and ophthalmoplegia, in 87 cases (73.3%). In our patient, nystagmus and changes to the mental status were evident, without documented ataxia due to lack of ambulation. In a prospective study of 318 patients undergoing laparoscopic Roux-en-Y gastric bypass with 1-year follow-up of their vitamin B1 levels, Clements et al.[13] reported deficiency in 18.3% of the patients, making it clear that supplementation and measurement of vitamins in all patients undergoing bariatric surgery are important because late diagnosis and management of this deficiency could lead to irreversible neurological sequelae and eventually progress into Wernicke's syndrome, which is a chronic state of Wernicke's encephalopathy[13]. In a study of 47 patients undergoing weight loss surgery, Punchai et al.[14] reported incomplete recovery in 4 patients. Therefore, early recognition of this problem is very important to initiate early management with vitamin B1 replacement and prevent long-term neurological sequelae.

Conclusions

Wernicke's encephalopathy is a neuropsychiatric disease that general and obesity surgeons should consider in all patients undergoing bariatric surgery, whether acute or chronic, as delayed diagnosis can lead to long-term neurological complications. The early recognition of this entity is important to prevent its progression, which can lead to chronic neurological sequelae and even death.

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Ethical disclosures

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

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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CASE REPORT

Pancreatic metastasis from undifferentiated pleomorphic sarcoma. An extremely rare entity

Metástasis pancreática de sarcoma pleomórfico indiferenciado. Una entidad extremadamente rara

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Abstract

Undifferentiated pleomorphic sarcoma (UPS) is a very aggressive malignant tumor that originates in bone or soft tissues, being its most frequent location in the extremities. We present the case of a 71-year-old man who, two years of follow-up after a lower right limb UPS excision surgery, presented a single metastasis of sarcomatoid origin in the pancreas that was treated by cephalic pancreaticoduodenectomy. Sarcomatoid metastases to the pancreas are extremely rare. Resection of the metastasis is the only therapeutic alternative that has reported benefit in terms of the survival of these patients.

Keywords: *Soft tissue sarcoma. Metastasis. Pancreatoduodenectomy. Pancreas.*

Resumen

El sarcoma pleomórfico indiferenciado (SPI) es un tumor maligno muy agresivo que se origina en el hueso o tejidos blandos, siendo su localización más frecuente en las extremidades. Presentamos el caso de un varón de 71 años que a los dos años de seguimiento tras cirugía de exéresis de un SPI presenta una metástasis única de origen sarcomatoide a nivel del páncreas que se trató mediante duodenopancreatectomía cefálica. Las metástasis sarcomatoides a nivel de páncreas son extremadamente raras. La cirugía de exéresis de la metástasis es la única alternativa terapéutica que ha reportado beneficio en cuanto la supervivencia de estos pacientes.

Palabras clave**:** *Sarcoma de partes blandas. Metástasis. Duodenopancreatectomía. Páncreas.*

Introduction

Undifferentiated pleomorphic sarcoma (UPS), also known as malignant fibrous histiocytoma, is the most common soft tissue sarcoma in adults. Its approximate incidence is 1 for every 100 000 individuals[1].

It is more common in men, between the 6th and 7th decades of life, and is most frequently located in the lower extremities[1]. Recurrence is predominantly local. The lung is the most common site of distant metastasis, being pancreatic metastases extremely rare[1].

Only 2% of tumors located in the pancreatic gland are metastases, and their most common presentation is in the context of a disease already disseminated to other organs[2,3]. The cancers most frequently causing

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metastases, generally solitary and localized at pancreatic level, are renal, followed by colorectal, melanoma, breast cancer, lung carcinoma, and sarcoma[2,3].

The benefit of pancreatic resection in these patients will be determined by the primary origin and its histopathological characteristics[2].

Up to 50% are asymptomatic and diagnosed during follow-up of the primary tumor[2]. Morphology and radiological characteristics vary based on their hyspothatology. Positron emission tomography may be useful to rule out metastases at other levels[2].

Case report

This is the case of a 71-year-old man who underwent wide musculoskeletal excision for a UPS located in the upper third of his right thigh. Adjuvant treatment was administered with radiotherapy (66 Gy) and chemotherapy (ifosfamide and doxorubicin). Pathological anatomy of the surgical specimen revealed a 13 cm x 11 cm x 6.8 cm UPS with free surgical margins. Due to its degree of differentiation, mitotic count, and tumor necrosis, it was categorized as grade 3 (stage IIIb) (AJCC, 8th edition)[4].

