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LETTER TO THE EDITOR

Post-COVID-19 sequelae: an imbricate network between neuroinflammation and dysbiosis

Secuelas post-COVID-19: una imbricada red entre la neuroinflamación y la disbiosis

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The coronavirus disease 2019 (COVID-19) still affects millions of people worldwide. Like other respiratory viruses, the main entry route for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is through the nasal passages, from where it can directly reach the respiratory system and the central nervous system (CNS). Both systems have cells that express the ACE2 receptor, among others, which mediate the virus entry into cells. Therefore, besides predominantly causing respiratory issues, the virus can affect the CNS. By expressing signals associated with the virus *per se* and damage signals, the pathogen can promote both systemic inflammation and CNS inflammation (central inflammation or neuroinflammation). In its acute phase, these exacerbated inflammatory phenomena aim to control the infection, but when sustained or persistent (chronic inflammation), they can amplify the damage. It is estimated that this chronic inflammation scenario is observed in 10% up to 30% of non-hospitalized infected patients and 50% up to 70% of hospitalized patients. This exacerbated peripheral and central inflammation promotes the development of post-COVID sequelae or post-COVID syndrome (PCS)[1]. In this context, PCS is already an emerging global health problem. Clinically, this condition is heterogeneous and multisystemic, with signs and symptoms that can persist beyond 12 weeks post-acute infection. The described signs can occur regardless of age and the clinical form of COVID-19 the infected person had.

One of the best-characterized clinical signs with the greatest impact on morbidity is neuropsychiatric, including neurocognitive alterations, fatigue, headache, anosmia/hyposmia, dizziness, diffuse pain, anxiety, or depression, which occur in more than 80% of those who have experienced severe COVID-19. Although the causes of PCS are unknown, various pathophysiological mechanisms may be involved; among these, immune system dysregulation with or without reactivation of underlying pathogens and intestinal dysbiosis seem to be determining factors. The outlook looks grim in Mexico, considering the high prevalence in the general population of conditions such as diabetes, hypertension, obesity, and periodontal disease, among others, which are characterized by a state of chronic inflammation closely related to dysbiosis and, consequently, neuroinflammation.

Those affected by PCS share clinical features with other post-viral syndromes, including changes to the immune response, both innate (activation of innate cells such as macrophages, neutrophils, and NK cells) and adaptive. In the latter, the number of several T cell subtypes is affected, including fewer effector memory CD4+ T cells, as well as markers of exhaustion (increased programmed death ligand 1 [PD-1], an immunoregulatory protein) in both CD4+ and CD8+ T cells, which persists for more than 12 months[1,2]. Interestingly, it has been reported that even 8 months after having had COVID-19, there is a loss of naive B and T cells, along with increased expression of type I

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interferons (IFN-α and IFN-β) and III (IFN-λ)[1,3]. These findings could be potentially useful for confirming the clinical diagnosis of PCS through flow cytometry tests.

Other alterations in the immune profile include the elevation of pro-inflammatory cytokines such as interleukin [IL] 1β, IL-6, tumor necrosis factor-alpha, and chemokines such as IFN-λ inducible protein-10 and eotaxin 1 (CCL11); the latter has been closely associated with cognitive dysfunction and microglial activation at the hippocampal level, as well as inhibition of neurogenesis in a murine model of SARS-CoV-2 infection[1,4].

Magnetic resonance imaging studies have shown a decrease in the cortical volume of gray matter, particularly in the orbitofrontal cortex and parahippocampal gyrus (regions functionally connected to the primary olfactory cortex) and a significant reduction in overall brain size in individuals with PCS[5]. Additionally, alterations in the gut microbiota have been reported since the acute phase of COVID-19, with fewer species such as *Faecalibacterium prausnitzii* and *Eubacterium rectale*, which have immunoregulatory properties, and more species such as *Ruminococcus gnavus* and *Bacteroides vulgatus*. These changes during the acute phase have been associated with the development of the pro-inflammatory cytokine storm but can persist chronically, even a year after the infection. Their persistence leads to changes such as the reduction of anti-inflammatory bacterial products like short-chain fatty acids, particularly butyrate (a metabolite derived from the fermentation of polymeric carbohydrates, like starch), increased intestinal permeability, and translocation of toxic microbiota components (bacterial like lipopolysaccharide [LPS] or fungal like galactomannan and β-D-glucan) into the blood, which strongly contributes to systemic inflammation and neuroinflammation[1]. The causal role of microbiota alterations in inflammation is supported by data on the transfer of microbiota from human individuals with PCS to healthy mice, which promotes various pathological changes such as impaired pulmonary defense mechanisms against bacteria and cognitive impairment, phenomena that collectively simulate the neurocognitive manifestations of PCS[6].

The persistence of systemic/neuroinflammatory phenomena induces deleterious effects on the brain, particularly due to sustained microglial and astrocyte activation (astrogliosis) and neuron loss, which could precipitate the development of neurodegenerative diseases. In this context, a scenario that warrants short-term attention is presented, particularly considering the ongoing circulation of SARS-CoV-2, which promotes the generation of new variants, the high prevalence of low-intensity chronic inflammatory states combined with an aging population, and the increase in neurocognitive and psychiatric signs in PCS. Early recognition of PCS may be important for proper treatment planning and preventive measures that could potentially help reduce the risk of neurodegeneration, such as regular nasal washes with saline solution, routine aerobic exercise, consumption of prebiotic polyphenols (coumarin, tannins, phenolic acids, flavonoids) through diet combined with probiotics, and cognitive therapy that could impact the homeostasis of the gut and nasal microbiome.

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ORIGINAL ARTICLE

Utilizing the lymphocyte-monocyte ratio in predicting the recurrence of spontaneous pneumothorax

Utilización de la proporción linfocitos-monocitos para predecir la recurrencia del neumotórax espontáneo

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Abstract

Objective: *Lymphocyte-to-monocyte ratio (LMR) has been introduced as a predictor and a prognostic factor for multiple diseases. This study aimed to determine the efficiency of LMR in predicting the recurrence of spontaneous pneumothorax.* **Materials and methods:** *A total of 374 patients who had received chest tubes at the first episode of primary spontaneous pneumothorax were examined in terms of age, gender, side of the pneumothorax, status of recurrence, LMRs at the time of admittance and recurrence, and the interval until the recurrence.* **Results:** *Recurrence was diagnosed in 106 (28.3%) patients, whereas the mean time until the recurrence was 15.32 ± 5.57 months. Significantly, the recurrence rate was higher, while the time until the relapse was shorter for patients with elevated levels of LMR. Moreover, LMR counting over 1.25 demonstrated a 70.8% sensitivity and a 94.4% specificity in predicting a potential recurrence.* **Conclusions:** *Calculation of LMR at the first episode of spontaneous pneumothorax contributes to predict a potential recurrence when combined with traditional risk factors.*

Keywords: *Spontaneous pneumothorax. Recurrence. Lymphocyte-to-monocyte ratio. Prediction. Surgery.*

Resumen

Objetivos: *La proporción de linfocitos a monocitos (PLM) se ha introducido como un predictor y un factor pronóstico para múltiples enfermedades. Este estudio tuvo como objetivo determinar la eficiencia de LMR en la predicción de la recurrencia del neumotórax espontáneo.* **Materiales y métodos:** *Un total de 374 pacientes que habían recibido tubos de tórax en el primer episodio de neumotórax espontáneo primario fueron examinados en términos de edad, género, lado del neumotórax, estado de recurrencia, PLM al momento del ingreso y recurrencia, y el intervalo hasta la recurrencia.* **Resultados:** *Se diagnosticó recidiva en 106 (28.3%) pacientes, siendo el tiempo medio hasta la recidiva de 15.32 ± 5.57 meses. Significativamente, la tasa de recurrencia fue mayor, mientras que el tiempo hasta la recaída fue más corto para los pacientes con niveles elevados de PLM. Además, el recuento de PLM superior a 1.25 demostró una sensibilidad del 70.8 % y una especificidad del 94.4 % para predecir una posible recurrencia.* **Conclusión:** *Calcular la PLM en el primer episodio de neumotórax espontáneo predice una posible recurrencia cuando se combina con los factores de riesgo tradicionales.*

Palabras clave: *Neumotórax espontáneo. Reaparición. Proporción de linfocitos a monocitos. Predicción. Cirugía.*

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Introduction

Primary spontaneous pneumothorax (PSP) is the accumulation of air in the pleural space without any underlying traumatic and iatrogenic etiology or an evident pulmonary disease. Tall and thin body habitus, male gender, smoking, and being aged between 19 and 25 years are frequently encountered clinical features whereas subpleural blebs and bullae appear to play a significant role in the pathogenesis of PSP at a rate as high as 80%[1,2].

The recurrence rate of PSP has been reported to be ranging over 30% after the first episode[3]. Although there have been conclusive studies that indicate the risks of recurrence, debates mostly consist of similar variables and surgical outcomes while the deficiency of presenting novel predictive factors still exists[1-4].

The lymphocyte-to-monocyte ratio (LMR) actually compels attention as a diagnostic tool for inflammatory events and a predictor of prognosis in malignancies for the concomitant advantages of easy accessibility and economical benefits.

Regarding that the pathological manifestations of PSP mostly develop in response to the inflammatory reactions produced by the parenchymal injury, this study aimed to investigate the efficacy of LMR in predicting the recurrence of PSP for the first time in the literature.

Material and methods

This study was approved by the Kırklareli Medical School Scientific Research Ethic Committee (P202200019-01/8.8.22). A retrospective study was conducted to include a total of 374 patients among 442 cases who had been diagnosed with PSP at the University Hospital between 2000 and 2021. Treatment with tube thoracostomy at the first episode and recurrent pneumothorax on the same side of the initial event were the principal inclusion criteria. Patients who had presented a secondary spontaneous pneumothorax, a history of chest surgery and any clinical or radiological suspicion of a local or a systemic infection, were excluded from the study. Regarding the well-accepted impact of smoking on the occurrence and also recurrence of PSP, the current and past history of smoking were accepted as exclusion criteria to provide a valid analysis of LMR as a potential risk factor. Follow-up period for the whole group of patients was 5 years.

In the first episode, all patients received 20 or 24 French chest tubes under local anesthesia. LMRs were calculated through whole blood counts that were obtained before interventions. The patients were invited to follow-up examinations during the 1st and 3rd weeks after being discharged or any time when they developed complaints similar to the initial admittance. The presence of recurrent pneumothorax was confirmed by chest X-ray or computed tomography. The patients with recurrence received chest tubes or underwent thoracotomy or thoracoscopy where partial parietal pleurectomy in addition to bullectomy or wedge resection was applied.

Whole group of patients was examined in terms of age, gender, side of the pneumothorax, LMR, status of recurrence, and the time until the recurrence. LMR was noted as a numerical value while the time of recurrence was stated as months.

The Statistical Package for the Social Sciences (SPSS) (IBM SPSS for Windows, Ver.24) statistical package program was used for calculations. The descriptive statistics were stated as mean, standard deviation, minimum, and maximum for continuous variables and as number and percentage for categorical variables. The calculations were checked for normal distribution by Kolmogorov–Smirnov ($n > 50$) test and parametric tests were applied. One-way analysis of variance (ANOVA) was performed to compare the mean values of the patient groups. Pearson correlation coefficients were used to reveal the relations between measurements. Sensitivity, specificity, and cut-off values of LMR were assessed by ROC analysis. Chi-square test was used to identify the relation between categorical variables. $p < 0.05$ were considered as statistically significant.

Results

The mean age of the patients including 296 (79.1%) males and 78 (20.9%) females was 22.45 ± 2.5 years. Pneumothorax was right sided in 177 (47.3%) and 197 (52.7%) cases. Mean LMR was calculated as 1.21 ± 0.31 at the first episode and 1.43 ± 0.58 at the time of relapse. Recurrent pneumothorax was diagnosed in 106 (28.3%) patients whereas the mean time between the first episode and the recurrence was 15.32 ± 5.57 months. Related data were summarized in table 1.

Statistical studies were unable to determine a significant difference in terms of gender and side of pneumothorax regarding the status of recurrence

Table 1. Demographic and clinical features of the patients

Parameters	Values
Age, mean ± SD (min-max), years	22.45 ± 2.51 (17-36)
LMR at first episode, mean ± SD (min-max)	1.21 ± 0.31 (0.7-2.5)
LMR at recurrence, mean ± SD (min-max)	1.43 ± 0.58 (0.9-2.7)
Time until recurrence, mean ± SD (min-max), months	15.32 ± 5.57 (6-28)
Gender, n (%)	
Male	296 (79.1)
Female	78 (20.9)
Side of pneumothorax, n (%)	
Right	177 (47.3)
Left	197 (52.7)
Recurrence, n (%)	
Present	106 (28.3)
Absent	268 (71.7)

SD: standard deviation; Min: minimum; Max: maximum; LMR: lymphocyte-to-monocyte ratio.

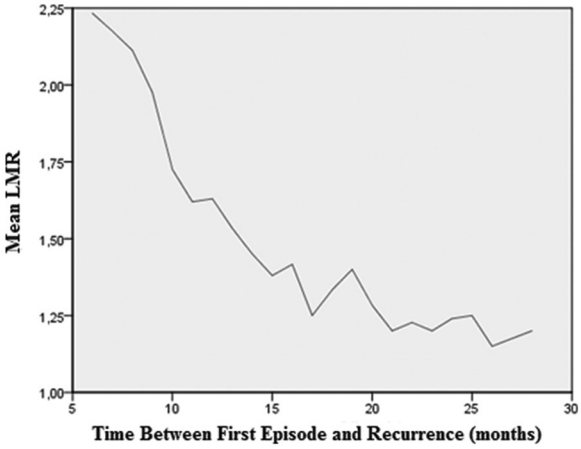

Figure 1. *Relation of lymphocyte-to-monocyte ratio and the time between first episode and recurrence of pneumothorax.*

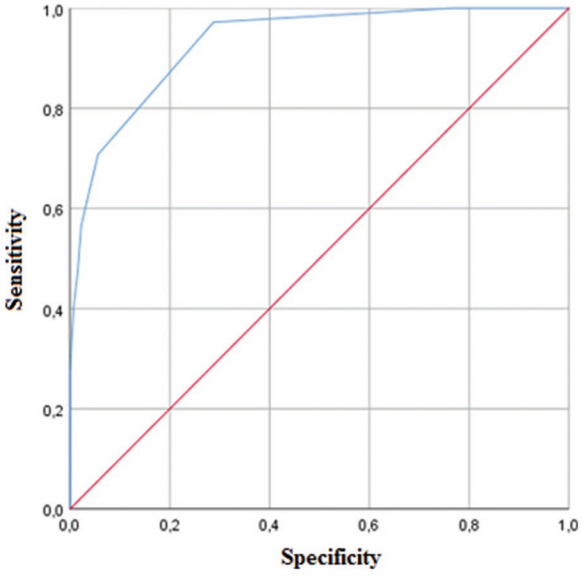

Figure 2. *Receiver operating characteristic analysis of lymphocyte-to-monocyte ratio as the predictor of recurrent pneumothorax.*

(p > 0.05). Furthermore, gender or side of the pneumothorax did not constitute a difference in the LMR counts (p = 0.075 and 0.727, respectively). However, mean LMR was 1.53 ± 0.35 for the patients who had developed recurrence and 1.08 ± 0.15 for the rest of the cases, showing that mean LMR was significantly elevated in the patients who would encounter a relapse (p < 0.05) (Table 2). With regard to the recurrence-developing group of patients, mean time that had passed until the recurrence was shorter for the cases who had higher counts of LMR considering that statistical analysis indicated a negative if correlation coefficient between these two variables (p = 0, r = –0.81) (Fig. 1).

LMR demonstrated a 70.8% sensitivity and a 94.4% specificity in predicting a potential recurrence for a cut-off value of 1.25 (area under the curve: 0.931, p = 0.001) (Fig. 2).

Among a total of 442 cases with the first episode PSP, 68 patients were only observed clinically and radiologically and discharged without any additional treatment or intervention. Thoracoscopy was performed for 78 (73.6%) and thoracotomy for 26 (24.5%) cases who had developed recurrence whereas 2 (1.9%) patients who had disapproved surgery were treated with tube thoracostomy.

Discussion

The findings of this study show that LMR exceeding the threshold value of 1.25 at the first episode of pneumothorax may contribute to predict a potential recurrence.

PSP more frequently occurs in young males with tall and thin habitus whereas bullous parenchymal lesions and smoking are considered as definite risk factors[2,4-8]. Although the optimal management strategy of first-episode PSP is still controversial, techniques of observing small PSPs without intervention and placing small-bore chest tubes for larger PSPs only if the attempts to success by simple aspiration fail have been approved[9]. A recent study by Brown et al. reported that conservative management of moderate-to-large PSPs provided resolution of pneumothorax within 8 weeks and resulted in lower rates of

Table 2. Factors associated with the recurrence

Parameters	Recurrence (n = 106)	Non-recurrence (n = 268)	p-value
Age, mean ± SD	21.3 ± 2.42	22.09 ± 2.26	0.263*
Gender, n (%)			0.081†
Male	83 (28)	213 (72)	
Female	23 (29.5)	55 (70.5)	
LMR at first episode, mean ± SD	1.53 ± 0.35	1.08 ± 0.15	< 0.001*
Side of pneumothorax, n (%)			0.848†
Right	51 (28.8)	126 (71.2)	
Left	55 (27.9)	142 (72.1)	

*ANOVA: analysis of variance.
†Chi-square.
SD: standard deviation.

recurrence when compared to interventional treatment[10]. Recurrence of PSP ranging from 16% to 52% and progressively increasing incidence of subsequent recurrences constitutes a significant challenge for both patients and physicians[2,5].

Histopathologic findings in the surgical specimens from the patients with pneumothorax mostly conform with chronic inflammation that demonstrates eosinophilic pneumonia-like changes, pleuritis, and hemosiderin deposition in both pleura and lungs[11]. This evidence has arised the efforts to consider the inflammatory events associated with pneumothorax to predict a potential relapse. De Smedt et al. reported that peripheral blood analysis in patients with first-episode pneumothorax indicated an increase in white blood cell, neutrophil, monocyte, and eosinophil counts and also a non-significant decrease in lymphocyte counts when compared to the control group of healthy individuals[12]. A study by Selvi et al. also announced that elevated neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios were associated with recurrence in the patients with PSP[13].

Utilization of LMR was announced to be efficient in the diagnosis and the determination of prognosis in both inflammatory diseases and malignancies. LMR was reported as an independent prognostic factor in the patients following antituberculous treatment and also a valuable independent indicator to identify the extent of involvement for active ulcerative colitis[14-16]. Moreover, recent studies reported that LMR was instructive in obtaining additional prognostic information in malignancies including colon cancer, hepatocellular carcinoma, and follicular lymphoma[17-19]. The current literature does not include any studies that address LMR as a risk or a predictive factor for the recurrence of pneumothorax. In this series, the presence of elevated LMR noticed at the first episode was related with a relapse. Moreover, the time interval until the recurrence demonstrated a significant negative correlation with higher counts of LMR. All these findings imply that LMR that elevates in relation to the severity of inflammatory processes lends assistance to predict the recurrence of pneumothorax as well as the prognosis of several malignancies. However, multicentered prospective studies with larger study populations and multivariate analysis are needed.

The principal limitations were the retrospective design over a long period of time during which the management for PSP has evolved and the strict norms for the exclusion of cases with secondary spontaneous pneumothorax, smoking, and a past history of chest surgery.

Conclusion

The value of LMR above the threshold value of 1.25 that is measured at the first episode of PSP may provide supporting evidence to predict a potential recurrence when combined with the traditional risk factors.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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

Abdominal aortic aneurysm characteristics and outcomes: a single-center retrospective cross-sectional study

Características y resultados de aneurismas aórticos abdominales: estudio transversal y retrospectivo de un solo centro

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Abstract

Objective: *The objective of the study is to evaluate the characteristics and outcomes of patients with abdominal aortic aneurysm (AAA) and its correlation with mortality in the first 30 days after the procedure was performed.* **Methods:** *Demographic information, clinical and radiological characteristics, as well as outcomes 30 days after the procedure was performed were assessed and compared. Continuous variables were analyzed with Student's t-test and categorical with Chi-square and Fisher's exact test.* **Results:** *Duration of the procedure (p = 0.001), blood loss (p < 0.001), age > 75 years (p = 0.027), aneurysm size > 65 mm (p = 0.01), open surgery (p = 0.001), presence of pain (p = 0.005), chronic kidney disease (p = 0.03), and rupture of the aneurysm (p < 0.001) were the factors significantly associated with mortality.* **Conclusion:** *It is essential that patient characteristics and comorbidities are assessed, as well as factors that may affect the outcomes to predict the prognosis in patients with AAA. At present, no mortality predictive model is universally applicable and highly variable performance across different populations might need a model that adapts to the population of interest.*

Keywords: *Aortic abdominal aneurysm. Characteristics. Outcomes. Mexico.*

Resumen

Objetivo: *Evaluar las características y resultados de los pacientes con aneurisma de aorta abdominal y su correlación con la mortalidad en los primeros 30 días después de realizado el procedimiento.* **Métodos:** *Se evaluó y comparó la información demográfica, las características clínicas y radiológicas, así como los resultados a los 30 días de realizado el procedimiento. Las variables continuas se analizan con la prueba de t de Student y las categóricas con Chi-cuadrado y la prueba exacta de Fisher.* **Resultados:** *La duración del procedimiento (p = 0.001), pérdida de sangre (p < 0.001), edad > 75 años (p = 0.027), tamaño del aneurisma > 65 mm (p = 0.01), cirugía abierta (p = 0.001), presencia de dolor (p = 0.005), enfermedad renal crónica (p = 0.03) y rotura del aneurisma (p < 0.001) fueron los factores asociados significativamente a la mortalidad.* **Conclusión:** *Es fundamental evaluar las características de los pacientes y las comorbilidades, así como los factores que pueden afectar los resultados para predecir el pronóstico en pacientes con aneurisma de aorta abdominal. En la actualidad, ningún modelo predictivo de mortalidad es universalmente aplicable y la alta variabilidad de resultados entre diferentes poblaciones podría necesitar un modelo que se adapte a la población de interés.*

Palabras clave: *Aneurisma de la aorta abdominal. Características. Resultados. México*

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Introduction

Abdominal aortic aneurysm (AAA) describes a segmental, full-thickness dilatation of the abdominal aorta exceeding the normal vessel diameter by 50%, although an aneurysm diameter of 3.0 cm is commonly regarded as the threshold[1]. The prevalence rates of AAA range from 1.9% to 18.5% in males and 0% to 4.2% in females[2]. Frequent risk factors associated with AAA are age, smoking, gender, chronic obstructive pulmonary disease, chronic kidney disease, hypertension, family history, and coronary artery disease[3]. They are usually asymptomatic unless complications occur. Patients at the highest risk of aortic rupture are those with larger diameter AAAs. Growth rates increase markedly with aneurysm diameter; for each 0.5 cm increase in AAA diameter, growth rates increased by 0.5 mm/year and rupture rates double[4,5]. The estimated annual rupture risk according to diameter is 0%, 0-5%, 13-15%, 10-20%, 20-40%, and 30-50% in cases with diameter less than 4 cm, 4-5 cm, 5-6 cm, 6-7 cm, 7-8, and > 8, respectively[6]. This catastrophic event is associated with a mortality of 50–80% and even with emergency surgical repair, mortality is about 40% to 50%[7,8]; the strongest predictor of in-hospital mortality has been found to be age[9]. There are currently open and endovascular techniques whose objective is to isolate the aneurysm from the circulation, eliminating the risk of rupture. Early complications after the procedure are common. They include endoleaks (persistent blood flow into the aneurysm sac after graft placement), access site complications (arterial rupture and dissection), atheroembolism, lower limbs ischemia, renal failure, and endograft migration.

Recent studies have found a significantly decrease in AAA rupture mortality rates, mainly due to improvements in public health awareness, screening, and management[10-12]. In view of the high morbidity and mortality rates, the importance of early diagnosis and treatment to decrease the public health burden, this study is aimed to evaluate the characteristics and outcome of patients with AAAs and its correlation with mortality in the first 30 days after the procedure was performed. To the best of our knowledge, this is the first analysis of the characteristics and outcomes of AAA including Mexican population.

Materials and methods

Study design and setting

This is a retrospective, cross-sectional study conducted at a national vascular surgery referral hospital in Mexico. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required. This retrospective study was approved by the institutional ethics review board and a waiver of consent was obtained.

Study population

From January 2016 to December 2021, patients with AAA presenting to the emergency department or in-hospital vascular surgery consultation were studied. For this study, patients with confirmed AAA were enrolled using census sampling method. Patients with an incomplete medical profile and those discharged against medical advice were excluded.

Data collection

Data were collected by reviewing medical records of the medical center. Pre-designed checklists containing medical history, demographic data (age, gender), chief complaint, characteristics of aneurysm (location, size), family history, presence or absence of leakage based on computed tomography scan findings, and treatment approach, as well as outcomes (mortality) (Fig. 1).

Statistical analysis

Data analysis was done using the Statistical Package for the Social Sciences version 25.0 statistical software. Findings were presented as mean ± standard deviation or frequency (%) for numerical and categorical variables, respectively. The utilized tests were chi-square, independent sample t-test, and Fisher's exact test. $p < 0.05$ was considered statistically significant.

Results

Characteristics of patients

During COVID-19 pandemic, the admission of patients reduced significantly, leaving 56 patients for analysis. Table 1 and Figure 2 show the baseline characteristics of studied patients. The mean age was 71.93 ± 10.21 (22-86). 80.4% (45) were male and 19.6% (11) were female. The most frequent chief

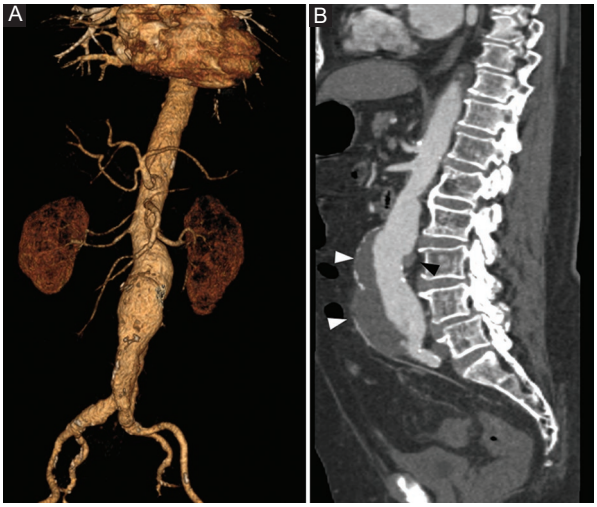

Figure 1. A: *CT reconstruction of the abdomen and pelvis shows a 7.1 cm AAA.* **B:** *sagittal CT with intravascular contrast shows an AAA with mural thrombus on both the anterior (white arrowheads) and posterior (black arrowhead) margin of the aorta.*

complaint was pain (51.8%), whereas abdominal pain being the most frequent location (37.5%), followed by lumbar pain (12.5%) and thoracic pain (8.9%). Limb ischemia presented in 7.1% and shock state only in 3.6%. The main duration of pain was 1.65 ± 4.33 months and mean aneurysmal size was 65.42 mm ± 15.26. Location of the aneurysm was found infrarenal in 89.3%, juxtarenal in 5.4%, and abdomino-thoracic aorta in 5.4%. Synchronous aneurysm presented on the right common iliac artery (14.3%), left common iliac artery (3.6%), and both iliac arteries (10.7%).

Outcomes

Elective procedure was performed in 80.4% (45). Open surgery was performed in 32.1% (18). Of all mortality in open surgery, ruptured aneurysm represented 80% (8). Endovascular procedure was performed in 67.9% (38) with a mortality of 10.5% (4). Ruptured aneurysms represented 19.6% (11) of cases, in which death was seen in 81.8% (9). 25% (14) patients did not survive 30 days after the procedure was performed, in which ruptured aneurysms represented 64.3% (9). Duration of the procedure ($p = 0.001$), blood loss ($p < 0.001$), age > 75 years ($p = 0.027$), aneurysm size > 65 mm ($p = 0.01$), open surgery ($p = 0.001$), presence of pain ($p = 0.005$), chronic kidney disease ($p = 0.03$), and rupture of the aneurysm ($p < 0.001$) were among the factors significantly associated with mortality (Table 2).

Table 1. Baseline characteristics of patients

Variables	Frequency, n (%)
Gender	
Male	45 (80.4)
Female	11 (19.6)
Pain location	
Abdominal	21 (37.5)
Lumbar	7 (12.5)
Thoracic	5 (8.9)
Shock state	2 (3.6)
Limb ischemia	4 (7.1)
Medical history	
Smoking	50 (89.3)
Hypertension	43 (76.8)
Ischemic heart disease	13 (23.2)
Diabetes mellitus	12 (21.4)
Chronic kidney disease	9 (16.1)
Dyslipidemia	6 (10.3)
Chronic obstructive pulmonary disease	5 (8.9)
Cerebrovascular accident	3 (5.4)
Iliac artery synchronous aneurysm	
Right common iliac artery	8 (14.3)
Bilateral common iliac artery	6 (10.7)
Left common iliac artery	2 (3.6)
Family history	1 (1.8)
Aneurysm location	
Infrarenal	50 (89.3)
Juxtarenal	3 (5.4)
Abdomino-thoracic	3 (5.4)

Discussion

In this study, we show the characteristics of patients with AAA, the outcomes after the procedure (open or endovascular), and its correlation with mortality in the first 30 days after the procedure was performed (Figs. 3 and 4). According to previous data, smoking is the main risk factor correlated to AAA[3]. Other risk factors include age, male gender, high blood pressure, coronary artery disease, family history of AAA, high cholesterol, lower extremity peripheral arterial disease, history of a cerebrovascular event, and obesity. Diabetes has been found as a negative association with AAA[13]. This correlates with our study, in which we observed smoking as the most frequent associated factor, followed by hypertension and coronary artery disease. More recent studies have found a positive correlation between chronic obstructive pulmonary disease, chronic kidney disease, and greater incidence of AAA[14,15].

The incidence of concomitant common iliac artery aneurysm has been reported from 12% to 40%, and

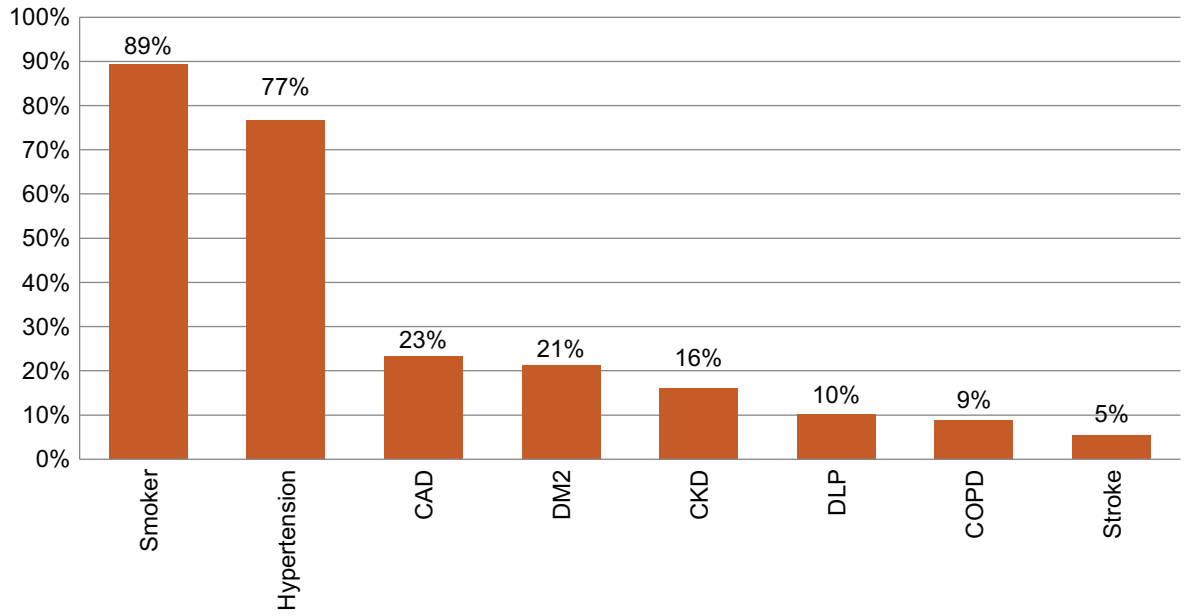

Figure 2. *Comorbidities of studied patients.*
CAD: coronary artery disease; DM: type 2 diabetes mellitus; CKD: chronic kidney disease; DLP: dyslipidemia, COPD: chronic obstructive pulmonary disease.

Table 2. Correlation between baseline characteristics, outcomes, and mortality

Variables	Survived, n (%)	Died, n (%)	p value	OR (CI 95%)
Age > 75	13 (59.1)	9 (40.9)	0.02	4.01 (1.1-14.3)
Aneurysm size > 65 mm	11 (55)	9 (45)	0.01	5 (1.3-18.4)
Open surgery	8 (44.4)	10 (55.6)	0.001	10.6 (0.6-42.7)
Female gender	7 (63.6)	4 (36.4)	0.43	0.5 (0.1-2)
Pain	17 (21.8)	12 (41.4)	0.005	8.8 (1.7-44)
Ruptured aneurysm	2 (18.2)	9 (81.8)	< 0.001	36 (5.9-216)
Cerebrovascular accident	1 (33.3)	2 (66.6)	0.15	6.8 (0.5-82)
Hypertension	31 (72.1)	12 (27.9)	0.48	2.1 (0.4-11)
Smoking	38 (76)	12 (24)	0.63	0.6 (0.1-3)
Diabetes mellitus	12 (100)	0 (0)	0.02	0.6 (0.5-0.8)
Chronic kidney disease	4 (44.4)	5 (55.6)	0.03	5.2 (1.1-23)
Ischemic heart disease	11 (84.6)	2 (15.4)	0.48	0.4 (0.09-2.4)
Chronic obstructive pulmonary disease	2 (40)	3 (60)	0.09	5.4 (0.8-36)
Length of stay (days) Mean ± DE	13.1 ± 6.9	10.2 ± 10.7	0.24	
Duration of procedure (min) Mean ± DE	233.9 ± 17.2	378.5 ± 173.6	0.001	
Blood loss (ml) Mean ± DE	467.6 ± 595	2971 ± 2885	< 0.001	

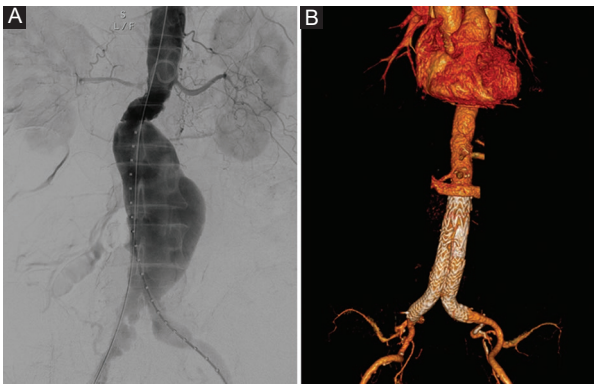

Figure 3. A: *diagnostic angiography demonstrating the presence of an infrarenal AAA.* **B:** *computed tomography 3D volume rendering after EVAR showing no stent-graft migration, limb occlusion, or endoleak.*

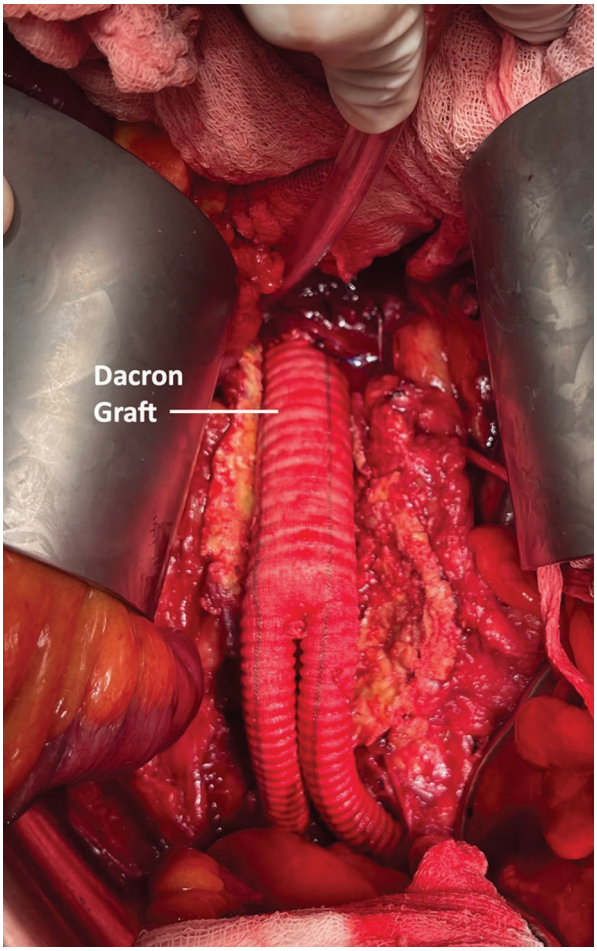

Figure 4. *Abdominal aortic aneurism repair with the placement of a dacron graft. Note the aneurysm sac surrounding the graft.*

that right sided is more common than left sided[16-18]. We report an incidence of 28.6%, also with right sided (14.6%) being more frequent than left (3.6%).

Factors significantly correlated with mortality 30 days after the procedure was performed were the duration of the procedure, blood loss, age > 75 years, aneurysm size > 65 mm, open surgery, presence of pain, chronic kidney disease, and rupture of the aneurysm at presentation. Several predictor models and risk factors for mortality after AAA repair in different clinical situations (elective or urgent; open or endovascular) have been described with contrasting and similar results, but the most consistent data associated with mortality are procedure performed, chronic obstructive pulmonary disease, cerebrovascular disease, renal insufficiency, aneurysm size, increasing age, female sex, serum creatinine level, cardiac disease, previous aortic surgery or stent, abnormal white cell count, and abnormal serum sodium level. Lijftogt et al.[19]. conducted a systematic review for mortality risk prediction models for AAA surgery and at present, no predictive model is universally applicable due to the lack of external validation, and they also demonstrated highly variable performance across different populations.

Randomized controlled trials[20-22] of AAA have shown marked benefits of EVAR with respect to 30-day mortality compared to open repair. Although aneurysm rupture is the most significant complication, aneurysm-related death is a relatively minor determinant of long-term survival in all three randomized trials[23], systematic reviews,[24] and retrospective studies[25,26]; atherosclerotic cardiovascular, end-stage renal disease, and cancer-related death represent a greater threat.