Two years after surgery, a computed tomography of the thorax, abdomen, and pelvis revealed the presence of a 50 mm x 47 mm heterogeneous mass at the duodenopancreatic junction without dilatation of the bile duct or Wirsung's duct (Fig. 1). Percutaneous biopsy suggested a sarcomatoid origin of the mass, prompting a cephalic duodenopancreatectomy (Figs. 2 and 3). Histopathological diagnosis confirmed the presence of a 5 cm x 4.5 cm x 4.2 cm UPS metastasis originating in the pancreatic uncinate process, with tumor-free margins and negative lymphadenopathies (Fig. 4). The patient had a good and uneventful postoperative recovery. He remains asymptomatic and withour signs of recurrence at the 1-year follow-up.

Discussion

Pancreatic metastases of sarcomatoid origin are extremely rare[2]. Most reports on this topic consists of case series and isolated case reports. After the World Health Organization's reclassification from 2002[5] only 3 cases of single pancreatic metastases from UPS have been reported[1,3,6]. Radical resection surgery is the only potentially curative treatment, and is associated with increased disease-free intervals[1,2]. There is

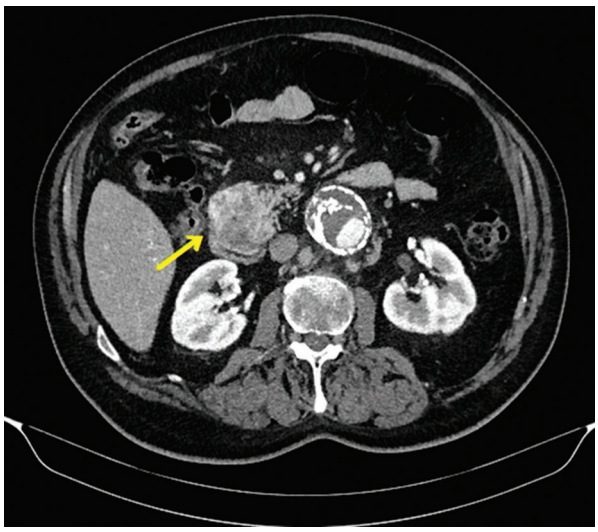

Figure 1. *Axial view of abdominal computed tomography: solid and heterogeneous mass of 50 mm x 47 mm at the duodenopancreatic junction.*

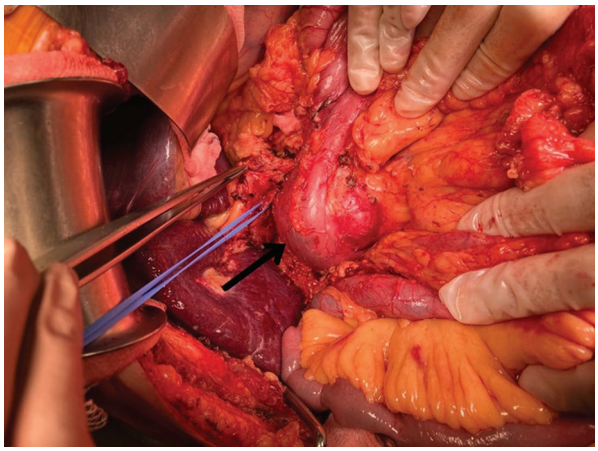

Figure 2. *Intraoperative image of a single mass in the pancreatic head-body uncinate process and duodenal compression.*

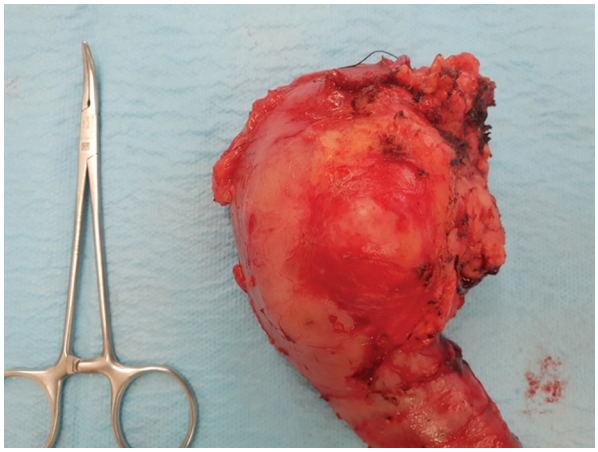

Figure 3. *Surgical specimen after cephalic duodenopancreatectomy with pylorus preservation.*