Considering that survival is influenced by these factors, this raises the issue of screening for AAA to ease early elective intervention at a younger age, ideally before the onset of comorbidity and therefore, higher risk of death. Evidence shows that screening reduces aneurysm-related mortality in certain populations, with the strongest recommendation for men aged 65-75 years[27]. Screening patients below 65 years old are unlikely to be economically viable (due to a low prevalence of disease), although expanded criteria for screening have been recently proposed[28]. It is therefore imperative that aside from perioperative details, patient characteristics and comorbidities are assessed, as well as factors that may affect the outcome to predict the prognosis in patients with AAA. These data might prove to be of clinical interest and relevance for the assessment of prognostic variables for short and long-term survival.

This study has some limitations. First, it is retrospective and therefore prone to inherent bias with such studies. This was a small retrospective study with only 56 patients, and its statistical power may be limited.

Second, the follow-up period was lost in some patients as to permit an investigation of the long-term clinical outcomes of overall survival. It is also important to note that several types of graft were utilized; however, this reflects real-world clinical practice.

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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 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 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

Activity-based locomotor training: improving the movement in children with spinal cord injury

Entrenamiento locomolocomo basado en la actividad: mejorar el movimiento en niños con lesión medular

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Abstract

Objective: *The objective of this study was to investigate the effects of activity-based locomotor training (ABLT) on motor function and walking ability in children with spinal cord injury (SCI).* **Materials and methods:** *The Chinese National Knowledge Infrastructure, WanFang, VIP, PubMed, and Web of Science databases were searched for related studies, with two reviewers subsequently evaluating the literature quality using the Cochrane Handbook.* **Results:** *A total of 11 studies were eligible, while only one met the ABLT standard program criteria. Overall, ABLT significantly improved the lower limb motor function, increased walking speed and distance, and improved the daily living ability of children with SCI.* **Conclusions***: The ABLT strategy is of great significance to the motor function and walking ability of children with SCI. At present, there exist few studies on the application of ABLT for pediatric SCI. Further control studies with a larger sample size are required to improve the ABLT program guidelines for children with SCI.*

Keywords: *Activity-based locomotor training. Children. Pediatric spinal cord injury. Walking ability. Motor function.*

Resumen

Objetivo: *Discuta el impacto del entrenamiento ejercicio basado en la actividad en la lesión de la médula espinal en la función de movimiento de los niños y la capacidad de caminar.* **Materials y métodos:** *Según China Zhiwang, Wanfang, VIP, PubMed, Science Network y otros documentos relacionados como fuente de datos. Dos revisores usan calidad de evaluación manual de Cochrane.* **Resultados:** *Un total de 11 estudios cumplen con las condiciones. Solo hay un estudio que cumple con los proyectos estándar de ABLT. General, ABLT mejora significativamente la función de los niños con lesiones de la médula espinal, aumenta la velocidad y la distancia de caminar y mejora la capacidad de la vida diaria.* **Conclusión:** *La estrategia ABLT es de gran importancia para la función de movimiento de los niños de la médula espinal y la capacidad de caminar. En la actualidad, ABLT tiene menos investigación en lesión pediátrica de la médula espinal. Es necesario mostrar la cantidad de muestra y controlar la investigación para mejorar las pautas del plan ABLT para el daño de la médula espinal a los niños.*

Palabras clave: *Entrenamiento ejercicio basado en actividad. Niños. Lesión de la médula espinal pediátrica. Capacidad de caminar. Función de ejercicio.*

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Introduction

Spinal cord injury in children (SCI) is a serious disabling disease caused by various factors[1]. The disease not only causes motor, sensory and autonomic nerve dysfunction below the injury level[2], and reduces the basic daily living and social participation abilities but also causes scoliosis, hip dislocation, pressure ulcers, and other complications[3]. The main clinical manifestations of SCI are sudden pain in the lower back, lower limb motor and sensory disorders, and urinary and fecal incontinence, while the attendant imaging reveals multi-stage abnormal spinal cord signals centered on T9 and T10[4]. The main goal of spinal cord rehabilitation is to restore walking ability and improve walking quality after SCI. Extensive locomotor training can restore locomotion function after SCI in humans.

Activity-based locomotor training (ABLT) is a rehabilitation strategy that, based on scientific and clinical evidence, is designed to enhance the recovery of postural control, balance, standing, walking, overall health, and quality of life following neurologic injury or disease. The program consists of treadmill training with partial weight support, overground assessment, and integration into family and community activities (Fig. 1). As an activity-based therapy, locomotor training is a therapeutic intervention that results in neuromuscular activation below the level of the lesion to promote the recovery of motor functioning with the aim of retraining the nervous system to regain the ability to handle and tackle specific tasks[5]. Activation of the neuromuscular system occurs during repetitive and progressive practice of the desired task, with the so-called 'activity-dependent plasticity' promoting the functional reorganization of the neuromuscular system. Locomotor training focuses on task-specific training of the injured components to return functioning to pre-injury levels of neuromuscular control as far as possible.

While studies have demonstrated that ABLT can effectively promote neuromuscular recovery and improve motor function in children with SCI, thus enhancing their social participation, there is a remarkable lack of standardization regarding the techniques and methods of assessment used to evaluate the effectiveness of rehabilitation[6]. Therefore, this study systematically reviews the clinical research status of the ABLT used for children with SCI and discusses the effects of the ABLT on rehabilitation in children with SCI. Overall, the study provides a reference and training guidelines for the clinical application of ABLT.

Materials and Methods

Protocol and registration

This systematic review was conducted according to the *Cochrane Handbook* and is reported following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses declaration (Fig. 2).

Information sources and search

The data sources were the Chinese National Knowledge Infrastructure, WanFang, VIP, PubMed, and Web of Science databases. To identify relevant studies, the following search terms were used: children or SCI or pediatric SCI and locomotor training, sports training, or ABLT.

Inclusion and exclusion criteria

The selection criteria were built based on the PICOs approach, which includes participants, interventions, comparators, outcomes, and study design.

The inclusion criteria were as follows: (i) studies compiled in Chinese or English; (ii) children aged 1-17 years with complete or incomplete SCI; (iii) intervention including body-weight-support treadmill training (BWSTT), robot-assisted gait training (RAGT), overground training (OGT), and community and family integration walking training; (iv) a control group was set up; (v) the outcomes mainly included the evaluation of body structure and function, activities and participation (e.g., American Impairment Scale [AIS], 6 min walking test [6MWT], 10 m walking distance [10WMD], Walking Index of SCI II [WISCI II] and the upper extremity and lower extremity motor score scales [UEMS, LEMS]); (iv) the study type was a randomized controlled study, cohort study, case report study, or cross-sectional study.

The exclusion criteria included the following: (i) duplicate studies; (ii) congenital SCI (spina bifida); and (iii) reviews or systematic reviews.

Data collection process

Literature screening and data extraction

The relevant databases were searched manually, and the resultant literature was imported into EndnoteX9.0. The titles and abstracts of the studies were initially screened to identify those that did not meet the

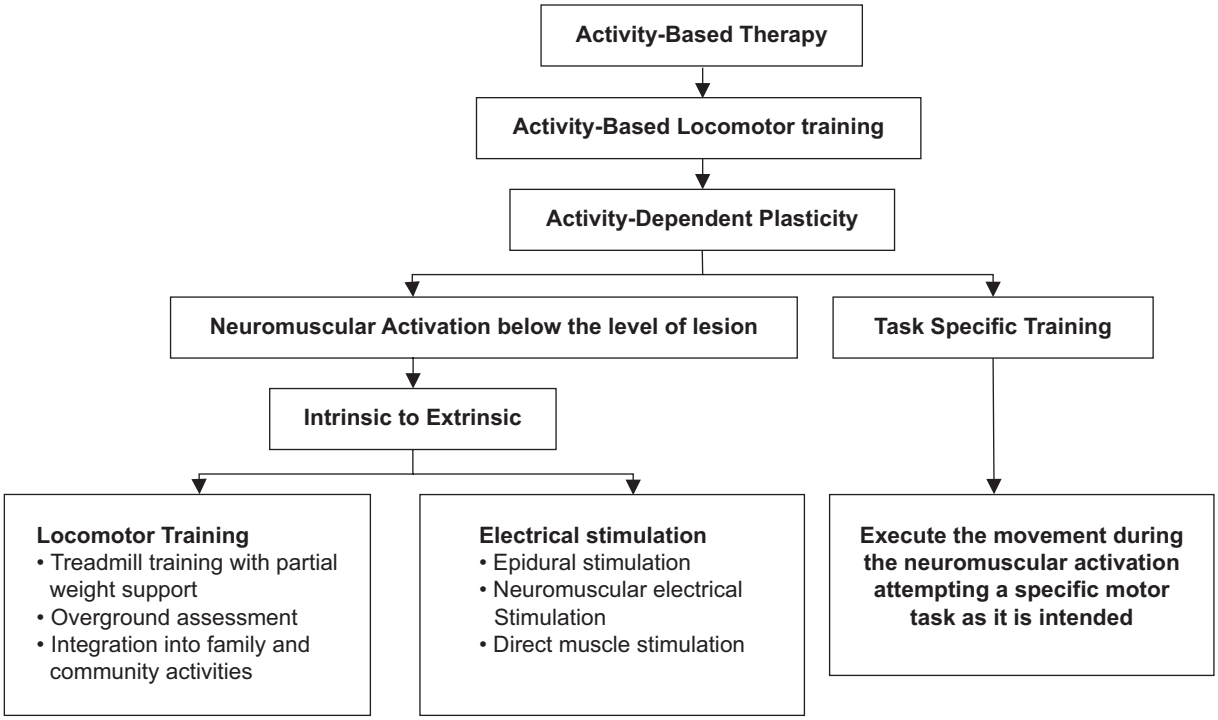

Figure 1. *Key elements and basis for activity-based locomotor training.*

inclusion criteria. Following this, the content was read to ascertain whether it conformed to this review. The assessment was conducted independently by two researchers, with any differences resolved through discussion and negotiation and the final results determined by the consensus of the research group.

Evaluation of the risk of bias

Two authors independently assessed the risk of bias. In the case of disagreement, the subject was discussed with another author. The risk of bias was assessed using the Cochrane risk-of-bias tool for literature. Here, a study is considered to be at a "low risk of bias" if all five domains are assessed to be at low risk of bias, while it is considered to be at an overall 'high risk of bias' if determined to be at a high risk of bias in terms of at least one domain. The tool was applied to each outcome of interest.

Results

Literature search and article selection

We identified 606 potentially relevant studies through the database search, including 30 from the Chinese database and 576 from the English database. In total, 37 studies were identified after inclusion and exclusion criteria were applied. Finally, by reading the full text, 11 studies were obtained for this review, including 10 case reports and 1 prospective study[7-17].

Risk of bias in the individual studies

As noted, the risk of bias was assessed independently by two researchers, with any differences resolved through discussion and negotiation and the final results determined by the consensus of the research group. The seven adopted items were as follows: (i) random sequence generation (10 studies had a high-risk bias and one a low-risk bias); (ii) distribution hiding (11 studies were high-risk bias); (iii) implementation bias (11 studies were high-risk bias; (iv) measurement bias (10 studies were high-risk bias and one was low-risk bias); (v) incomplete data (11 studies had low-risk bias); (vi) selective reporting bias (eight studies had high risk of bias, one had low risk of bias and two studies had unclear risk of bias); and (v) other bias (11 were low-risk bias). The quality assessment results are shown in figure 3.

Basic characteristics of children with SCI

The 11 selected studies included 38 subjects, ranging in age from 1 to 17, with more males than females. The most frequently involved localization was the chest

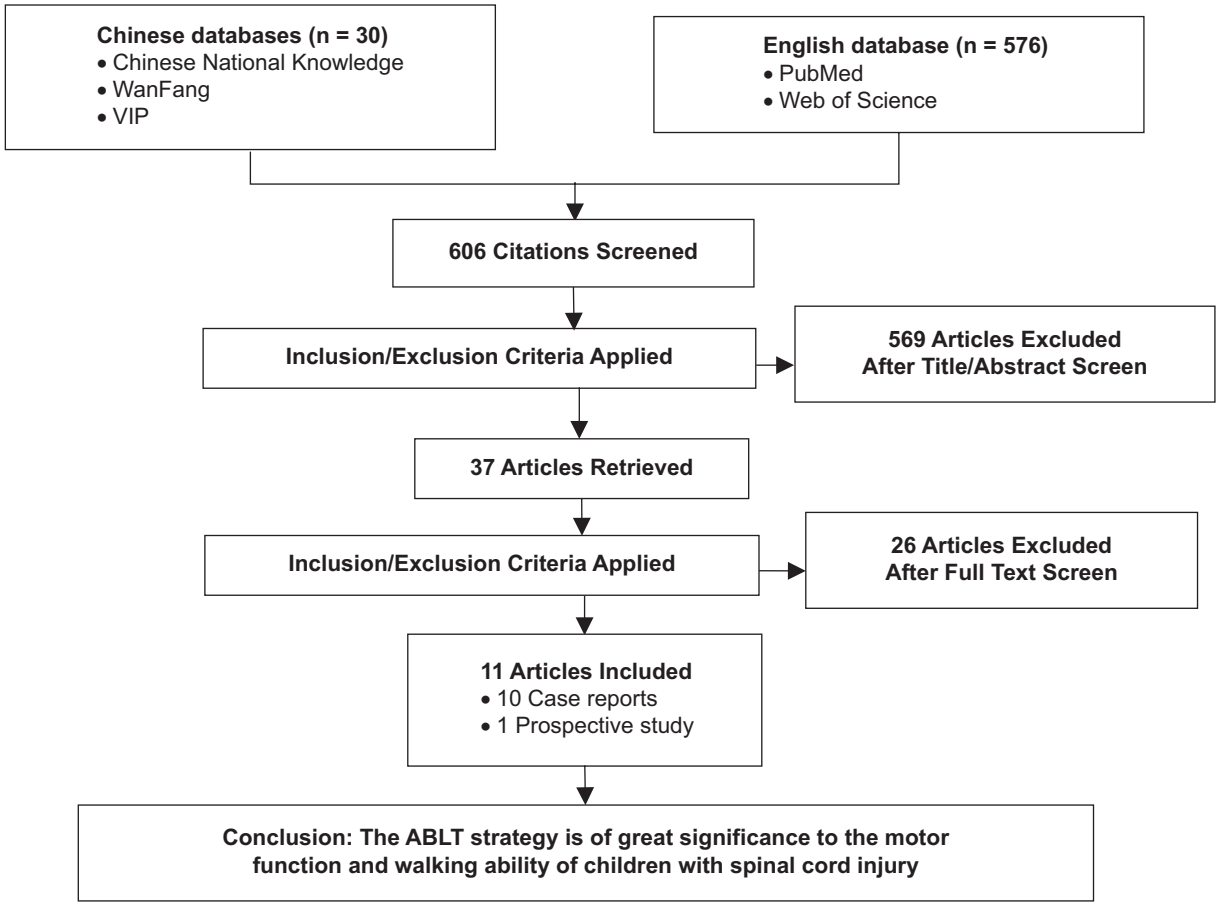

Figure 2. *Flow chart of the system review.*

of the spinal cord, followed by the cervical segment and the lumbar segment. The cause of injury in seven of the studies was traumatic SCI (motor vehicle accident, snowboarding accident, football match accident, gunshot accident), and two studies involved non-traumatic SCI (spinal cord disease). Two studies involved traumatic or non-traumatic SCI but were not specifically documented. The sensorimotor function of the patients was evaluated according to the International Standards for Neurological Classification of SCI Scale[18]. Here, there were seven A-level subjects, six B-level subjects, nine C-level subjects, and four D-level subjects.

Efficacy of ABLT in children with SCI

Improvement in motor function and walking ability

Eight studies evaluated the LEMS, and only one study reported a decrease in the LEMS score[12]. Six studies reported that ABLT improved the WISCI II score, five reported that ABLT improved the 6MWT scores, and seven reported that ABLT improved the 10MWT scores. The AIS grading of three children changed and that of five children did not. The motor function and walking ability scales are shown in table 1.

Improvement in daily living ability

Four studies recorded the patients' abilities for basic daily activities. Except for the study by Fox et al.[12], the scores on the daily living ability scale were all improved, indicating that the children's ability to participate in basic daily life was improved after receiving ABLT. Six studies recorded that the patient needed assistive devices to complete family or community walking, including activities using rolling walkers, wheelchairs, crutches, hip, knee, and ankle orthoses, and orthopedic insoles. Among them, the O'Donnell and Harvey[13] study reported that these children achieved independent walking. The daily living ability scale scores are shown in table 2.

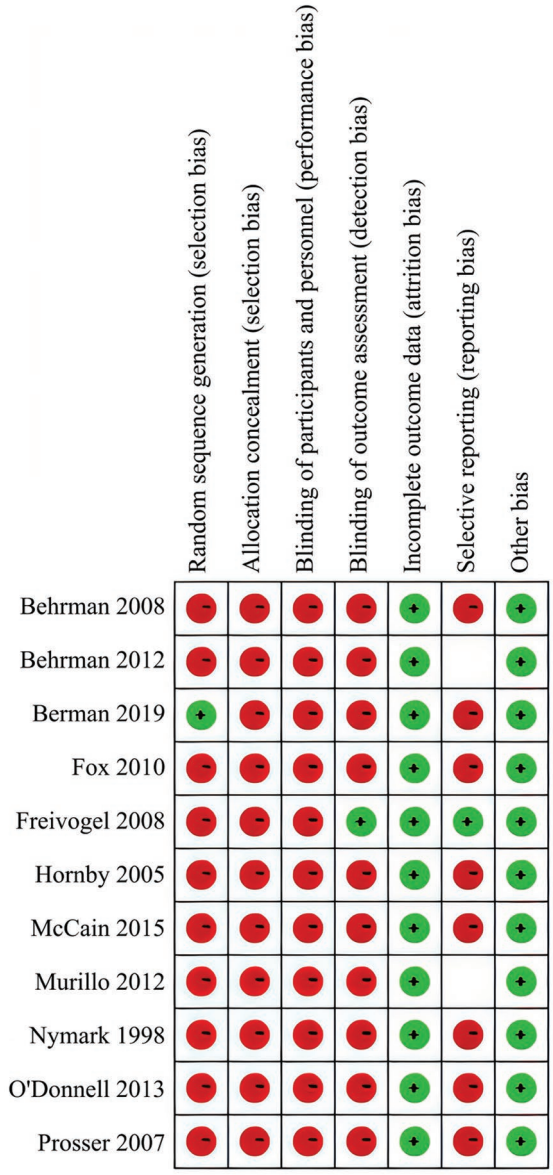

Figure 3. *Risk of bias summary: review authors' judgments about each risk of bias item for 11 literatures.*

Table 1. Motor function and walking ability scale score

Study \ Scale	LMES	WISCI II	6MWT	10MWD	AIS
Nymark et al.[7]	Unclear	Unclear	Unclear	↑0.70	Unclear
McCain et al.[8]	↑6	↑12	↑61.57	↑0.17	C→D
Freivogel et al.[9]	Unclear	Unclear	Unclear	↑0.70	Unclear
Behrman et al.[10]	↑0	↑13	Unclear	Unclear	C→C
Prosser[11]	↑23	↑12	Unclear	Unclear	A→C
Fox et al.[12]	↓3	↑0	Unclear	Unclear	C→C
O'Donnell and Harvey[13]	↑2	↑3	↑12.90	↑1.4	C→C
Berman et al.[14]	↑0	Unclear	↑245.33	↑0.90	C→C
	↑5	Unclear	↑35.00	↑0.26	C→D
	↑1	Unclear	↑6.40	↑0.42	C→C
Hornby et al.[15]	↑42	↑16	↑237.00	↑0.26	Unclear
Murillo et al.[16]	Unclear	Unclear	↑200.00	↑0.15	Unclear
Behrman et al.[17]	↑11.4	Unclear	Unclear	Unclear	Unclear

LEMS: lower extremity motor score; WISCI II: walking index of spinal cord injury II; 6MWT: 6 min walking test; 10MWD: 10 m walking distance; AIS: American impairment scale.
↑Represents the numerical value of each scale improvement after training.

Discussion

In this systematic review of 11 included studies, we found that ABLT can be an effective intervention in helping to develop or restore walking ability in children with SCI.

The incidence of pediatric SCI in the USA is approximately 2/10,000 children[19]. Spinal cord injuries in children have devastating consequences. SCI often leads to severe disability due to permanent neurological impairment. Walking recovery, or the development of walking, is a major goal for children with SCI and their families. ABLT is a rehabilitation strategy designed to enhance the recovery of postural control, balance, standing, walking, health, and quality of life after neurologic injury or disease based on scientific and clinical evidence[20,21]. At present, other than locomotor training, few broadly accepted clinical treatments for SCI exist.

ABLT has a good effect on the rehabilitation of SCI. The study by Harkema et al.[22] indicated that rehabilitation that includes intensive activity-based therapy can result in functional improvements in individuals with chronic incomplete SCI. The study by Lucas et al.[23] reported that the improvements in children with acquired SCI following ABLT were maintained, indicating that the program is neurotherapeutic. While not achieving complete recovery of trunk control, the immediate effects and sustained improvements provide support for a clinical shift to neurotherapeutic approaches and for continued research to achieve enhanced recovery. Following SCI, ABLT can induce the body to release neurotrophic factors to generate new structures or functions, including the germination of nerve fibers and synapses and the regeneration of injured distal nerve fibers, thus enhancing the plasticity of the spinal cord and promoting the reorganization of neuronal circuits[24].

Table 2. Daily living ability scale score

Study	Scale	Score	Auxiliary appliance
Nymark et al.[7]	Unclear	Unclear	Unclear
McCain et al.[8]	Unclear	Unclear	Crutches, AFOs, orthopedic insoles
Freivogel et al.[9]	Unclear	Unclear	Unclear
Behrman et al.[10]	Unclear	Unclear	Rolling walker
Prosser[11]	Wee FIM II	Unclear	Rolling walker
Fox et al.[12]	GMFM-66	0	Rolling walker
O'Donnell and Harvey[13]	Unclear	Unclear	Independent walking
Berman et al.[14]	FIM	Unclear	The wheelchair
	ADL	↑6	Unclear
	Unclear	Unclear	Manual wheelchairs, LKAFO
Hornby et al.[15]	Unclear	Unclear	Unclear
Murillo et al.[16]	Unclear	Unclear	Unclear
Behrman et al.[17]	Unclear	Unclear	Unclear

Wee FIM II: The Functional Independence Measure-II for Children; GMFM-66: Gross Motor Function Measurement-66; FIM: functional independence measure; ADL: activities of daily living; AFOs: ankle foot orthoses; LKAFO: left knee-ankle-foot orthosis.
↑Represents the numerical value of each scale improvement after training.

No one form of locomotor training has been determined to be superior. The combination of multiple rehabilitation programs is the best way to achieve the rehabilitation effect of children with SCI[17]. The ABLT reported in this study consisted of BWSTT, RAGT, OGT, and community and family integration walking training. The BWSTT method allows patients to be in an upright position using suspension devices, which can reduce the issue of upper limb weight for lower limb walking to varying degrees and can change the weight loss ratio and treadmill speed, such that walking training can be carried out with the assistance of therapists[25]. With the help of therapists, the LEMS, WISCI II, 6MWT, and 10MWD scores of the children in a number of the studies were improved[8,13,15]. Murillo et al.[16] found that after 2 months of RAGT, children with thoracic complete SCI could use a walker for therapeutic walking with the help of therapists. Moreover, this method has a good effect on preventing pressure ulcers and improving intestinal function and lower limb blood circulation. The reconstruction of lower limb motor function is of great significance to the self-care and social integration of affected children[7-11,13-17]. Altizer et al.[26] demonstrated that following RAGT, children can engage in simple family activities, participate in community entertainment activities, and eventually return to school and integrate into collective life.

The ABLT program not only significantly improved motor function and walking ability, as assessed by the 6MWT, 10MWD, and WISCI II scores, in children with SCI, but also had additional benefits. LT has the potential to decrease secondary complications that result from SCI in childhood. The majority of children in a review study completed by Schottler et al.[27] demonstrated that children with SCI developed scoliosis if they had a complete injury. Hip dysplasia also occurred in 57% of children. Increased upright mobility, including ABLT, can potentially decrease these complications. Research with adults supports that standing for > 20 min, 3-4 times/week, following SCI, can improve personal well-being, circulation, spasticity, bowel and bladder function, and digestion. One study within this review assessed bowel and bladder function to have improved in children with SCI following ABLT[16]. Therefore, outcomes such as improved bowel and bladder management, bone density, cardiovascular endurance, and overall quality of life should also be assessed in addition to just ambulation outcomes such as the 6MWT, 10MWD, and WISCI II with future research.

This review has some limitations. The studies that were relevant to this review were mainly case reports, and the effects of different training methods on the motor function and walking ability of children could thus not be compared. Furthermore, the application of ABLT to children with SCI is in its nascent stages.

Conclusions

The ABLT method is a means of rehabilitation for children with SCI. Compared to other conventional exercise training programs, intelligent exercise training is characterized by high accuracy, high intensity, repeatability, and fun, which provides a strong guarantee for the recovery of children's walking ability, an enhancement in lower limb muscle strength, an improvement in quality of life, and the prevention of complications. With the development of intelligent rehabilitation programs, ABLT will be more widely used to benefit more children with SCI.

Funding

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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 no patient data appear in this article.

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

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ORIGINAL ARTICLE

The effect of pre-operative sleep quality on post-operative pain and emergence agitation: prospective and cohort study

El efecto de la calidad del sueño preoperatorio sobre el dolor posoperatorio y la agitación de emergencia: estudio de cohorte prospectivo

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Abstract

Objective: *Our study aimed to investigate the effect of pre-operative sleep quality on post-operative pain and emergence agitation.* **Materials and methods:** *Our study was performed 80 patients with American Society of Anesthesiologists I-II and 18-65 years of age. The patients were divided into poor (Group A, n = 40) and good sleep quality (Group B, n = 40). All patients were operated on under standard general anesthesia. The emergence agitation and pain status of all groups were evaluated in the recovery room and post-operative period. Results: There was no significant difference between the groups regarding demographic data. Post-operative numeric rating scale scores and analgesic consumption were significantly higher in Group A than in Group B ($p < 0.05$). There was no significant difference between the groups regarding post-operative emergence agitation and extubation quality ($p > 0.05$).* **Conclusion:** *In our study, poor pre-operative sleep quality increases post-operative pain and analgesic consumption; however, emergence agitation is not associated with sleep quality in the pre-operative period.*

Keywords: *Emergence agitation. Post-operative pain. Sleep quality.*

Resumen

Objetivo: *Nuestro estudio tuvo como objetivo investigar el efecto de la calidad del sueño preoperatorio sobre el dolor posoperatorio y la agitación de emergencia.* **Materiales y métodos:** *Nuestro estudio se realizó en 80 pacientes con ASA I-II y de 18 a 65 años de edad. Los pacientes se dividieron en mala (grupo A, n = 40) y buena calidad del sueño (grupo B, n = 40). Todos los pacientes fueron operados bajo anestesia general estándar. La agitación de emergencia y el estado del dolor de todos los grupos se evaluaron en la sala de recuperación y en el período postoperatorio.* **Resultados:** *No hubo diferencia significativa entre los grupos con respecto a los datos demográficos. Las puntuaciones NRS postoperatorias y el consumo de analgésicos fueron significativamente más altos en el Grupo A que en el Grupo B ($p < 0.05$). No hubo diferencia significativa entre los grupos con respecto a la agitación de emergencia postoperatoria y la calidad de la extubación ($p > 0.05$).* **Conclusión:** *En nuestro estudio, la mala calidad del sueño preoperatorio aumenta el dolor posoperatorio y el consumo de analgésicos; sin embargo, la agitación de emergencia no se asocia con la calidad del sueño en el período preoperatorio.*

Palabras clave: *Agitación de emergencia. Dolor postoperatorio. Calidad del sueño.*

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Introduction

Sleep is a temporary period of unconsciousness that can become conscious again with internal and external stimuli[1]. Besides being a basic need, sleep is also an important part of the recovery process in the post-operative period. Sleep quality is a measure of a person's well-being. This concept includes parameters such as sleep duration, sleep time, number of night awakenings, and sleep depth[1]. Sleep quality is affected by various factors such as environmental factors, work, lifestyle, social life, general health, and stress[2].

Impaired sleep quality was found to be associated with a weakened immune system, susceptibility to infection, increased risk of post-operative cardiovascular and cerebrovascular events, and prolonged hospital stay. In addition, it has been shown that poor sleep quality lowers the pain threshold and causes hyperalgesia[3].

Post-operative pain is one of the factors that closely affect the healing process of the patient. Therefore, determining the etiological causes is an important step in pain management. Recent studies have shown that sleep quality is a triggering factor for acute pain and has an important role in exacerbating chronic pain. Therefore, poor sleep quality is a predictor of post-operative pain[4]. Considering all these, it should not be forgotten that poor sleep quality in the pre-operative period is an important risk factor for post-operative sleep disturbance and pain.

Agitation during recovery from general anesthesia is an important recovery problem. There are studies investigating the relationship between pre-operative sleep disorder and post-operative pain[4-6]. However, studies investigating the relationship between pre-operative sleep disturbance and post-operative emergence agitation have not been found. For this reason, we determined our hypothesis in this study: sleep quality in the pre-operative period may reduce post-operative pain and emergence agitation.

Materials and methods

Our study was planned as a prospective clinical study between January 2021 and September 2021 after the approval of the local ethics committee (Karadeniz Technical University Faculty of Medicine Ethics Committee, 2020/376).

A total of 96 patients were scheduled to undergo elective open cholecystectomy and thyroidectomy in the general surgery operating room of our hospital. Sixteen patients were excluded from this study since 10 patients were American Society of Anesthesiologists (ASA) III, four patients were > 65 years old, and two patients had serious systemic illnesses. The study was carried out on 80 patients with ASA risk classification I, II, and 18-65 years of age, whose written and verbal consents were obtained, who were scheduled for open cholecystectomy and thyroidectomy in the general surgery operating room of our hospital.

Patients with a body mass index (BMI) of more than 30 kg/m^2, who have obstructive sleep apnea syndrome, who use induction agent(s), drugs related to opioid allergy, psychiatric disorder, chronic pain, and chronic sleep disorder, who have an active infection, who need follow-up in the post-operative intensive care unit, who were uncooperative, and were unable to compare physical and verbal performance were excluded from the study. During the examination performed in the pre-operative anesthesia outpatient clinic 1 day before the operation, patients who met the appropriate criteria were informed about the study, and their written and verbal informed consent was obtained.

The pre-operative sleep quality of the patients to be included in the study was evaluated with the Pittsburgh Sleep Quality Index (PSQI). Patients with a PSQI score above 5 were classified as poor sleep quality (Group A, n = 40), and patients with a PSQI score below 5 were classified as good sleep quality (Group B, n = 40). A consort flow diagram of the study is shown in figure 1. Pre-operative PSQI and age, gender, weight, BMI, and ASA risk scores of all patients were recorded.

State-Trait Anxiety Inventory (STAI) was used to evaluate the pre-operative anxiety levels of all patients. STAI-I and II are two different forms consisting of 20 questions, STAI-I indicates situational anxiety level, and STAI-II indicates trait anxiety level. Scoring varies between 20 and 80. Patients who were informed about STAI were asked to fill in the STAI-I and STAI-II forms. As a result of the STAI I-II evaluation, it was evaluated as 0-19 points as absent, 20-39 points as mild, 40-59 points as moderate, 60-79 points as severe, 80 points, and above as panic (very severe).

In standard anesthesia monitoring of patients taken to the operating room, non-invasive mean arterial pressure (MAP), heart rate (HR), peripheral oxygen saturation (SpO_2), electrocardiograph, end-tidal carbon dioxide ($EtCO_2$), and bispectral index (BIS) (Aspect) Medical Systems, Norwood, MA, USA) were applied.

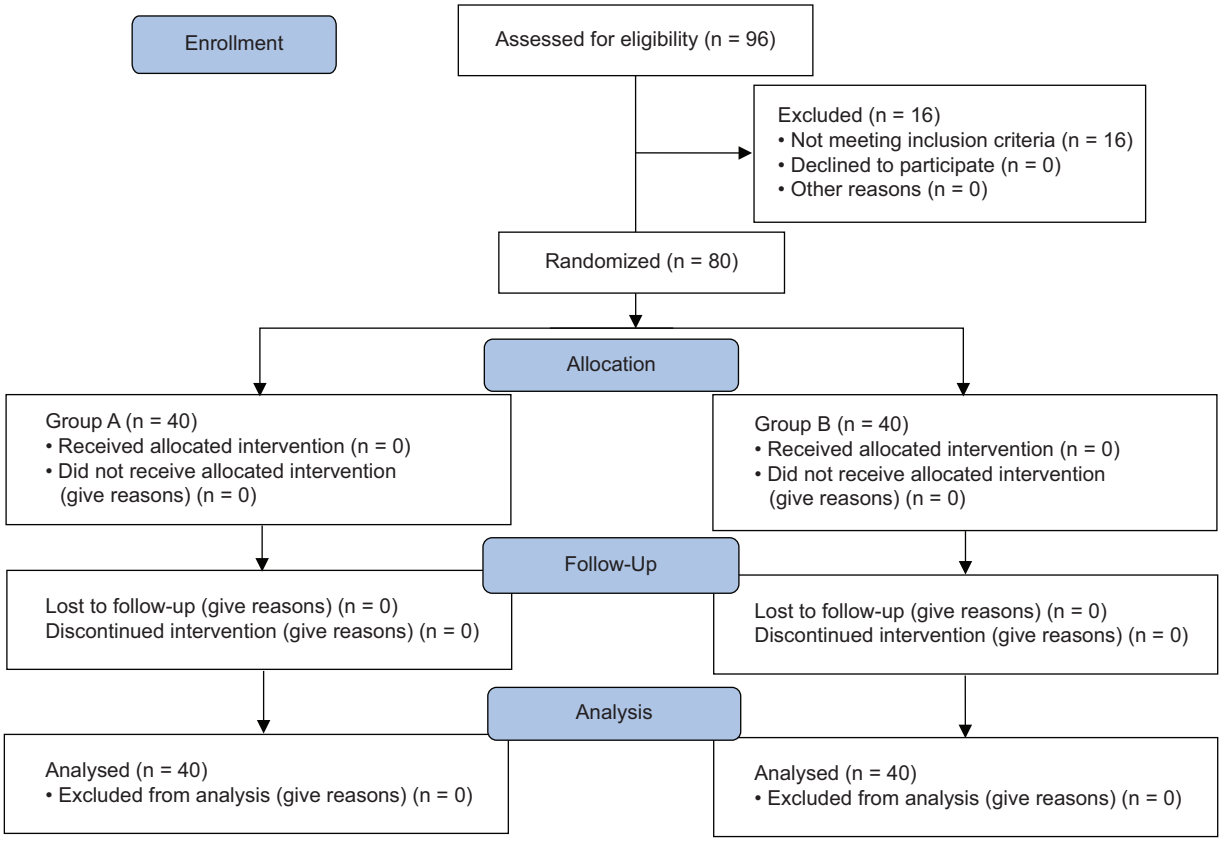

Figure 1. *Consort flow diagram of the study.*

In the induction of anesthesia, intravenous (iv) 1 μg/kg fentanyl, 5-7 mg/kg pentothal, and 0.6 mg/kg rocuronium were administered, and endotracheal intubation was performed after sufficient time for muscle relaxation. Mechanical ventilation was applied with a tidal volume of 6-8 ml/kg, a respiratory frequency of 12/min, and $EtCO_2$ of 32-35 mmHg. Anesthesia was maintained at a BIS of 40-60 with 50% O_2/air, 2% of sevoflurane, and an iv infusion of 0.1 mcg/kg/h remifentanil. Additional doses of rocuronium were administered to the patients when necessary. MAP, HR, SpO_2, and $EtCO_2$ values of all patients were recorded at baseline, intubation, 20-min intervals after intubation, and just before extubation.

At the end of the operation, all patients were extubated after removing oropharyngeal secretions when it was observed that the depth and number of respirations were adequate, the cardiovascular findings were stable, and the BIS value was above 80. The extubation quality levels of the extubated patients were evaluated with the "Extubation Quality Scale" of 5 (1 = no coughing, comfortable breathing, 2 = quite soft, mild coughing (1-2 times), 3 = moderate coughing (3-4 times), 4 = severe coughing, and labored breathing (5-10 times), and 5 = laryngospasm, severe coughing and labored breathing)[7].

Post-operative agitation scoring was done in the recovery room using the Richmond Agitation-Sedation Scale (RASS)[8]. The highest agitation score of the patients in this period was recorded, and it was accepted that emergence agitation developed in patients with a RASS score of ≥ 2. In the first stage, verbal suggestions were made to patients who developed emergence agitation, and iv 10-20 μg dexmedetomidine was administered to those who did not respond. Patients with sufficient muscle strength (ability to raise their head and move their extremities in response to commands) and airway safety were taken from the operating room to the post-anesthesia care unit (PACU). Patients with an Aldrete score ≥ 9 were sent to the service from the PACU.

The pain status of all patients was evaluated with the numeric rating scale (NRS) at the 2nd, 12th, and 24th h postoperatively. Patients with NRS > 3 were administered iv 50 mg dexketoprofen as an additional analgesic. In addition, iv 4 mg ondansetron was administered to

Table 1. Demographic data and clinical characteristic

Parameters	Group A (n = 40)	Group B (n = 40)	p
Age (year)	47.0 ± 11.5	46.4 ± 12.2	0.799*
Weight (kg)	71.1 ± 8.8	73.5 ± 10.4	0.276*
Height (cm)	165.2 ± 7.1	167.0 ± 6.6	0.198†
BMI (kg/m^2)	26.2 ± 2.9	25.8 ± 3.0	0.530†
ASA (I/II)	13/27	20/20	0.173‡
Sex (F/M)	32/8	30/10	0.88‡
Operation time (min)	73.5 ± 24.0	70.1 ± 29.5	0.260†
Anesthesia time (min)	85.0 ± 24.8	80.5 ± 28.6	0.336†
STAI-I Scor	43.0 ± 6.5	41.6 ± 5.1	0.461†
STAI-II Scor	47.8 ± 6.6	45.2 ± 7.9	0.053†
Type of surgery			
Thyroidectomy	2	9	0.655‡
Cholecystectomy	8	1	
Length of stay in hospital (day)	2.04 ± 0.82	1.75 ± 0.67	0.121†

*t-test.
†Mann–Whitney U-test.
‡Ki-kare test.
Statistics presented as Mean ± SD or N. Group A: worse sleep quality group, Group B: good sleep quality group. BMI: body mass index; ASA: American Society of Anesthesiologists Classification; STAI I-II: State-Trait Anxiety Inventory.

patients who developed nausea and vomiting. Additional analgesic and antiemetic use were recorded in the service follow-ups in the post-operative 24-h period.