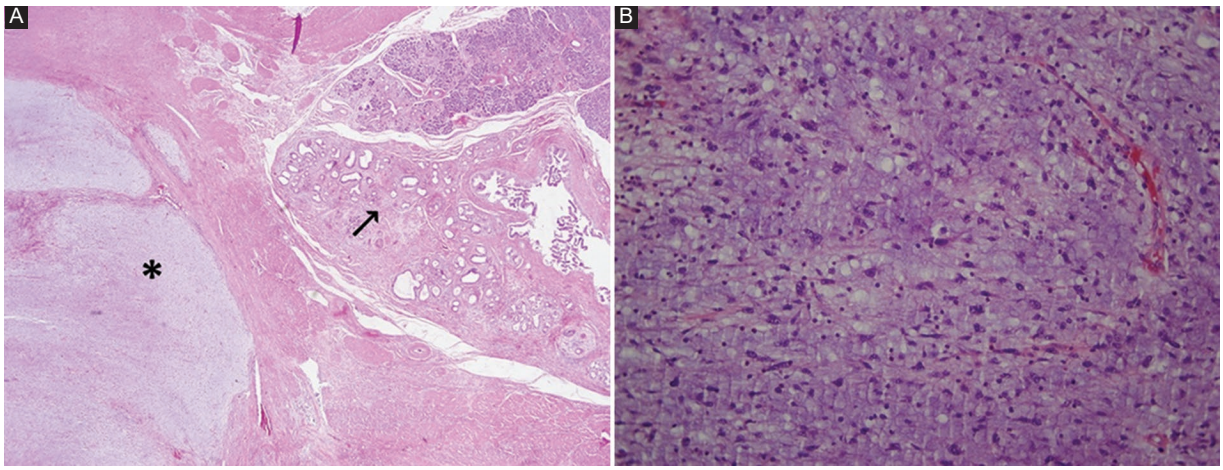

Figure 4. *Pathological anatomy with hematoxylin-eosin staining:* **A:** *relationship of the tumor (asterisk) with healthy pancreatic tissue (arrow) (X2).* **B:** *spindle-shaped atypical tumor cells (X20).*

no consensus on the benefit of adjuvant chemotherapy or radiotherapy regarding these tumors[1].

Atypical pancreatic resections or enucleations increase the risk of local recurrence and have a high rate of pancreatic fistulas, which is why standardized pancreatectomy is advised[2,7,8]. Such surgeries should be performed in high-volume centers specialized in pancreatic surgery[2].

Patient prognosis depends on the aggressiveness of the primary tumor, with renal origin tumors having a better prognosis[9]. Local recurrence is a common thing.

The absence of prospective studies and meta-analyses on single pancreatic metastases of sarcomatoid origin prevents accurate knowledge on the prognosis and survival of these patients.

Conclusions

Published series on pancreatic metastasis resections are limited, but authors report a long disease-free interval in many patients. Therefore, although treatment should be individualized, surgery is advised whenever possible[2,3,10].

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Conflicts of interest

None declared.

Ethical disclosures

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

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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REVIEW ARTICLE

Impact of COVID-19 on pre-existing liver disease

Impacto de COVID-19 en enfermedad hepatica pre-existente

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Abstract

Patients with chronic liver disease of any etiology who become infected with SARS-CoV-2 have been found to have a higher risk of mortality compared to those patients who do not have chronic liver disease. A literature review was conducted in the relationship between COVID 19 and preexistence of liver disease. The proportion of COVID-19 patients with abnormal liver function on admission ranged from 40 % to 75 % and the proportion with liver injury was close to 30%. Current studies show an important association between preexisting liver disease and COVID-19. The presence of cirrhosis is now an independent predictor of severity for COVID-19 and prolonged hospitalization in this group of patients. Patients with cirrhosis have a higher mortality rate, and this rate rises with increasing severity.

Keywords: *Pre-existing liver disease. COVID-19. COVID and cirrhosis.*

Resumen

Pacientes con enfermedad hepática crónica de cualquier etiología que se infectan con SARS-CoV-2 tienen un mayor riesgo de mortalidad en comparación con aquellos pacientes que no tienen enfermedad hepática crónica. Se llevó a cabo una revisión de la literatura en relación a lo publicado de COVID 19 y enfermedad hepática pre-existente. La proporción de pacientes con COVID-19 con función hepática anormal al ingreso osciló entre el 40 % y el 75 % y la proporción con daño hepático fue cercana al 30 %. Los estudios actuales muestran una asociación importante entre la enfermedad hepática preexistente y la COVID-19. La presencia de cirrosis es ahora un predictor independiente de gravedad para COVID-19 y hospitalización prolongada en este grupo de pacientes. Los pacientes con cirrosis tienen una mayor tasa de mortalidad y esta tasa se incrementa con el aumento de la gravedad de la enfermedad hepática.

Palabras clave: *Lesión hepática pre-existente. COVID 19. COVID y cirrosis.*

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Introduction

COVID-19, the disease caused by Coronavirus SARS-CoV-2, emerged in 2019 causing a worldwide public health problem. The infectiousness of COVID-19 impacted all age groups. Patients with different etiologies of chronic liver disease were some of the more affected. Although initial data reported that previous liver disease was not associated with severity, later studies showed an important association between pre-existing liver disease like hepatitis B, hepatitis C and metabolic associated fatty liver disease (MAFLD) and the severity of COVID-19 infection[1], even increasing risk of mortality compared with patients without liver disease[2]. Patients with alcohol-related liver disease, nonalcoholic fatty liver disease, cirrhosis and hepatocellular carcinoma are at higher risk of both severity and chance of death after infection[3]. Several theories might explain the hepatic involvement of COVID-19, including the direct viral effect on the liver cells, the abundance of ACE receptors in cholangiocytes and SARS-CoV-2 affinity to these receptors, drug-induced liver injury, and reactivation of Hepatitis B Virus (HBV) with the use of immunosuppressive medications[4]. Other factors relevant to liver injury are related to immune-mediated collateral damage, dysbiosis, hypoxia, and exacerbation of preexisting liver disease[3,4].