Statistical analysis

IBM SPSS 23.0 statistical package program was used to analyze the data. Descriptive statistics of the evaluation results are given as numbers, percentages for categorical variables, and mean and standard deviation for numerical variables. The conformity of the variables to the normal distribution was examined with the Kolmogorov–Smirnov test. In comparing the mean values of the measurement variables between the groups, the t-test was used when the variable was suitable for normal distribution, and the Mann–Whitney U-test was used when it was not. The Chi-square test was used to compare categorical data. The statistical significance level was accepted as $p < 0.05$.

Within the scope of the study, it was aimed to reach the maximum number that can be reached in the included surgeries and during the data collection period. The power analysis results using the mean and standard deviation values of the groups for sleep quality, which is the study's main hypothesis, showed that while the power was 100% for the NRS 2nd h and 12th h, it was 99.67% for the 24th h. In this context, a total of 80 patients, including 40 with poor and 40 with good sleep quality, were included in the study.

Results

The patients' demographic data, including age, gender, weight, height, BMI, ASA risk scores, operation and anesthesia times, and pre-operative STAI-I and STAI-II scores, are shown in table 1. There was no statistically significant difference between the groups ($p > 0.05$). Intraoperative variables such as MAP, HR, peripheral oxygen pressure, and $EtCO_2$ of the patients are shown in figure 2. There was no statistically significant difference between the groups during the follow-up periods ($p > 0.05$).

NRS changes and analgesic consumption of the patients at the post-operative 2nd, 12th, and 24th h are shown in table 2, and it was found to be statistically significantly higher in Group A compared to Group B in all follow-up periods (respectively, for all NRS; $p < 0.001$, $p = 0.048$).

The extubation quality scores, post-operative agitation scores, and dexmedetomidine consumption of the patients are shown in table 3, and there was no statistically significant difference between the groups ($p > 0.05$).

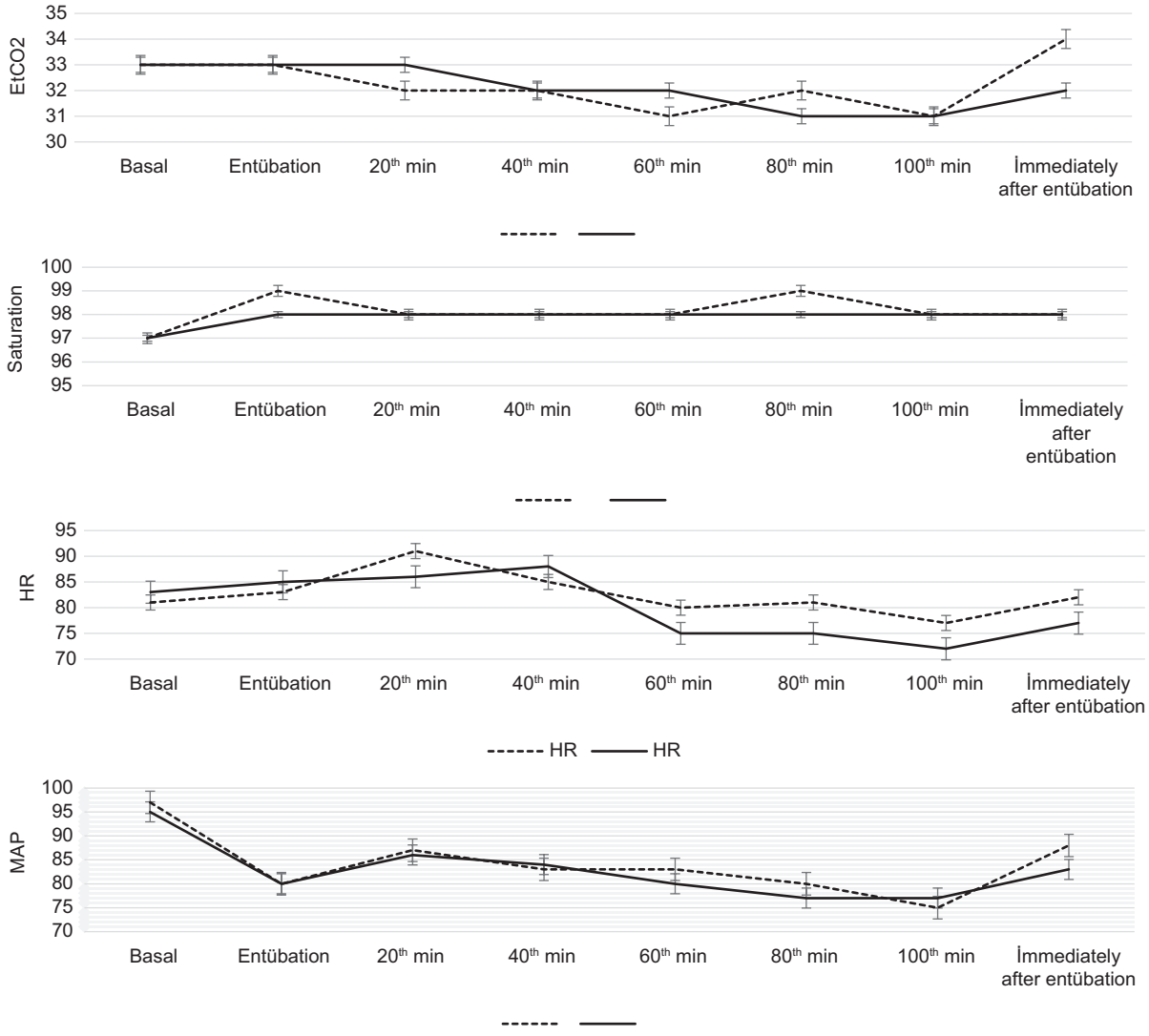

Figure 2. *Intraoperative variables.*

Discussion

Our study observed that patients with poor sleep quality in the pre-operative period had high pain scores and increased additional analgesic consumption in the post-operative period. However, there was no difference between patients with poor and good sleep quality regarding emergence agitation.

Sleep, one of the basic components of a healthy life, plays a key role in many biological activities. In addition to being a basic need, sleep is also an important part of the recovery process in the post-operative period[1]. Impairment in sleep quality can lead to deterioration in both physical and cognitive functions. It can also cause changes in many systems, including endocrine, cardiovascular, neurological, and immune systems[3].

Table 2. NRS and analgesic consumption change of groups

Parameters	Group A (n = 40)	Group B (n = 40)	p
NRS 2th h	5.05 ± 1.57	2.45 ± 1.09	< 0.001*
NRS 12th h	3.28 ± 1.40	1.20 ± 0.82	< 0.001*
NRS 24th h	1.30 ± 0.56	0.75 ± 0.49	< 0,001*
Analgesic Consumption (deksketoprofen) (mg)	26.43 ± 10.40	16.67 ± 12.91	0.048*

*Mann–Whitney U-test.
Statistics presented as mean ± SD. Group A: worse sleep quality group, Group B: good sleep quality group. NRS: numbering rating scale.

Table 3. Comparison of recovery period

Parameters	Group A (n = 40)	Group B (n = 40)	p
RASS score ≥ 2	7 (77.8)	2 (22.2)	0.154*
RASS score < 2	33 (46.5)	8 (53.5)	
Extubation quality score	1.9 ± 1.1	1.7 ± 1.1	0.379†
Deksmedetomidine consumption (mg)	0.017 ± 0.005	0.015 ± 0.007	0.593†

*Ki-kare test.
†Mann–Whitney U-test.
Statistics presented as Mean ± SD or N (%).Group A: worse sleep quality group, Group B: good sleep quality group. RASS: Richmond Ajitasyon Sedasyon Skalası.

Many physiological, psychological, and environmental factors can affect the quality and quantity of sleep. Among these, age, gender, anxiety, and surgical stress are important factors[9,10].

Pain, one of the complications developing in the post-operative period, may cause a prolongation of hospital stay. On the other hand, impairment in sleep quality can also prolong hospital stays by lowering the post-operative pain threshold. Wang et al., in their study on breast cancer cases, reported that patients in the poor sleep group had higher pain levels and, as a result, a longer hospital stay[5]. Luo et al. concluded that the decrease in pre-operative sleep times in patients who underwent joint arthroplasty might reduce the post-operative pain threshold, and the patients need more time to recover from post-operative surgical trauma, resulting in a longer hospital stay[6]. When our study was evaluated in terms of hospital stay, no statistically significant difference was found between the good and poor sleep groups. In our study, patients in the group with poor sleep quality had higher post-operative pain levels and post-operative additional analgesic consumption, which can be explained by the fact that post-operative pain levels were controlled as a result of close follow-up and early intervention.

Pain is a sensory, unpleasant emotional sensation, a behavior pattern that originates from a specific part of the body due to severe tissue damage or not, related to the subjective, primitive protective experiences of the person in the past[11]. Determining the etiological causes is an important step in managing pain, which is one of the most critical recovery problems of the post-operative period. It is known that sleep quality affects pain[12]. There is a bidirectional relationship between pain and sleep quality. While severe pain may impair sleep quality, a decrease in sleep quality may cause hyperalgesia by lowering the pain threshold[12]. Thus, sleep disorders are an important modifiable risk factor for pain. Many studies compare sleep quality and post-operative pain levels[4-6]. Wang et al. investigated the effect of sleep quality on post-operative pain in breast surgery cases. The patients were divided into two groups, good and poor sleep quality, by pre-operative PSQI test. They concluded that the pain levels and the need for post-operative analgesics were higher in the group with poor sleep quality at the post-operative 2nd, 12th, and 24th h, and as a result, the hospital stay was longer[5]. In the study of Zinger et al., in which they examined the cases who underwent cesarean section, it was observed that the pain level was higher in the first 24 h postoperatively in patients with poor pre-operative sleep quality, and the consumption of analgesics was less in the group with good sleep quality. As a result of the study, it was concluded that impairment of sleep quality during pregnancy is an expected situation, and pain management should be handled carefully by predicting the increase in post-operative pain levels due to poor sleep quality[4]. In the study of Luo et al., in patients who underwent total joint arthroplasty, it was observed that post-operative pain scores were higher, additional analgesic needs were higher, and the length of hospital stay was longer in patients with high PSQI scores. As a result, they concluded that pre-operative sleep quality is directly related to clinical parameters and that poor pre-operative sleep quality should be detected and treated[6]. In the study of Büyükyılmaz et al., in which knee-hip arthroplasty was performed, and sleep quality was evaluated with PSQI, it was observed that patients with poor sleep quality had higher pain scores, and similarly, those who had more pain had a decrease in sleep quality. It was concluded that there is a vicious cycle between pain and sleep quality[13]. In our study, in which we investigated the relationship between sleep quality and post-operative pain, we observed that post-operative pain levels and analgesic consumption were higher in patients with poor pre-operative sleep quality, in line with the literature.

Complications such as hypertension, tachycardia, laryngeal edema, bronchospasm, aspiration, bronchopneumonia, and atelectasis can be seen in patients after extubation, which reveals the importance of extubation quality in post-operative complications[14]. There is no study evaluating the relationship between extubation quality and sleep quality. In our study, no significant difference was found between patients with poor and good sleep quality in terms of extubation quality.

Recovery problems such as agitation, disorientation, and violence observed in the early post-operative period are defined as emergence agitation, and its incidence in adults is between 4.7% and 21.3%[15]. Various factors, such as the patient, surgery, or anesthesia method, may be effective in the emergence of emergence agitation. Although pre-operative anxiety and post-operative pain are known risk factors for emergence agitation, we could not find any study investigating the relationship between pre-operative sleep quality and emergence agitation. Although we expected emergence agitation to be higher in the poor sleep group compared to the good sleep group, which was the hypothesis of our study, and the number of patients with emergence agitation was higher in the poor sleep group, no statistically significant difference was found between the two groups.

In studies investigating the relationship between anesthesia method and emergence agitation in the literature, it is known that it is more common, especially in the pediatric age group, due to sevoflurane used in the maintenance of anesthesia. However, it has been found that the use of remifentanil as an analgesic in addition to sevoflurane reduces emergence agitation[16-18]. In the study of Sun et al. on patients who underwent lobectomy, they were divided into two groups: those using sevoflurane and sevoflurane/remifentanil in the maintenance of anesthesia. Emergence agitation was found to be significantly less in the post-operative period in the group that used remifentanil in addition to sevoflurane in the maintenance of anesthesia[16]. In the study of Dong et al., the pediatric patient group who had adenotonsillectomy was discussed. The patients were divided into two groups, those using sevoflurane and sevoflurane/remifentanil. In terms of emergence agitation in the post-operative period, emergence agitation was found to be significantly less in the group in which remifentanil was used in addition to sevoflurane[17]. In a meta-analysis by Wang et al., it was observed that using remifentanil as an adjuvant with sevoflurane reduced emergence agitation[18]. In all these studies, it can be concluded that the use of remifentanil in addition to sevoflurane in the maintenance of anesthesia reduces emergence agitation.

Remifentanil is an opioid derivative with an ester bond and is generally used as a continuous infusion intraoperatively due to its faster onset and end of action than other opioids[19]. However, due to its faster elimination feature, pain and hyperalgesia in the early post-operative period, which also cause emergence agitation due to remifentanil use, is a common concern[20,21]. Although it is more common, especially in high doses and long-term use, it has been reported that the frequency of hyperalgesia is lower in infusions up to 0.2 μg/kg/min[22]. It is not clear why remifentanil used with sevoflurane reduces EA. Possible mechanisms include remifentanil's increased analgesic properties due to the combined use of both drugs in reducing EA, despite its short half-life, deep inhibition of pharyngeal and laryngeal reflexes after head and neck surgeries specific to the surgery to be performed, direct or indirect inhibition of the paradoxical excitatory effects of sevoflurane due to the current excitatory activity in the locus coeruleus region of the central nervous system by μ-opioid agonists[17,22-24].

In our study, remifentanil infusion was used in addition to sevoflurane in anesthesia maintenance. The lack of significant difference in emergence agitation in the poor sleep group is due to remifentanil used in the maintenance of anesthesia due to possible mechanisms described in the literature.

Many pharmacological agents have been used to prevent emergence agitation. These include opioids, benzodiazepines, alpha-2 agonists, ketamine, non-steroidal anti-inflammatory drugs, N2O, and propofol[25,26]. Many studies have reported that dexmedetomidine, an alpha-2 agonist, prevents emergence agitation. Garg et al. investigated the effect of dexmedetomidine on emergence agitation in patients undergoing nasal surgery under general anesthesia and reported that dexmedetomidine reduced the incidence of emergence agitation by 89.5%[27]. In our study, we preferred dexmedetomidine in patients who developed emergence agitation in the post-operative period. We did not detect a significant difference between the groups regarding dexmedetomidine consumption.

Limitations

First, the sleep parameters of our study were evaluated with subjective scales. Second, methods such as polysomnography can provide more objective results. However, subjective assessment methods assess sleep parameters closer to patients' true feelings. Finally, remifentanil infusion is frequently used as an analgesic in the maintenance of anesthesia to reduce the concentration of sevoflurane used to prevent EA due to sevoflurane use. Although we used sevoflurane and remifentanil infusions as standard in both groups in our study, we could not follow the sevoflurane use of the groups to determine how much they reduced the use of sevoflurane. The literature on the relationship

between emergence agitation and sleep quality is limited, and there is a need for a study with a larger case series on this subject.

Conclusion

Poor sleep quality may have undesirable effects in the post-operative period. Therefore, evaluating patients in terms of sleep quality in the pre-operative period will help determine the method of post-operative pain and analgesia. In addition, emergence agitation seen in the post-operative period is not associated with good or poor sleep quality in the pre-operative period but can be prevented due to sevoflurane and remifentanil used in the maintenance of anesthesia.

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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 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

Clinical outcomes and radiological assessment of vascular anatomy in patients who underwent D3 left hemicolectomy

Resultados clínicos y evaluación radiológica de la anatomía vascular en pacientes sometidos a hemicolectomía izquierda D3

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Abstract

Background. *Adequate blood supply is one of the key factors for colorectal anastomosis healing. Various variants of vascular anatomy often come as a surprise to surgeons during operations.* **Objectives.** *The aims of this study were to carry out a comparative analysis of three-dimensional-computed tomography (3D-CT) angiography data with intraoperative data and a detailed analysis of variants of the anatomy of splenic flexure.* **Material and methods.** *In this study, we included 103 patients (56 males and 47 females; mean age 64.2 ± 11.6) with the left-sided colon and rectal cancer who underwent preoperative 3D-CT angiography at Ternopil University Hospital between 2016 and 2022.* **Results.** *According to the recently proposed classification, there are four types of blood supply to the splenic flexure of the colon: Our analysis showed that type 1 was found in 83 (80.6%) patients, type 2 in 9 (8.7%), type 3 in 10 (9.7%), and type 4 in 1 (1%). All patients underwent local left radical hemicolectomy with resection of complete mesocolic excision (CME), central vascular ligation (CVL) and resección (R0). Seven cases were operated laparoscopically; and the median quantity of removal lymph nodes was 21.54 ± 7.32. Positive lymph nodes were revealed in 24.3% cases. AL was diagnosed in one patient.* **Conclusions.** *Careful pre-operative analysis of vascular anatomy on 3D-CT angiography will assess the vascularization of the splenic flexure of the colon, reduce intraoperative time to identify structures, and develop a personalized strategy for surgery which potentially can reduce the risk of anastomotic leakage.*

Keywords: *Three-dimensional-computed tomography angiography. Left colic artery. D3 lymph node dissection. Colorectal cancer.*

Resumen

Antecedentes. *El suministro de sangre adecuado es uno de los factores clave para la curación de la anastomosis colorrectal. Varias variantes de la anatomía vascular a menudo sorprenden a los cirujanos durante las operaciones.* **Objetivo.** *Realizar un análisis comparativo de los datos de la angiografía tridimensional por tomografía computarizada (3D-TC) con los datos intraoperatorios y un análisis detallado de las variantes de la anatomía del ángulo esplénico.* **Método.** *Se incluyeron en el estudio 103 pacientes con cáncer de colon y recto del lado izquierdo que se sometieron a una angiografía 3D-TC preoperatoria en el Hospital Universitario de Ternopil.* **Resultados.** *De acuerdo con la clasificación propuesta recientemente, existen cuatro tipos de irrigación del ángulo esplénico del colon. Nuestro análisis mostró que el tipo 1 se encontró en 83 (80.6%)*

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pacientes, el tipo 2 en 9 (8.7%), el tipo 3 en 10 (9.7%) y el tipo 4 en 1 (1%). Todos los pacientes fueron sometidos a hemicolectomía radical izquierda local con resección de escisión mesocólica completa (CME), ligadura vascular central (CVL) y resección (R0). Siete pacientes fueron operados por vía laparoscópica. La mediana de ganglios extirpados fue de 21.54 ± 7.32. Se revelaron ganglios linfáticos positivos en el 24.3% de los casos. Se diagnosticó fuga anastomótica en un paciente. **Conclusiones.** *El análisis preoperatorio cuidadoso de la anatomía vascular en la angiografía 3D-TC evaluará la vascularización del ángulo esplénico del colon, reducirá el tiempo intraoperatorio para identificar estructuras y desarrollará una estrategia personalizada para la cirugía.*

***Palabras clave*:** *Angiografía 3D-TT. Arteria cólica izquierda. Linfadenectomía D3. Cáncer colorrectal.*

Introduction

Anastomotic leakage (AL) is an eternal problem in surgery. Pre-operative identification of AL risk factors is a key point. One of the most significant etiological factors of is various disorders with blood supply[1]. The colon is protected from ischemia by well-developed collaterals, including the Drummond marginal artery and arcade anastomoses between the basins of the superior (SMA) and inferior mesenteric arteries (IMA). It is well known that vascular anatomy is quite variable and the colon has certain vulnerabilities, some authors call them ischemic zones[2,3]. Of particular interest is the Griffith Point, which is located in the mesentery of the splenic angle of the colon and is one of the so-called "blind", ischemic or least blood-supplied areas of the colon, as it is located on the border of the ascending branch of the left colon and Drummond's marginal artery. Approximately 5% of patients do not have this anastomosis and small capillary network may be absent for 1.2-2.8 cm^3 of mesentery area[4]. Moreover, the splenic flexure of the colon is the boundary between two different embryological rudiments: middle (forms the distal duodenum, small intestine, cecum, ascending, and proximal two-thirds of the transverse colon) and posterior (forms the distal third of transverse colon, descending, sigmoid, and rectum) intestines. Different embryological roots also contribute to the different biology of the tumor process proximal and distal to the splenic angle[5].

It should be noted that the splenic flexure is also considered one of the most difficult and complex anatomical parts of the colon for mobilization during laparoscopic surgery for colorectal cancer (CRC)[6]. The difficulty of performing such operations is added by various anatomical variants of the structure of the branches of the SMA and IMA. According to the literature, the frequency of AL when performing left hemicolectomy is 5-10%[7].

Widely implemented in clinical practice, three-dimensional-computed tomography (3D-CT) angiography allows the analysis of vascular anatomy in the pre-operative stage and has a clear 3D reconstruction during left hemicolectomy[8,9]. It is important to adhere strictly to the scanning protocol, as well as to take into account the individual comorbid aspects of each patient, which may affect the quality of the data obtained.

The aim of the given article is to analyze the clinical and radiological aspects of patients with cancer of distal third of transverse and left-sided colon, which usually need to be discussed before a surgery by a multidisciplinary team as well as to carry out a comparative analysis of 3D-CT angiography data with intraoperative data and a detailed analysis of variants of the anatomy of splenic flexure, to conduct a retrospective analysis of the results of surgical treatment in patients who underwent left hemicolectomy.

Methods

Description of patients

In this study, we included 103 patients (56 males and 47 females; mean age 64.2 ± 11.6) with the left-sided colon and rectal cancer who underwent pre-operative 3D-CT angiography at Ternopil University Hospital between 2016 and 2022. The exclusion criteria were stage IV process and locally advanced forms of cancer. Furthermore, from the retrospective analysis, we excluded cases where the examination was performed with non-compliance with the scanning protocol or for one reason or another it was performed without contrast. The informed consents were obtained from all patients, and this study was passed by the ethics commission of Ternopil National Medical University.

Scan protocol

3D-CT angiography was performed using a Philips Brilliance 64 CT machine with IV contrast (100 mL of

iodinated contrast agent [370 mg/mL]). Contrast was injected into the ulnar vein at a rate of 4.5 mL/s. The bolus tracking method was used for scanning. Arterial phase scanning automatically began when the contrast in the abdominal aorta at the level of the abdominal trunk reached 180 HU. The 64-slice multidetector CT scanner can generate 0.75 mm slices that can be reconstructed into a 0.5 mm image. Therefore, to obtain high-quality CT angiography for preoperative analysis, a scanning protocol should be maintained: sublingual nitrate intake, high contrast rate (4-5 mL/s), early arterial phase (20-30'), stress reduction (80-100 kV), and doubling the mAs. Image processing was performed using 3D volume imaging technique, VRT, and MIP. All patients underwent standard bowel preparation for CT (dietary + laxative).

Statistical analysis

Quantitative variables were calculated with the use of the median. All calculations were performed using the Statistica 64 software.

Results

Radiological results

According to the recently proposed classification, there are four types of blood supply to the splenic flexure of the colon: Type 1 – the left branch of the middle colic artery (LMCA) branches from the common trunk of middle colic artery (MCA) + left colic artery (LCA); type 2 – LMCA branches independently of the right branch of the MCA directly from the SMA + LCA; type 3 – additional middle colic artery (AMCA) + LCA; and type 4 – splenic flexure of the colon is supplied exclusively by LCA[8]. Our analysis showed that type 1 was found in 83 (80.6%) patients, type 2 in 9 (8.7%) patients, type 3 in 10 (9.7%) patients, and type 4 in 1 (1%) patient.

In the arterial structure of the splenic flexure of the colon, there are several arcades: the aforementioned marginal artery of Drummond, as well as the arc of Riolan and the artery of Moskovich[1,6].

Marginal artery of Drummond is a collateral pathway that connects the SMA and IMA systems closest to the colon wall[1]. In our study, we found the presence of this artery in all 103 (100%) patients (Figs. 1-3).

Riolan's arch is an "intermediate" anastomosis between the branches of the SMA and IMA in the mesentery of the colon[2,4]. In our study, we found the presence of this structure in 47 (45.6%) patients (Figs. 1-3).

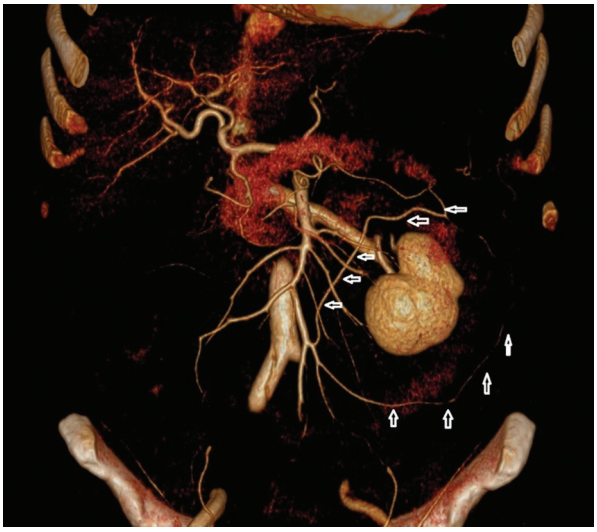

Figure 1. *Three dimensional-computed tomography angiography: Riolan's arc (transverse arrows) and Drummond's marginal artery (longitudinal arrows).*

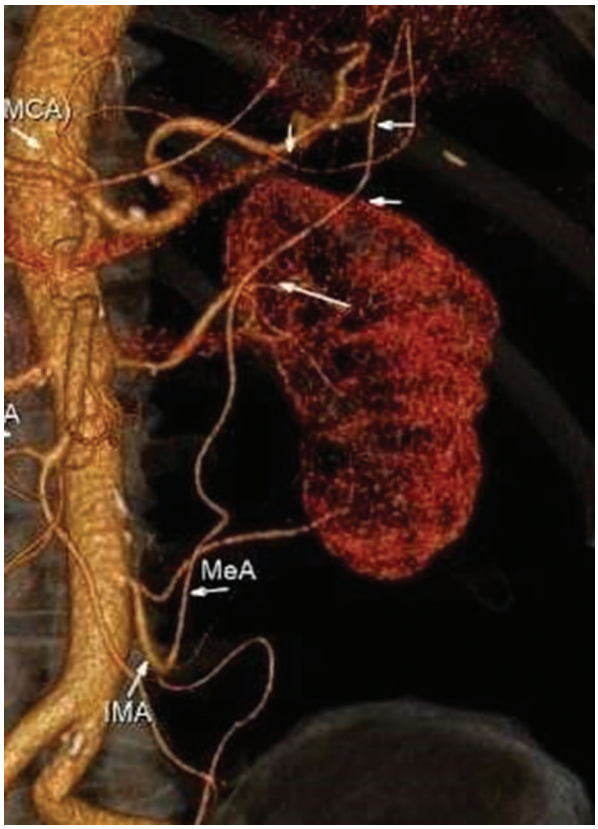

Figure 2. *Three-dimensional-computed tomography angiography: Moskovich's artery marked by arrows (MeA).*
IMA: inferior mesenteric artery; MCA: middle colic artery.

The Moshkovich's artery, also known as the tortuous mesenteric artery, is a lesser-known collateral route and is another link between the SMA and IMA. The

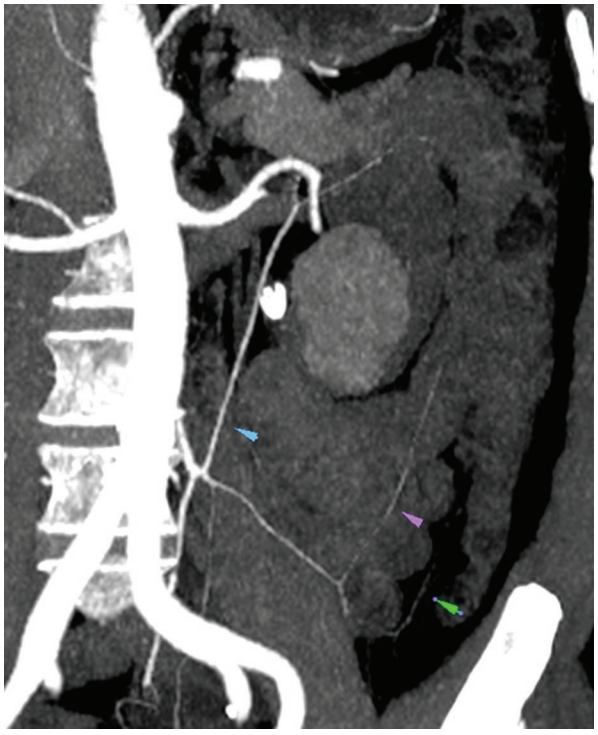

Figure 3. *Two dimensional-computed tomography angiography: left to right vascular arcades of Moshkovich, Riolan and Drummond.*

Moshkovich's artery runs along the base of the mesentery of the colon and is the connecting link between the proximal segment of the MCA and the ascending branch of the LCA[2,6]. In our study, we found the presence of this artery in only 1 (1%) patient (Fig. 2 and 3).

Analysis of the course of IMV showed that most often IMV flowed into the splenic vein (SV), there were 72 (69.9%) of such cases, IMV fell into superior mesenteric vein (SMV) in 27 (26.2%) patients, and IMV, SV, and SMV created a common confluence of the portal vein in 4 (3.9%) patients. We do not observe any venous injuries during mobilisation.

Clinical results

All patients underwent local radical left hemicolectomy with complete mesocolic excision (CME), central vascular ligation (CVL), and R0 resection; one case was operated laparoscopically; the median quantity of removal lymph nodes was 21.54 ± 7.32 (range 12-45). Positive lymph nodes were revealed in 24.3% cases. The incidence of metastatic lymph nodes in D1 zone was 25%, D2 zone – 6.2%, and the zone D3 – 3.1%. Mean operative time was 82 min (range 63-130 min). Median intraoperative blood loss was 65 mL (range, 32-280 mL); no patients required intraoperative blood transfusion. Post-operative complications were developed in seven patients. AL was diagnosed in one patient on the 8th post-operative day for whom relaparotomy, lavage and end stoma were performed (Fig. 4). Unfortunately, on the 1st day after patient discharge from the hospital, he died from massive thromboembolic complication despite maintaining prophylaxis therapy. Retrospective analysis of 3D-CT angiography showed the presence of third type of blood supply to the splenic flexure of the colon (AMCA + LCA) (Fig. 4). Due to oncological radicalism and the requirements of D3 lymphadenectomy, MCA was ligated in the base of SMA (tumor was located were closely to both branches of MCA), which caused irreversible ischemic changes in the area of anastomosis on the 8th post-operative day.

One patient suffered from paralytic ileus in an early post-operative period. Median staying in hospital after operation was 8.4 days.

Discussion

The most critical post-operative complication in patients with CRC is AL. The key factors that affect AL are the condition of blood supply to the edges of the anastomosis and its tension[1]. According to the literature, the incidence of AL after the left hemicolectomy is 5-10%. In our study, we have found out that the AL was in one case.

The ischemic zone of the splenic flexure of the colon is a serious risk factor for AL, because the disruption of blood supply to both ends of the anastomosis leads to the development of this complication. Some authors believe that the three vascular arcades of Drummond, Riolan, and Moshkovich should be excluded from use in the scientific literature, and instead introduce the concepts: marginal artery (most peripheral arcade), "V-shaped (intermediate) arcade" end of the ascending branch of LCA and LMCA or AMCA and "rare" intermesenteric trunk, which is located more centrally in the mesentery of the colon[2]. Nevertheless, the presence, detection, and evaluation of these vascular arcades at the preoperative stage of 3D-CT angiography analysis are an important element of surgery planning. For most surgeons when performing open or laparoscopic left hemicolectomy, the presence of a proximal arcade between the systems of SMA and IMA (Moshkovich's artery) is an unexpected finding and a debatable question in the feasibility of its ligation[6].

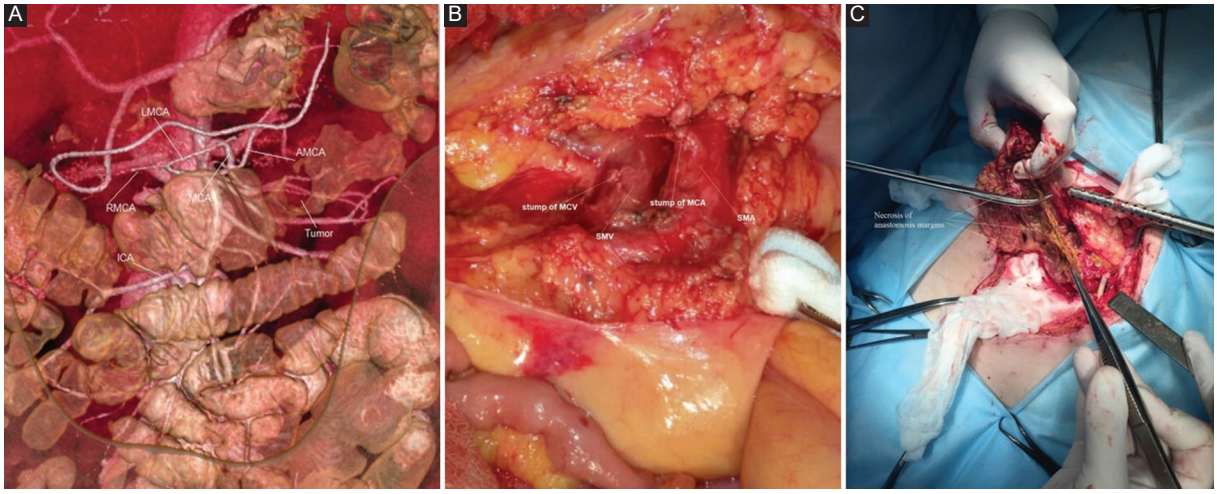

Figure 4. *Clinical case of anastomotic leakage (AL).* **A:** *intraoperative photo after D3 lymphadenectomy (SMA – superior mesenteric artery, SMV – superior mesenteric vein, stump of MCA and MCV);* **B:** *retrospective 3D reconstruction;* **C:** *relaparotomy, AL (necrosis of anastomosis margins).*

CME, CVL with D3 lymph node dissection, is the widely accepted surgical concept in colon cancer. However, the incidence of metastasis in the apical group of lymph nodes (D3 zone) in our study observed only in 3.1% cases, according to the literature ranges from 3% to 11%[3,4]. By the way, the left-sided colon cancer has less aggressive tumor biology so it is needed furthermore investigations and standardization about the volume of lymphadenectomy, especially D3 zone of middle and distal thirds of transverse colon[9].

In arterial supply of splenic flexure, quite rarely present AMCA which passes caudally to the lower margin of the pancreas to the distal transverse colon[10-12]. In our study, we found that AMCA was present in 10 (9.7%) cases and originated from MCA. It is a sophisticated question about the arterial structure of splenic flexure because we have not only the aim to make resection, but, firstly, we should perform the correct and radical oncological procedure. It is not a debatable question to preserve the feeding tumor artery in the case of cancer of splenic flexure. In the literature, there are some studies that describe originating AMCA from IMA or even from celiac arteries[12]. Another interesting and not completely standardized question is who and how classifies certain structures, specifically in the case when AMCA originated from IMA or maybe it is Moshkovich artery. By the way, for all colorectal surgeons, the presence of AMCA or Moshkovich artery is always a surprise during operation and it is another one of the arguments for careful assessment of pre-operative 3D CT angiography.

Along with the arterial anatomy, it is also important to have a clear understanding of the course of the venous branches (IMV, SV, and MCV) tangential to the splenic angle of the colon to avoid their damage[10,11].

Contrast-enhanced CT is the gold standard for diagnosing and staging patients with colon cancer and distant metastases[9,12]. 3D-CT angiography is a noninvasive modality which can be useful for preoperatively evaluating the vascular anatomy of the colon. 3D reconstruction can demonstrate different rare abnormalities. The goal of the 3D-CT angiography is not just about the acquisition of a “pretty picture” but could have additional diagnostic value especially in rare «casuistic» abnormalities. When staging a colorectal cancer, it is essential to achieve an early arterial phase of upper and lower abdomen in addition to venous phase. Early arterial phase 20-30 s post injection or immediately after bolus tracking is the phase of the best visualization and further 3D reconstruction of the arteries[13]. However, 3D CT angiography has a number of diagnostic limitations. First, the pre-operative CT protocol for patients with colon cancer usually does not involve performing an early arterial phase, which makes it difficult to perform adequate 3D reconstruction. Second, the caliber of the SMA and IMA branches is usually small and cannot always be well visualized on 3D-CT angiography. In the preoperative assessment of such vascular structures of the splenic angle of the colon as: Drumond’s marginal artery, Riolan’s arch and to a lesser extent Moshkovich’s artery, this creates additional visualization difficulties. This fact is a significant limitation in the qualitative assessment of pre-operative

vascular anatomy. In case of poor visualization of the above structures on 3D-CT angiography, the analysis should be performed in the usual 2D mode[3,7,8].

Actually, our study has some limitations. This study is partly retrospective (observation period from 2016 to 2018) and partly prospective (observation period from 2019 to 2022), so we can not fully conduct an effective analysis between anatomical variations of vascular anatomy with post-operative complications in a group of cases that were retrospectively analyzed.

Conclusions

Careful pre-operative analysis of vascular anatomy on 3D-CT angiography will assess the vascularization of the splenic flexure of the colon, reduce intraoperative time to identify structures, and develop a personalized strategy for surgery which potentially can reduce the risk of AL. Identification and taking for consideration of rare types of vascular supply of splenic flexure is a key point in avoiding surgical complications. New studies and further standardization for transverse colon cancer are needed to provide.