Epidemiology

Gastrointestinal and liver manifestations were reported in up to 40% of Mexican patients infected by SARS-CoV-2 since the beginning of the pandemic. Medical associations related to gastroenterology and hepatology issued guidelines for the identification, management and treatment of patients with COVID-19 hepatic manifestations, as well as for patients with pre-existing liver disease and liver transplant[5,6].

Overall, the prevalence of abnormal liver function tests (LFT) on admission in COVID-19 patients ranged from 40% to 75%, while liver injury approached 30%. Mexican patients showed mild aspartate transaminase (AST) and alanine transaminase (ALT) elevation, accompanied by a slight elevation in the total bilirubin, a mild decrease in albumin levels[5] and a cholestatic pattern (gamma glutamyl transferase (GGT) and alkaline phosphatase (ALP) increased) in up to 20% of the patients. Patients with abnormal LFT on admission presented higher mortality 18.7% compared to those with normal liver biochemistries 12.2% ($p < 0.0001$). After excluding patients with a history of chronic liver disease, abnormal LFT on admission were independently associated with death and severe COVID-19, both adjusted by age, gender, diabetes, pneumonia and body mass index > 30. Similar results were shown in a recent prospective multicenter international cohort among 829 hospitalized patients (203 from Mexico), in whom hypertransaminasemia was present in 267 patients (32.3%) and liver injury during hospitalization was associated with a higher hospital stay (> 10 days) and worse outcome[6].

MAFLD and COVID-19

Obesity is a known risk factor for respiratory infection and many other chronic diseases, including MAFLD. Nowadays, it has been considered an independent predictor for SARS-CoV-2 complications in adults. As expected, due to the high prevalence of overweight and obesity in our population, studies in Mexican COVID-19 patients have found a high prevalence of metabolic comorbidities, including hypertension, MAFLD and type 2 diabetes. In a retrospective study in 155 hospitalized Mexican patients, abnormal LFT was present in 96.8%, prevalence of steatosis was 42.6% and of significant liver fibrosis was 44.5%[7]. Liver fibrosis by FIB-4 was associated with risk of intensive care unit (ICU) admission (OR 1.74; $p = 0.023$) and mortality (OR 6.45, $p = 0.002$); but no independent associations were found. A more recent study[8] found in 432 hospitalized patients with COVID-19 that 40.6% fulfilled criteria for MAFLD. Although the authors did not find significant differences in the outcomes of hospitalized patients with MAFLD and those without MAFLD, a significant increase in the risk of mechanical ventilation requirement, acute kidney injury, and mortality in patients with MAFLD and advanced liver was found[9,10].

In the liver, the innate immune mechanisms play a central role in COVID-19 outcome and in the transition to hepatic inflammation, macrophages have a critical role. Some studies suggested receptors for SARS-CoV-2 are also present in liver cells. DPP4, the potential SARS-CoV-2 receptor, is multifunctional including its roles in glucose homeostasis, inflammation, and the immune system. Indented as a novel adipokine in adipose tissue (AT), DPP4 is strongly expressed on the apical surfaces of the polarized epithelium of various organs such as lung and liver, and increased DPP4 results in failures to resolve inflammation and chronic subclinical activation of the immune system[10,11].

The presence of inflammatory pathways, mainly cytokine storm, present either in obesity and in COVID-19 patients could increase liver inflammation or be a marker of metabolic risk factors further aggravating the clinical outcome. Thus, MAFLD should be considered as prognostic indicator during COVID-19[10]. A systematic review concluded that the risk of severe COVID-19 is 4-6 times higher in patients with MAFLD associated with obesity, fibrosis and age of > 60 year. Until now in our country, no studies have been published linking the prevalence of MAFLD and the severity of COVID-19[12]. Obese patients with no alcoholic steatohepatitis (NASH) show a higher expression of ACE2 and TMPRSS2, suggesting that the advanced stages of MAFLD could predispose individuals to SARS-CoV-2 entry factors. In patients with metabolic disorders, and in consequence adipocyte dysregulation, the involvement of the angiotensin 1-7 system and its underlying inflammatory environment, SARS-CoV-2 infection leads to a more severe outcome[13,14]. In several reports it had been observed that COVID-19 patients with fatty liver had a four-fold increased risk of severe COVID-19 compared with patients without fatty liver[15-17].