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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 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

Comparison of bipolar radiofrequency thermotherapy and transurethral prostate resection in treatment of benign prostate hyperplasia

Comparación de la termoterapia por radiofrecuencia bipolar y la resección transuretral de próstata en el tratamiento de la hiperplasia prostática benigna

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Abstract

Objectives: *Lower urinary tract symptoms due to benign prostatic hyperplasia in men increase with aging. Risks related to anesthesia and surgery have led a search for alternative treatments. Bipolar radiofrequency (RF) thermotherapy is one of the methods adopted in patients with high surgical risks. The aim of this study is to compare the effect of bipolar RF thermotherapy and transurethral resection of the prostate (TURP) methods on voiding symptoms and on post-operative complication rates especially in patients carrying high surgical risks.* **Methods:** *Pre-operative, post-operative 1st and 6th month International Prostate Symptom Score (IPSS), Qmax, quality of life, prostate volumes, and postoperative complications of the patients underwent TURP and RF for benign prostatic hyperplasia (BPH) were compared.* **Results:** *In the RF group, the pre-operative median IPSS was 30, prostate volume 41.5 cc, post-void residual (PVR) 80 ml, and Qmax is 5.85 ml/s.; In the TURP group, these were 29, 40 cc, 85 ml, and 5.3 ml/sec, respectively. In the Bipolar RF group, post-operative 1st- and 6th-month median values were IPSS 18, 21; prostate volume 40, 40; PVR 40, 35; Qmax 10.9, 9.15 and in the TURP group IPSS 9, 8; prostate volume 20, 20; PVR 30, 10; Qmax 17.25, 19.1, respectively.* **Conclusion:** *Bipolar RF thermotherapy is an applicable treatment method for BPH patients with high surgical risks.*

Keywords: *Prostatic hyperplasia. Radiofrequency. Transurethral resection of prostate. Transurethral Thermotherapy.*

Resumen

Objetivos: *La termoterapia bipolar por radiofrecuencia es uno de los métodos adoptados en pacientes con alto riesgo quirúrgico. El objetivo de este estudio es comparar el efecto de la termoterapia de radiofrecuencia bipolar y los métodos de RTUP en los síntomas de vaciado y en las tasas de complicaciones posoperatorias, especialmente en pacientes con alto riesgo quirúrgico.* **Métodos:** *Se compararon el IPSS, el Qmax, la calidad de vida, los volúmenes de próstata y las complicaciones posoperatorias de los pacientes sometidos a RTUP y RF para la HBP preoperatorios, posoperatorios al primer y sexto mes.* **Resultados:** *En el grupo de RF, la mediana preoperatoria del IPSS fue de 30, el volumen prostático de 41.5 cc, el PVR de 80 ml y el Qmax de 5.85 ml/seg.; En el grupo RTUP estos fueron 29, 40 cc, 85 ml y 5.3 ml/seg, respectivamente. En el grupo de RF bipolar, los valores medianos postoperatorios del primer y sexto mes fueron IPSS 18, 21; volumen de próstata 40, 40; PVR 40, 35; Qmax 10.9, 9.15 y en el grupo TURP IPSS 9, 8; volumen de próstata 20, 20; PVR 30, 10; Qmax 17.25, 19.1, respectivamente.* **Conclusión:** *La termoterapia de RF bipolar es un método de tratamiento aplicable para pacientes con HPB con alto riesgo quirúrgico.*

Palabras clave: *Hiperplasia prostática. Radiofrecuencia. Resección transuretral de prostata. Termoterapia transuretral.*

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Introduction

Lower urinary tract symptoms (LUTS) in men increase with aging[1,2]. Although there are many underlying causes to those symptoms, the most common cause is bladder outlet obstruction due to benign prostatic hyperplasia (BPH)[3]. LUTS decrease the quality of life, falls and bone fractures due to nocturia can be seen, as a result of these, even death may occur[4].

Depending on the size of the prostate, methods such as open prostatectomy and transurethral resection of the prostate (TURP) are used in the surgical treatment of BPH for decades. In patients with prostates < 80 cc, TURP is the most commonly used and gold standard surgical modality[5].

Risks related to anesthesia and surgery increase due to chronic diseases, drugs which must be used continuously or discontinuation of these drugs in the pre-operative period[6]. In patients receiving anticoagulant therapy, the need for transfusion, hematuria forming clots in the bladder, and lastly thromboembolic events are observed more frequently[7]. Today, despite the increase to the use of bipolar devices, TURP syndrome is encountered at a rate of 0.8% while the mortality has been observed at a rate of 0.1% after that surgery[8]. Due to these risks, there is an unending search for alternative treatments of TURP. Bipolar radiofrequency (RF) thermotherapy is also one of the methods adopted in patients with high surgical risks[9]. The main aim of this thermal ablation therapy is to destroy an entire tissue using heat to kill the target cells in a minimally invasive modality without damaging adjacent structures[10]. In the present study, it was aimed to evaluate the results of RF in comparison TURP to give an insight to that therapy as there is not a comparative study in the literature.

Methods

Approval was obtained from the Local Ethics Committee (Date of the decision: 10.07.2020, Approval Code of the decision: 350). Forty-two patients who underwent bipolar radiofrequency thermotherapy and 45 patients underwent bipolar TURP between June 2018 and January 2020 were included in this retrospective study.

Inclusion criteria of patients were diagnosis of BPH unresponsive to medical therapy, prostatic urethral length in the range of 23-50 mm, prostate volume between 30 cc and 80 cc, international prostate symptom score (IPSS) > 20, maximum urine flow rate (Qmax) < 14 ml/sec, high surgical risk due to comorbidities (American Society of Anesthesiology [ASA] 3 and above), and between the ages of 50 and 95. Exclusion criteria of patients were the presence of urethral stricture, prostate cancer diagnosis, and the presence of the prostatic median lobe.

Before performing bipolar radiofrequency thermotherapy, the patients were informed about the procedure, and consent form was obtained. Prostatic urethral length was measured with transrectal ultrasound (TRUS). The patient was placed in a supine position and a lubricant gel containing 2% lidocaine was squeezed out of the urethral meatus, the urethra was clamped and waited for 5 min. A 16 F urethral catheter with six heat rings at the tip was inserted transurethrally into the bladder. After the urine output was observed, the balloon of the catheter was inflated with 10 cc saline solution and placed on the bladder neck. The connection cable that provides the transmission of radiofrequency energy is connected to the computer system of RF generator.

The patient's identity information and prostatic urethral length have been entered into the system. The temperature of the electrodes was adjusted to 55°C and the process was started. According to the length of the prostatic urethra and the temperature values coming from the receptors in three different rings, the system activates the electrodes and keeps the temperature constant at 55°C. The process was applied for 1 h.

After the procedure was completed, the RF catheter was removed and a 16F 2-way foley catheter was placed. This catheter was removed after 3 days in all patients. Anti-inflammatory treatment was given for edema that may develop due to the procedure.

Patients who underwent B-TURP were informed before the procedure and consent forms were obtained. Spinal anesthesia was applied to all patients. PlasmaKinetic ™ SuperPulse Generator, Gyrus Plasmakinetic Superpulse Pk™- Superloop, Karl-Storz (Germany) 26F Resectoscope Sheath and 30° Karl-Storz Telescope (Solingen, Germany) were used. Patients were placed in the lithotomy position and a lubricant gel containing 2% lidocaine was squeezed out of the urethral meatus before the procedure. The procedure was performed by a single experienced surgeon (more than 100 cases). At the end of the procedure, bleeding was controlled and a 22F 3-way Foley catheter was placed in the bladder. The Foley catheter was removed after 3 days in all patients.

Pre-operative, post-operative 1st- and 6th-month IPSS, Qmax, quality of life, prostate volumes, and post-operative complications of the patients were compared.

Statistical method

The data analyses were performed with PASW 18 (SPSS/IBM, Chicago, IL, USA) software. Kolmogorov–Smirnov and P-P Plot tests were used to verify the normality of the distribution of continuous variables. The results were reported as mean ± SD, or in situations in which the distributions were skewed, as the median (minimum-maximum). Categorical variables were given as percentages. Mann–Whitney U test was used for the intergroup analysis of continuous variables. Categorical variables were analyzed with Chi-square test. The difference between pre-operative and post-operative values was assessed by Wilcoxon signed rank test, $p < 0.05$ was considered as statistically significant.

Results

The results of 87 patients who underwent Bipolar RF (n = 42) and Bipolar TURP (n = 45) were evaluated. There were no significant differences in pre-operative descriptive variables of two groups as shown in table 1.

Pre-operative results in the 1st and 6th months in both groups were evaluated. Table 2 shows a summary of the findings at the 1st and 6th month.

The ASA score of 36 (80%) of the patients who underwent TURP was 3, and 9 (20%) patients was 2 while the ASA score of 6 (14.3%) of the patients who underwent RF was 4, and the ASA score of remaining 36 (85.7%) was 3 (p = 0.001).

In TURP group, 3 (6.8%) patients had hematuria that did not require transfusion, one patient (2.3%) had indwelling catheterization, and one patient (2.3%) had epididymitis complications postoperatively while no complications were observed in the RF group. In 4 patients (9.5%), treatment was unsuccessful and could not get rid of the indwelling catheter.

Table 1. Pre-operative descriptive variables of the patients

Preoperative values	RF (n = 42)	TURP (n = 45)	p
Age (year)	74.5 ± 7.29 (60-93)	70.04 ± 7.34 (51-83)	0.06
Prostate volume (cc)	41.5 ± 11.4 (30-75)	40.0 ± 8.74 (30-66)	0.591
IPSS	30.0 ± 4.7 (18-35)	29.0 ± 5.68 (20-35)	0.496
Qmax (ml/s)	5.85 ± 3.23 (1.8-13.1)	5.3 ± 2.71 (2.1-13.2)	0.165
PVR (ml)	80.0 ± 69.7 (0-300)	85.0 ± 64.6 (0-200)	0.523

Values are presented as mean ± standard deviation (minimum-maximum).
RF: radiofrequency; TURP: transurethral resection of the prostate; IPSS: International Prostate Symptome Score; Qmax: maximum flow rate; PVR: post-void residual.

Discussion

BPH is a common diagnosis in the aging male population. It can affect the quality of life by causing LUTS. Treatment options for men with BPH exist in a broad spectrum and are determined by the symptoms. TURP has long been considered the gold standard for operative treatment; it is indicated for failure of medical therapy for LUTS, obstructive nephropathy, bladder stone formation, or recurrent episodes of urinary retention[5].

Numerous innovative treatment options have been developed in recent years, but their both short and long-term effects remain to be determined[11-17]. One of those innovative and minimally invasive treatment options is prostate thermal therapy. That therapy is often applied using RF currents, microwaves, ultrasound, laser, and thermal conduction sources by transurethral, transrectal, or external applicators. Treatments that procure temperatures lower 44°C are referred to as hyperthermia, those that procure temperatures over 44.5°C as thermotherapy, and those that procure temperatures beyond 65°C as themoablative[18].

Our study is to compare bipolar RF thermotherapy and bipolar TURP methods in patients carrying high surgical risks. Although there are many studies in the literature regarding these methods, there are very few studies on bipolar radiofrequency thermotherapy. To the best of our knowledge, there is no study comparing bipolar RF and TURP methods in the literature.

The mechanism by which thermal therapy causes a decrease in LUTS is not exactly understood. There are various theories that focus on changes in prostate innervation, or changes in the morphological organization of the prostate. The primary of these ideas appears to be based on the dynamic phenomenon of prostatic obstruction, in which the tone of the prostate's smooth muscle causes obstruction. Thermal damage to adrenergic fibers is thought to primarily cause long-term α-blockade[19]. Reduced prostatic urethral sensation may result in decreased input in the urethra-detrusor excitatory reflexes, resulting in an overall improvement in the perception of voiding symptoms.

Another effect of thermal therapy is to induce apoptosis and coagulation necrosis in prostate cells. Temperatures of up to 45°C do not completely impress the

Table 2. 1st- and 6th-month values of IPSS, prostate volume, PVR and Qmax, and QoL in RF and TURP groups

	1st month			6th month		
	RF	TURP	p	RF	TURP	p
IPSS	18 (3-30)	9 (2-25)	< 0 0.001	21 (2-35)	8 (2-16)	< 0.001
Prostate volume (cc)	40 (27-71)	20 (10-28)	< 0.001	40 (25-67)	20 (10-25)	< 0.001
PVR (ml)	40 (0-250)	30 (0-150)	0.428	35 (0-200)	10 (0-120)	0.032
Qmax (ml/s)	10.9 (3.5-19.6)	17.25 (4.5-23.5)	< 0.001	9.15 (3.5-11.3)	19.1 (5.6-23.9)	< 0.001
QoL	2	2	0.015	3	1	< 0.001

Values are presented as the median (minimum-maximum).
RF: radiofrequency; TURP: transurethral resection of the prostate; IPSS: International Prostate Symptome Score; Qmax: maximum flow rate; PVR: post-void residual; QoL: quality of life.

prostate cells. Cell death solely commens at temperatures over this threshold. The destruction persists even after the procedure is completed, which is known as the delayed effect. Delayed effects include ischemia and reperfusion damage, inflammation-induced cytokine release, and initiation of the immune system's response[20]. According to our study, a significant reduction in prostate volume was observed (p < 0.001). Prostate cells that are developed at 55°C may undergo apoptosis and coagulation necrosis, which would result in a decrease in prostate volume. Benli et al. found a significant increase in Qmax but no significant change in prostate volume[21]. Salar et al. and Engin et al. found improvement in voiding symptoms, but they have not evaluate prostate volume[22,23]. Based on our study, the transurethral RF method is applied and significant improvement was observed in voiding parameters in the 1st and 6th months (p < 0.001). It is obvious that the voiding parameters from the 6th month are superior when the findings of the 1st and 6th months are compared. Although the treatments for both groups were successful, TURP was more effective than bipolar RF thermotherapy (p = 0.0001). Clinically, prostate gland size does not always correlate with the severity of obstructive urinary symptoms a prolonged effect can be obtained due to thermal destruction of alpha adrenergic fibers and probably reduction in prostate volume[24].

While Sergey et al. reported acute urinary retention after catheter removal as a complication[25], Diri et al. and Salar et al. reported no complication in their groups after RF[22,26]. In our groups, 3 (6.8%) of the patients who underwent TURP had hematuria that did not require transfusion, 1 (2.3%) had an indwelling catheter, and 1 (2.3%) had epididymitis complications. No complications were observed in the RF group. The treatment was unsuccessful in 4 (9.5%) of the patients and they could not get rid of the indwelling catheter. When evaluated in terms of complications, there was no statistically significant difference between the groups (p = 0.204). Beside RF, there are also different thermal ablative procedures such as laser ablative therapy, microwave ablation, and cold (cryoablation) that provide the heat required to induce coagulation necrosis. RF system uses alternating electric current, vibrating at high frequency between anode and cathode to agitate tissue ions and produce frictional heat[10]. In monopolar systems, the applicator probe works as the cathode and uses grounding pad while in bipolar systems, the electric current is limited to the applicator tip, which contains anode and cathode[27]. Thus, bipolarity eliminates the side effects of monopolar systems such as skin burns in the contact area of grounding pads and on pacemaker implants.[28,29]. The biggest advantages of the procedure are the absence of the need for general anesthesia, the non-discontinuation of drugs used due to comorbidities, and the absence of hospitalization also no optical system is required[26]. It may be a viable treatment option in elderly patients due to the absence of side effects or complications.

The limitations of this study were that the data were obtained retrospectively, the number of patients was small, the follow-up period was only 6 months, and patients in the RF group had higher surgical risks. There is a need for expanded and long-term studies to observe the long-term effect of RF thermotherapy in patients with a high ASA score. However, this study was planned because there are only a few studies in the literature and there is no comparison with TURP.

Conclusion

Overall, RF is a relatively effective and safe technique that may be applied in selected patients with

symptomatic BPH. Although RF significantly improves many uroflowmetry parameters and IPSS scores, it cannot achieve as much efficacy and long-term success as TURP. On the other hand, RF appears to be superior to TURP in terms of associated morbidity, anesthetic requirements, length of hospital stay, and cost-effectiveness.

There are insufficient data in the literature regarding the precise mechanism of action of the technique and other factors involved in the success of the treatment. Comparative studies of RF with other minimally invasive treatments, durability with studies out to greater than at least a few years, and the overall cost-effectiveness ratio of the technique would be of critical importance to determine the exact role of RF in the treatment of symptomatic BPH.

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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 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 clinical effect of minimally invasive stereotactic puncture intracranial hematoma removal in the treatment of patients with cerebral hemorrhage: a meta-analysis

Efecto clínico de la extracción de haematoma intracraneal con punción mínimamente invasiva estereotáctica en el tratamiento de pacientes con hemorragia cerebral: un metanálisis

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Abstract

Objective: *The objective of the study was to systemically evaluate the clinical efficacy of minimally invasive stereotactic puncture for intracranial hematoma evacuation in patients with cerebral hemorrhage.* **Materials and Methods:** *Relevant studies in PubMed, Web of Science, MEDLINE, China National Knowledge Infrastructure, Wanfang, and VIP databases were searched. A meta-analysis was performed following the inclusion and exclusion criteria screening, data extraction, and literature quality evaluation.* **Results:** *Fifteen studies involving 1312 patients were included with 673 participants in the experimental group and 639 in the control group. The results of the meta-analysis showed that, compared with traditional craniotomy or treatment, minimally invasive stereotactic puncture intracranial hematoma removal had a higher clinical total effective rate in patients with cerebral hemorrhage, an outcome that could significantly shorten the hospitalization time of patients with cerebral hemorrhage. The level of post-operative activities of daily living was significantly higher, the incidence of postoperative complications was lower, and the mortality rate was lower. However, there was no significant difference in the degree of post-operative neurological deficit.* **Conclusion:** *Compared with traditional craniotomy or conservative treatment, minimally invasive stereotactic puncture intracranial hematoma removal has a higher clinical efficacy in the treatment of patients with cerebral hemorrhage, which can improve the post-operative daily life and abilities of patients.*

Keywords: *Guided stereotactic. Intracranial hematoma. Cerebral hemorrhage.*

Resumen

Objetivo: *Evaluación sistemática de la eficacia clínica de la punción estereotáctica mínimamente invasiva para la evacuación de hematomas intracraneales en pacientes con hemorragia cerebral.* **Material y métodos:** *Se realizaron búsquedas en estudios relevantes en PubMed, Web of Science, MEDLINE, Infraestructura Nacional de Conocimiento de China, base de datos Wanfang y base de datos VIP. El metanálisis se realizó después de la selección de criterios de inclusión y exclusión, la extracción de datos y la evaluación de la calidad de la literatura.* **Resultados:** *Se incluyeron 15 estudios en los que participaron 1.312 sujetos, 673 en el grupo experimental y 639 en el grupo control. En comparación con la Craneotomía tradicional o el tratamiento, el aclaramiento estereotáctico mínimamente invasivo de hematomas intracraneales tiene una alta eficiencia clínica total en pacientes con hemorragia intracerebral y puede acortar significativamente el tiempo de hospitalización*

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de los pacientes con hemorragia intracerebral. El nivel de actividad de la vida diaria postoperatoria (ADL) aumentó significativamente, la incidencia de complicaciones postoperatorias disminuyó y la mortalidad disminuyó. Sin embargo, no hubo diferencia significativa en el grado de déficit neurológico postoperatorio. **Conclusión:** *En comparación con la Craneotomía tradicional o el tratamiento conservador, la Craneotomía estereotáctica mínimamente invasiva tiene un mayor efecto clínico en el tratamiento de la hemorragia cerebral y puede mejorar la capacidad de la vida diaria de los pacientes después de la operación.*

Palabras clave: *Orientación estereotáctica. Hematoma intracraneal. Hemorragia cerebral.*

Introduction

Cerebral hemorrhage is one of the most common neurological diseases. With the growing ageing population in China, the incidence of cerebral hemorrhage has increased yearly[1]. The incidence of intracerebral hemorrhage is 12-15/100,000 person/year. In Western countries, intracerebral hemorrhage accounts for approximately 15% of all strokes and 10-30% of all hospitalized stroke patients. The proportion of intracerebral hemorrhage is higher in China, accounting for 18.8-47.6% of stroke incidences[2]. It is characterized by critical onset, rapid development, and high mortality. Hypertension, hyperlipidemia and smoking are common risk factors for cerebral haemorrhage[3]. Patients with cerebral hemorrhage often suffer from disability, aphasia and other complications, which not only decrease their safety but also impose a significant burden on their families and society[4]. At present, minimally invasive surgery, craniotomy, conservative treatment, and drug therapy are mainly used to treat the disease in clinical practice, but different treatment methods have different levels of clinical efficacy. For example, the risk of a brain tissue injury during a craniotomy is significant, as is the risk of serious brain edema, and the mortality rate is also high[5]. Surgical treatment mainly includes craniotomy drilling hematoma aspiration, stereotactic hematoma evacuation and endoscopic and computed tomography (CT) intracerebral hematoma evacuation[6]. Minimally invasive stereotactic puncture evacuation of an intracranial hematoma is a new surgical method that combines stereotactic surgery with the minimally invasive evacuation of an intracranial hematoma. It establishes a brain coordinate system according to the principle of stereotactic geometric coordinates and installs a directional instrument on the patient's skull to achieve accurate localization of target lesions[7]. This method has to date been widely used in clinical practice. In this paper, evidence-based medicine was used to strictly evaluate and analyze existing literature reports, and the clinical efficacy, postoperative neurological deficits, activities of daily living (ADL), the incidence of complications and mortality of minimally invasive stereotactic puncture evacuation of intracranial hematoma and traditional craniotomy in the treatment of patients with cerebral hemorrhage were evaluated.