Liver injury is much worse in severe COVID-19 patients than in patients with mild symptoms. Singh et al. investigated the interaction of preexisting liver disease and COVID-19. Based on a large, diverse cohort of 2,780 COVID-19 patients in the United States, this study indicated that liver abnormalities were found in the vast majority of patients regardless of preexisting liver disease, but patients with liver disease were at higher risk for hospitalization and mortality[18,19]. It has been reported that among patients with preexisting liver disease, MAFLD was the most frequent (about 40%) and this patient had a higher risk of progression to severe COVID-19, higher abnormal liver tests at admission to discharge and longer viral shedding time[19].

Zheng et al. evaluated 214 patients with confirmed COVID-19 from three hospitals in Wenzhou, China, and 66 had MAFLD (45 with and 21 without obesity). The presence of obesity in MAFLD patients conferred a six fold higher risk of severe infection (unadjusted OR 5.77, 95% CI 1.19–27.91, p = 0.029) and the association with obesity and COVID-19 severity remained after adjustment for age, sex, smoking habits, diabetes, hypertension, and dyslipidemia (adjusted OR 6.32, 95% CI 1.16–34.54, p = 0.033)[20]. In nondiabetic patients with COVID-19, the presence of MAFLD was associated with an increased risk of severe infection and it was higher by increasing the number of metabolic factors[21]. A recent meta-analysis reported that a higher NLR (Neutrophil-to-Lymphocyte Ratio) is strongly associated with poorer hospital outcomes in patients with COVID-19. In the same cohort of 310 Asian patients, it has been recently demonstrated that patients with imaging- defined MAFLD and increased NLR values on admission have higher risk of severe illness from COVID-19 independently of age, sex, and metabolic comorbidities[22,23].

Vázquez-Medina et al. was to explore the implications of MAFLD and to study the interaction between advanced fibrosis (AF) and each of these diseases in the death and intubation of patients hospitalized with COVID-19. Study retrospective with 359 patients hospitalized with confirmed COVID-19 infection. The death rate was statistically significantly higher in the MAFLD group compared to the control group (55% vs. 38.3%, p = 0.02). The MAFLD (44.09% vs. 20%, p = 0.001) group had statistically significantly higher intubation rates than the control group[24].

Liver fibrosis, cirrhosis and COVID-19

Chronic liver disease can remain compensated for a long time even if the cause that generated it remains, however, if a second injury or damage is added to it, it is presumably that it will decompensate. In a prospective cohort study coordinated by the Latin American Association for the Study of the Liver (ALEH) in 1611 hospitalized patients with confirmed SARS-CoV-2 infection in 38 different hospitals in 11 Latin American countries, liver function tests were found to be abnormal at admission in 45.2% of the cohort. Overall, 8.5% had chronic liver disease and 3.4% had cirrhosis. Patients with abnormal liver tests at admission had a higher mortality of 18.7% compared to those with normal liver biochemistry of 12.2%. The authors concluded that the presence of abnormal liver tests at admission is independently associated with mortality and severe COVID-19 in hospitalized patients with COVID-19 infection and can be used as a surrogate marker of inflammation[1]. Patients with cirrhosis have a 20-30% risk of decompensation presenting as acute decompensation in chronic liver failure and high 30-day mortality.

Mantovani A et al. included 11 observational studies for a total of 2034 adult individuals (median age 49 years [IQR 45–54], 57.2% men). The overall prevalence of chronic liver disease at baseline was 3%.

Individuals with severe COVID-19 disease had relevant alterations of liver enzymes and coagulation profile, probably due to the innate immune response against the virus, and chronic liver disease was not shown to influence the severity of COVID-19[25]. Furthermore, in another retrospective study in hospitalized patients with COVID-19, the prevalence of hepatic steatosis and advanced liver fibrosis using noninvasive assessment prediction models was high; at least one liver function test abnormality was observed in 96.8% of COVID-19 patients[7]. The study of these patients and defining the role of cirrhosis in the evolution has been difficult since most patients present some of the associated comorbidities. A multicenter study done by Bajaj et al. in patients with cirrhosis + COVID-19 (n = 37) compared with age/gender-matched patients with COVID-19 alone (n = 108) and cirrhosis alone (n = 127). It was concluded that cirrhosis plus COVID-19 had similar mortality compared with patients with cirrhosis alone but higher than patients with COVID-19 alone[26]. On the other hand, a large study by Moon et al. in 103 patients with cirrhosis and 49 with non-cirrhotic chronic liver disease were enrolled, it showed a mortality of 12.2% of chronic liver disease without cirrhosis, 24% Child-Pugh class A, 43% Child-Pugh class B, and 63.0% Child-Pugh class C. The cause of death in patients with cirrhosis was reported as COVID-19 lung disease in 78.7%, cardiac-related in 4.3%, and liver-related in 12.2%[27]. In a study by Sarin et al[28]. the patterns of liver damage were studied, thus collecting data in 13 Asian countries on patients with known or newly diagnosed chronic liver disease with confirmed COVID-19, in 228 patients (185 with chronic liver disease without cirrhosis and 43 with cirrhosis) it was determined that 80% presented comorbidities, 61% associated with MAFLD and 60% of viral etiology. 43% of patients with chronic liver disease without cirrhosis presented with acute liver injury, and 20% of patients with cirrhosis also presented with acute-on-chronic liver failure. In decompensated cirrhotic patients, liver injury was progressive in 57% of patients, with a mortality of 43%. Increased bilirubin and the AST/ALT ratio predicted mortality among patients with cirrhosis, with a Child-Turcotte Pugh score of 9 or greater at presentation predicting high mortality. Patients with chronic liver disease, diabetes and associated obesity had a worse evolution, they are more vulnerable and need to be closely monitored.

Two international registries collected data from 745 patients with chronic liver disease (CLD) and SARS-CoV-2 (including 386 with and 359 without cirrhosis) and compared them with data from patients without CLD with SARS-CoV-2 from a UK hospital network. Mortality was 32% in patients with cirrhosis versus 8% in those without ($p < 0.001$). Mortality in patients with cirrhosis increased according to Child-Pugh class (A [19%], B [35%], C [51%]) and the main cause of death was respiratory failure (71%). Acute liver decompensation occurred in 46% of patients with cirrhosis, of whom 21% had no respiratory symptoms. Half of those with liver decompensation had acute-on-chronic liver failure. The authors concluded that as the largest such cohort to date, early-stage liver disease and alcohol-related liver disease were shown to be independent risk factors for death from COVID-19. These data have important implications for the risk stratification of CLD patients worldwide during the COVID-19 pandemic. This international registry study demonstrates that patients with cirrhosis are at increased risk of death from COVID-19. COVID-19 mortality was particularly high among patients with more advanced cirrhosis and those with alcohol-related liver disease[29].

Viral hepatitis and COVID-19

Some medications used to treat SARS-CoV-2 include cortisone and immunosuppressive medications such as tocilizumab, increases the risk of hepatitis B virus reactivation. Few studies have evaluated the evolution of patients with hepatitis B infection who are infected with COVID-19. It has been documented that these patients have alterations in liver function tests, such as elevation of aminotransferases (AST, ALT), particularly when admitted to an intensive care unit. The results of these studies are rather contradictory. Some studies have shown that there is no basis for the aggravation of hepatic injury in SARS-CoV-2/HBV coinfection or extended stay in hospital. On the other hand, other studies reported that coinfection is associated with the severity and poor prognosis of COVID-19 and that liver function should be frequently assessed in these patients[30]. The risk of drug hepatotoxicity in COVID-19 patients is high, steroid use has been linked to hepatitis B virus reactivation, especially in those patients who received high doses of steroids, but also with other immunosuppressants such as tocilizumab or baricitinib.

On the other hand, in patients who are being treated for hepatitis B with tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF), care should be taken

with the interaction with COVID-19 drugs such as lopinavir-ritonavir, as they may increase the concentration of TDF or TAF. Treatment for hepatitis B in new patients can be started despite the COVID-19 pandemic, patients already receiving treatment for hepatitis B it is important not to stop medications as they could have a relapse of HBV[31].

In patients with COVID-19, a history of Hepatitis C Virus (HCV) and seropositive HCV infection leads to accentuated SARS-CoV-2 viral virulence and is a strong predictor of in-hospital mortality irrespective of baseline comorbidities, admission laboratory variables, or COVID-19-induced liver injury. The pathophysiology of the infection of HCV and SARS-CoV-2 may have similar pathways. SARS-CoV-2 uses the ACE-2 receptor as a main point of entry to the target cell[32]. One molecule that has been identified to potentiate SARS-CoV-2 viral entry is the transmembrane protease serine 2 (TMPRSS2), which is suggested to affect the S protein at the cell surface and induces SARS-CoV-2-cellular membrane fusion[33]. Importantly, TMPRSS2 is over-expressed in patients with HCV which may lead to the exaggerated SARS-CoV-2 infection in these patients. Studies have shown that in chronic HCV infection there is a correlation between the production of pro-inflammatory cytokines, such as INF-γ and TNF-α, and progressive liver injury, while the regulatory cytokines such as IL-4 and IL-10 may modulate the pro-inflammatory immune response induced by the virus[34]. The history of HCV in these patients seems to add a cumulative mortality risk to any clinical or laboratory profile. The mechanisms involved may be related to extrahepatic effects of HCV leading to enhanced ACE2/TMPRSS mechanisms of SARS-CoV-2 viral entry and may also be related to baseline cytokine-mediated pro-inflammation and endothelial dysfunction. The realization and understanding of these mechanisms may help in better characterization of the disease and investigating possible therapeutic options in this subgroup of patients, which is of significant importance as an initial step towards the selection of at-risk groups that can benefit the most from developing vaccines at an earlier stage of the disease.

Drug-induced liver injury (DILI) and COVID-19

DILI is a common cause of liver injury, identified by the elevation of liver enzymes associated with the initiation or suspension of a suspected drug. In the first and second wave of COVID-19 cases, DILI was described as an injury pattern predominantly hepatocellular, instead of a cholestatic pattern. Histologically, microvesicular steatosis, portal fibrosis, inflammatory infiltrate, and necrosis have been found. The mechanism of hepatic injury is multifactorial and includes the presence of the COVID-19 virus in the vascular endothelium affecting the porta-hepatic system, in addition to hypoxia-reperfusion and release of reactive oxygen species[35]. Several therapeutic strategies have been implemented since the beginning of the Pandemic, most of them have been identified as causing DILI with the following patterns of involvement described: tocilizumab (predominantly cholestasis), remdesivir (hepatocellular), chloroquine (hepatocellular), azithromycin (predominantly cholestasis), acetaminophen (hepatocellular, dose-dependent), lopinavir/ritonavir (hepatocellular, cholestasis or mixed). For the evaluation of the suspected causality of the drug, it is recommended to use the CIOMS/RUCAM scale to prevent risks associated with its use[36,37].

The evaluation of DILI in patients with COVID-19 is a challenge in clinical practice due to unclear factors and polypharmacy that interact in the clinical course of patients[38]. In an initial systematic review of 12 articles, it was reported that the combined incidence of DILI was 25.4% (95% CI, 14.2-41.4) and particularly the incidence of DILI in 208 patients treated with remdesivir was 15.2% (95% CI, 6.4-32), while the incidence was higher with lopinavir/ritonavir 37.2% (95% CI, 22.7-54.6) in a series of 775 patients with COVID-19. Concerning the biochemistry affectation of the liver, hyperbilirubinemia was the most frequent adverse effect of lopinavir/ritonavir, whereas DILI by remdesivir frequently elevated aminotransferases more. In some studies, DILI was attributed to more than one drug[39].

DILI should be considered among the important differentials of liver injury in COVID-19 patients. In Mexico, as in other parts of the world, the desperation for effective therapy at the beginning of the pandemic led to the indiscriminate and irrational use of drugs that could potentially trigger DILI. It is probable that many of the abnormal LFT in our Mexican patients were associated with the following drugs: hydroxychloroquine, ivermectin, dexamethasone, azithromycin, lopinavir/ritonavir, baricitinib, tocilizumab and remdesivir[40].

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

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

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LETTER TO THE EDITOR

New insights into the use of biomarkers in patients undergoing surgery for ulcerative colitis

Nuevas perspectivas sobre el uso de biomarcadores en pacientes con colitis ulcerosa que se someten a cirugía

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To the Editor:

Ulcerative colitis (UC) is an idiopathic, chronic, relapsing-remitting inflammatory disease that usually affects the rectum and colon at the same time. Emergency department visits, hospitalization, and short-term surgery have all decreased as a result of major advancements in medical care, particularly the introduction of biologics in the previous 20 years. Extensive trials of medical therapy are thought to minimize the need for urgent or emergent colectomy, which has poorer outcomes than elective surgery[1,2].

Several biomarkers have been demonstrated to predict the course of disease. Their ability to perform this role has sparked speculation about whether they are likewise linked to the necessity for surgical intervention and has led to their inclusion in prediction algorithms. The capacity to correctly predict which patients will eventually undergo colectomy would be extremely beneficial in patient counseling. Although no one test will likely become the gold standard for determining who needs surgery, there are a few tests that may be useful in minimizing the length of ineffective medical treatment, especially when used in combination[3].

Certain biomarkers such as C-reactive protein (CRP), hypoalbuminemia, and peripheral eosinophilia have been associated with surgical decision-making and have the potential to predict treatment failure. However, the precise significance of biomarkers in predicting which patients will require surgery and when they should undergo surgery is still being determined.

For decades, CRP has been regarded as an important component of UC evaluation. CRP elevation is highly associated with the absence of a functional gastrointestinal disorder, but it has limited sensitivity and is not specific for UC. Besides, the CRP response in UC is quite variable. Due to the short half-life of CRP, serial measurements can be utilized to evaluate treatment response. In hospitalized patients with acute illness, persistently and significantly increased CRP levels have been linked to steroid-resistant disease and the need for surgery[4].

On the other hand, eosinophilia was assumed to be linked to active disease at the time. Recent research has found that peripheral blood eosinophilia (PBE) can be used as a biomarker for disease activity.

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Click et al. conducted a registry analysis of 2066 IBD patients in which they found a link between peripheral eosinophilia and a severe disease phenotype. PBE was linked to severe disease, active disease, primary sclerosing cholangitis, aggressive medical treatment, increased health-care utilization, hospitalization, and the requirement for surgery in people with UC. PBE was linked to hospitalization and surgery in UC, with adjusted odds ratios of 2.35 and 1.76, respectively, according to multivariate analysis. Furthermore, UC patients with PBE had a considerably shorter time to colectomy, according to time-to-event analysis. Additional research verifying the predictive capacity of PBE regarding surgical intervention will be necessary before this tool can be used in decision-making[5]. Multiple biomarkers have been combined to increase the accuracy of predicting which patients would need surgery to treat their disease. To develop best practices, more research is needed on the best usage and combination of biomarkers, as well as the effects of earlier surgical intervention as required by such a predictive model.

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LETTER TO THE EDITOR

Variant ELMO1 rs1345365 is associated with pseudoperniosis in patients with COVID-19

La variante rs1345365 de ELMO1 está asociada a pseudoperniosis en pacientes con COVID-19

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To the Editor,

Pseudoperniosis, known as chilblains on the hands and skin, corresponds to areas of lesions with erythema or purplish discoloration, vesicles, and pustules, typically asymmetrically distributed. It is considered the 5th most common dermatosis in patients infected with SARS-CoV-2 (COVID-19) and is the most characteristic one too. It is often seen in young patients and in the later stages of the disease[1]. Due to its clinical nature, various vascular factors, such as endothelial dysfunction and COVID-19-induced microangiopathy have been proposed as possible biological determinants[1]. In this regard, the rs1345365 polymorphism of the ELMO1 gene is a candidate marker for describing this condition, as it regulates vasculogenesis, angiogenesis, fibrogenesis, inflammation, apoptosis, and cell migration[2], which are all dysregulated processes in patients with COVID-19.

With these considerations, 830 men were selected out of a total of 4370 COVID-19 patients treated at CIMETP and ME Piel Centro Dermatológico, 415 of whom presented with unilateral (n = 812) or bilateral pseudoperniosis (n = 18), while the remaining 415 had not develop any type of dermatosis and were age-matched with the cases (range, 18-45 years). The patients were diagnosed with COVID-19 using the real-time polymerase chain reaction (PCR) assay. DNA was extracted from peripheral blood using the GeneCatcher kit (Invitrogen) to amplify the rs1345365 polymorphism of the ELMO1 gene through an allele-specific PCR assay, with the previously reported primers and reaction mixture conditions, amplification program, and polyacrylamide gel electrophoresis[2]. Thus, the ancestral homozygous G/G genotype was found more frequently in patients with pseudoperniosis, while the reference homozygous A/A genotype was more common in controls. A total of 5 models were analyzed using multiple logistic regression (MLR), and the homozygous G/G genotype was found to be associated with higher risk in different models (Table 1).

This is the first study ever conducted showing a possible relationship between pseudoperniosis in COVID-19 patients and the rs1345365 variant of the ELMO1 gene. There is this possibility of false positives (and negatives) regarding ELMO1 variant genotyping due to the allele-specific PCR; however, the primer design includes the introduction of mutations that increase specificity and decrease the rates of false-positives or false-negatives[2]. There is also this possibility of false negatives with COVID-19 and pseudoperniosis due to mutations in the S gene that escape qRT-PCR, such as the 69-70 deletion; in both

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Table 1. Distribution of the rs1345365 polymorphism of the ELMO1 gene in COVID-19 pseudoperniosis

Genotypes	Cases (n)	Controls (n)			
GG	75	21			
GA	105	126			
AA	235	268			
Alleles A					
G	575	662			
	255	168			
MLR models	**X2**	**Correlation coefficient**	**p**	**Risk ratio (odds)**	**95%CI**
GG genotype vs GA+AA	33.5	0.403	0.0000001	1.67	1.4-1.9
GG+AA genotype vs GA	2.6	0.012	0.1039	1.07	0.9-1.1
GG genotype vs GA	29.25	0.515	0.0000001	1.7	1.4-2.6
GG genotype vs AA	31.84	0.397	0.0000001	1.6	1.4-1.9
GA genotype vs AA	0.1019	0.004	0.749	0.9	0.8-1.1

MLR, multiple logistic regression; 95%CI, 95% confidence interval .

cases, false negatives can be reduced by sequencing PCR products. Certainly, the models presented confirm that pseudoperniosis was better explained by a predominance of the recessive model, in which heterozygotes do not have a greater influence. In light of these findings, the lack of specificity of the variant, is related to the multifactorial nature of this trait, which is why markers in other candidate genes should be looked into. However, the fact that this gene has been frequently explored in melanomas and other dermatological diseases, such as psoriasis[3,4], supports its role in the development of pseudoperniosis.

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Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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