Materials and methods

Search strategy

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidebook, a systematic literature search of the PubMed, MEDLINE, Web of Science, China National Knowledge Infrastructure, Wanfang and China Science and Technology Journal databases was performed from January 2010 to December 2021. A search strategy combining subject headings and free words was used. The search terms included *cerebral hemorrhage*, *cerebellar hemorrhage*, *intracerebral hemorrhage*, *ICH*, *stereotactic minimally invasive*, *minimal surgical procedures*, *frameless stereotactic*, *intracranial puncture*, *burr hole drainage*, *keyhole,* and *craniotomy surgery*. To avoid literature omission, we searched manually, reading the relevant systematic reviews to obtain related target literature on stereotactic hematoma evacuation and craniotomy hematoma evacuation in the treatment of patients with cerebral hemorrhage.

Inclusion and exclusion criteria

The study's inclusion criteria were as follows: (1) Chinese and English studies published in peer-reviewed journals; (2) randomized controlled trial or observational studies; (3) study participants aged $\geq$ 18 years; (4) patients with a cerebral hemorrhage or those diagnosed with a cerebral hemorrhage using a brain CT scan met the diagnostic criteria of the Chinese Guidelines for the Diagnosis and Treatment of Cerebral Haemorrhage (2019)[8]; (5) the location of bruises were

in the basal ganglia, suprauli, frontal lobe and occipital lobe, using minimally invasive stereotactic puncture; and (6) the case data in the literature were complete, and the main outcome measures included the overall clinical response rate, length of hospital stay, postoperative neurological deficit evaluation, postoperative ADL and the incidence of complications and mortality.

The study's exclusion criteria were as follows: (1) patients who had other causes of bleeding, including bleeding due to vascular abnormalities, for example, tumor bleeding, vascular malformations, aneurysms or vascular amyloidosis; (2) conference articles, systematic reviews and other types of literature; (3) articles with insufficient outcome information to extract data; and (4) articles that had been repeatedly published or were not available in full.

Study selection and data extraction

Two researchers independently screened the literature, performing preliminary screening using titles and abstracts and then reading the full text according to the inclusion and exclusion criteria for the secondary screening. When inconsistent opinions were encountered, the opinions of a third researcher were solicited and discussed to reach a unified agreement. After the literature screening, data extraction was performed independently by two researchers, and the extracted contents included the name of the first author, nationality and year of publication, the type of study, total sample size, hematoma evacuation time or hematoma elimination rate, operation time, length of hospital stay, postoperative neurological deficit evaluation, post-operative ADL, and any incidence of complications.

Quality evaluation

Two researchers independently performed the quality evaluation of the included literature. In case of disagreement, the opinion of a third researcher was solicited and discussed to reach a unified agreement. Randomized controlled trials were evaluated according to the Cochrane Handbook for Systematic Reviews 5.1.0[9]. This included the generation of random sequences, allocation concealment, the blinding of study participants and implementers, the blinding of outcome assessors, completeness of the outcome data and selective reporting of the study results and other sources of bias; each was evaluated as "low," "unclear" or "high" risk.

Statistical analysis

The Revman 5.3 software was used for statistical analysis. The effect size of measurement data was expressed as an odds ratio (OR), and the enumeration data were expressed as the standardized mean difference (SMD). Both indicators were used to estimate the interval range of the effect size with a 95% confidence interval (CI). If the original literature only provided median and range data; these were transformed into mean and standard deviation using a formula and included in the analysis. A heterogeneity evaluation was used to determine the size of heterogeneity using the I^2 test; if $I^2 < 50\%$ or $p > 0.1$, the included literature was considered homogeneous, and the Mantel-Haenszel was used for analysis assuming a fixed effect model. If $I^2 > 50\%$ or $p \leq 0.1$, the included studies were considered heterogeneous, and the DerSimonian-Laird random effect model was used for analysis. If the heterogeneity was large, sensitivity analysis or subgroup analysis was used to explore the source of heterogeneity. The test level of the meta-analysis was set as alpha = 0.05.

Results

Literature search results

A total of 384 relevant literature papers were retrieved for the current study. After the systematic search and screening of Chinese and English databases, 15 literature studies that met the criteria were finally included[10-24]. A flowchart of the literature retrieval and screening processes is shown in figure 1.

Basic characteristics of included studies and literature quality evaluation

Five studies were published from 2005 to 2015, and 10 were published from 2016 to 2021. Fifteen studies were from China, and they were all were randomized controlled studies. The total sample size of the 15 studies was 1312, with 673 in the experiment group and 639 in the control group. There were three high-quality, nine medium-quality and three low-quality articles. All of the randomized controlled trials stated that the principle of "randomization" had been followed, with one article not specifying a randomization scheme[10] and two articles not elaborating on neurological deficit scoring criteria[8,12]. These were evaluated

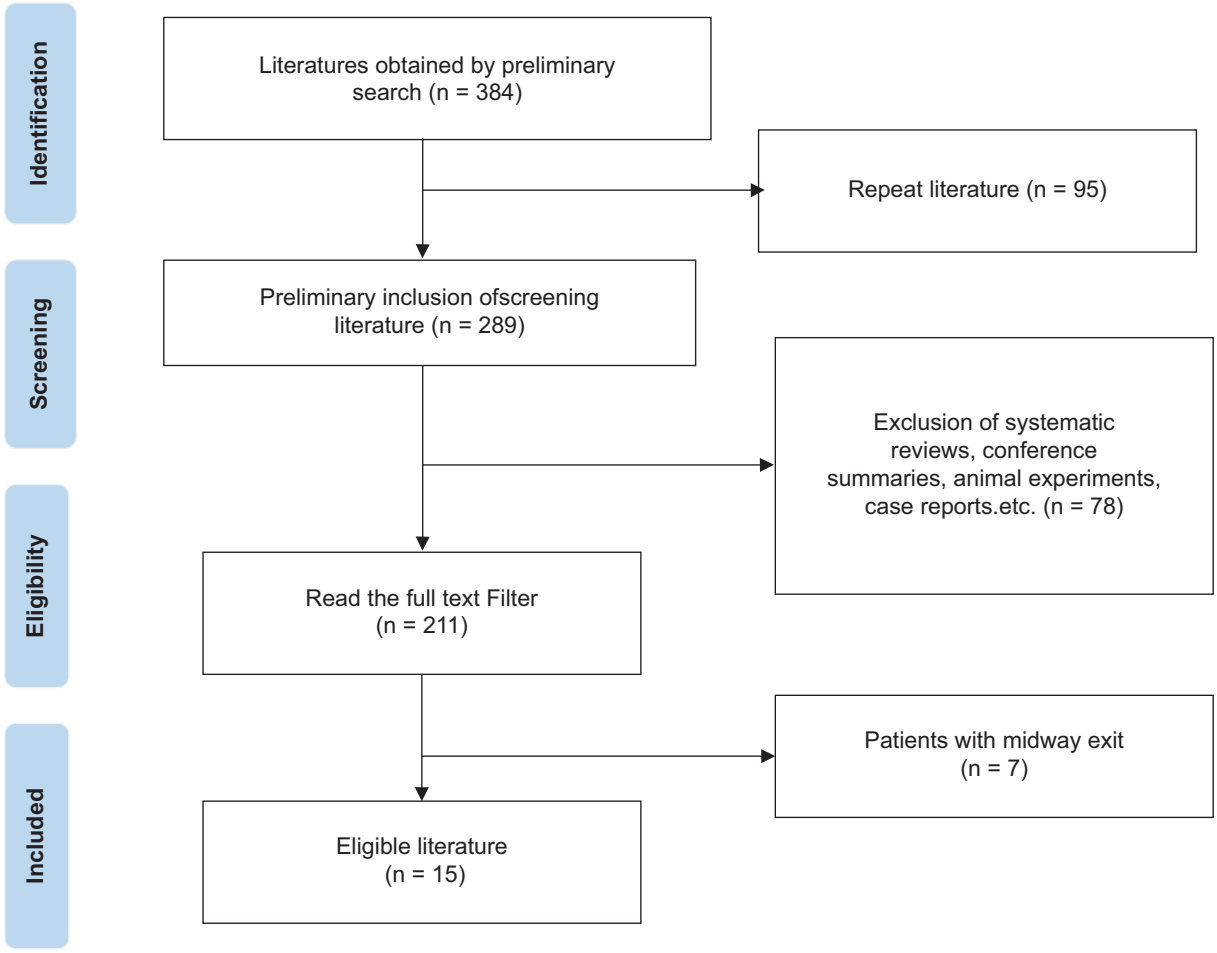

Figure 1. *Literature screening and flow chart.*

as low-quality articles. The basic characteristics and quality evaluation of the included articles are shown in table 1.

Meta-analysis results of the primary outcome measures

The clinical efficacy of minimally invasive stereotactic puncture evacuation of intracranial hematoma in the treatment of patients with cerebral hemorrhage

A total of eight literature papers compared the clinical efficacy of minimally invasive stereotactic puncture evacuation of intracranial hematoma (experiment group) with traditional craniotomy or treatment methods in the treatment of patients with cerebral hemorrhage (control group). The heterogeneity evaluation indicated homogeneity across studies (I^2 = 0%, p = 0.55); therefore, the fixed effects model was used to calculate the pooled statistics. The meta-analysis showed that minimally invasive stereotactic puncture evacuation of intracranial hematoma had a higher overall clinical response rate in patients with cerebral hemorrhage compared with traditional craniotomy or treatment, with a pooled effect size of OR = 4.84 (95% CI: 3.30, 7.10, p < 0.00001) as shown in figure 2.

The effect of minimally invasive stereotactic puncture evacuation of intracranial hematoma on neurological deficits in patients with cerebral hemorrhage

Twelve articles compared the effect of minimally invasive stereotactic puncture evacuation of intracranial hematoma (experiment group) with traditional craniotomy or treatment methods (control group)

Table 1. Basic characteristics of included studies and literature quality evaluation table

Included articles	Publication Year	Published country	Study type	Sample Size		Surgical method		Outcome Measures	Literature quality evaluation grade
				Experimental group	Control group	Experimental group	Control group		
Huang Xiantuan	2019	China	Randomized controlled trial	40	40	Stereotactic minimally invasive puncture intracranial hematoma removal	Drug therapy	①②	Middle
Ma Xiankun et al.	2012	China	Randomized controlled trial	28	27	Frameless stereotactic hematoma evacuation	Craniotomy	③⑥	Middle
Gao Jianguo, et al.	2005	China	Randomized controlled trial	82	60	Stereotactic minimally invasive puncture intracranial hematoma removal	Craniotomy	①⑤⑥	Low
Song Anjun et al.	2016	China	Randomized controlled trial	30	30	Stereotactic minimally invasive puncture intracranial hematoma removal	Drug therapy		Middle
Wang Hong et al.	2020	China	Randomized controlled trial	36	36	Stereotactic minimally invasive puncture intracranial hematoma removal	Craniotomy	⑤②	Low
Yang Lichao et al.	2017	China	Randomized controlled trial	16	16	Stereotactic minimally invasive puncture intracranial hematoma removal	Craniotomy	②③④	Middle
Li Liang et al.	2020	China	Randomized controlled trial	40	40	Stereotactic minimally invasive puncture intracranial hematoma removal	Craniotomy	④⑤②	Middle
Zheng Jianghuan et al.	2013	China	Randomized controlled trial	60	60	Stereotactic minimally invasive puncture intracranial hematoma removal	Expectant treatment	②⑤	Low
Fu Qiang et al.	2021	China	Randomized controlled trial	30	30	Stereotactic minimally invasive puncture intracranial hematoma removal (Improved-soft channel)	Craniotomy	①②④⑤	Middle
Wang Junfeng et al.	2019	China	Randomized controlled trial	82	82	Stereotactic minimally invasive puncture intracranial hematoma removal (Improved-soft channel)	Expectant treatment	①⑤	Middle
Huang Lihua	2015	China	Randomized controlled trial	25	25	Stereotactic minimally invasive puncture intracranial hematoma removal (Improved-soft channel)	Craniotomy	⑤⑥③	Middle

(Continues)

Table 1. Basic characteristics of included studies and literature quality evaluation table *(continued)*

Included articles	Publication Year	Published country	Study type	Sample Size		Surgical method		Outcome Measures	Literature quality evaluation grade
				Experimental group	Control group	Experimental group	Control group		
Lin Xiaoqiang et al.	2018	China	Randomized controlled trial	33	31	Stereotactic minimally invasive puncture intracranial hematoma removal	Expectant treatment	①②④	High
Ma Xiaoqiang et al.	2021	China	Randomized controlled trial	32	30	Stereotactic minimally invasive puncture intracranial hematoma removal	Craniotomy	③	Middle
Zhou et al.	2011	China	Randomized controlled trial	64	58	Stereotactic minimally invasive puncture intracranial hematoma removal	Craniotomy	②④⑥	High
Jing et al.	2021	China	Randomized controlled trial	75	74	Stereotactic minimally invasive puncture intracranial hematoma removal	Craniotomy	②③④⑥	High

① Hospital stay (d) ② Postoperative neurological deficit score ③ Postoperative activities of daily living score ④ Incidence rate of complications (%) ⑤ Effective rate ⑥ Mortality rate

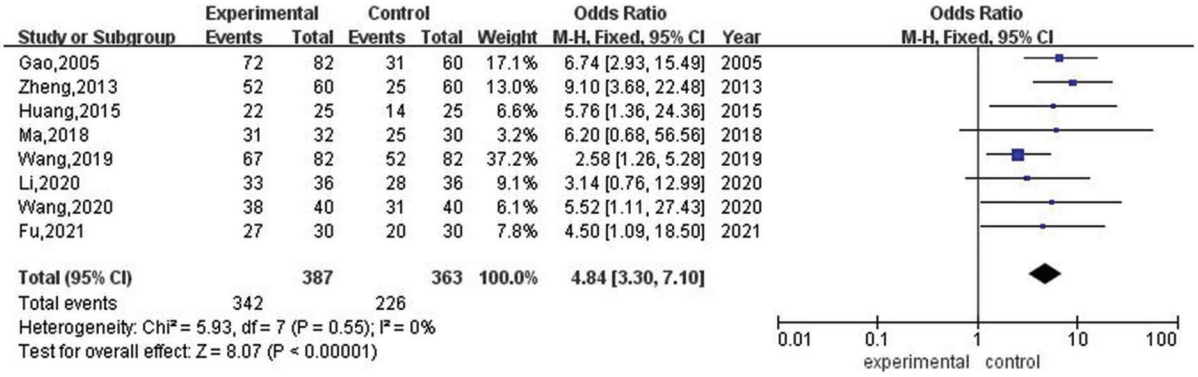

Figure 2. *Clinical efficacy.*

concerning the degree of neurological deficits in patients with cerebral hemorrhage. The heterogeneity evaluation indicated a high degree of heterogeneity among studies (I^2 = 98%, p < 0.00001); accordingly, the random effects model was used to calculate the pooled statistics. The meta-analysis showed that patients with cerebral hemorrhage who had been treated with minimally invasive stereotactic puncture intracranial hematoma evacuation had a lower degree of post-operative neurological deficits compared with a craniotomy or treatment modalities used in the control group (SMD = –0.32, 95% CI: –1.33, 0.70), but the difference between the experiment and control groups was not statistically significant (p = 0.054) as shown in figure 3.

The sensitivity analysis showed that, after removing three studies that scored neurological deficits using the Glasgow Outcome Scale[13,19,21], heterogeneity among the included studies was reduced by 1%, but the difference between the experiment and control groups remained statistically insignificant (SMD = –0.99, 95% CI: –2.03, 0.06, p = 0.06).

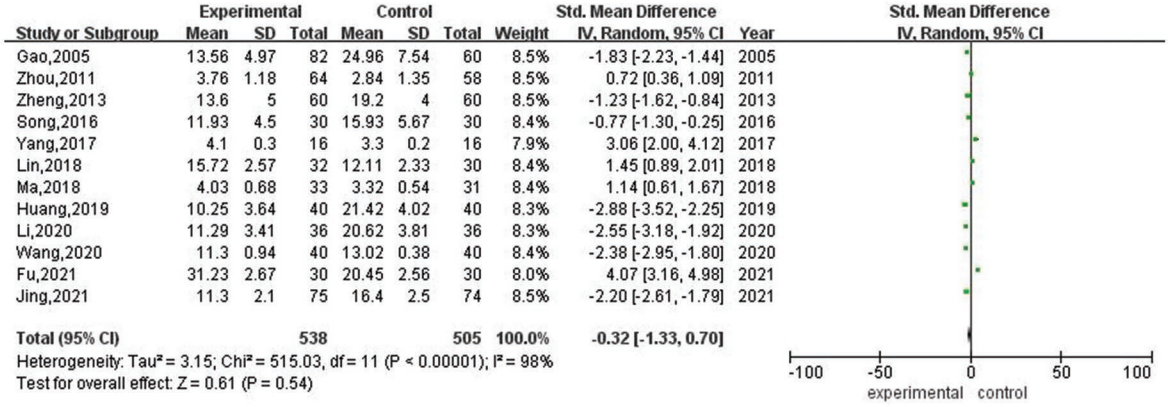

Figure 3. *Neurological deficits.*

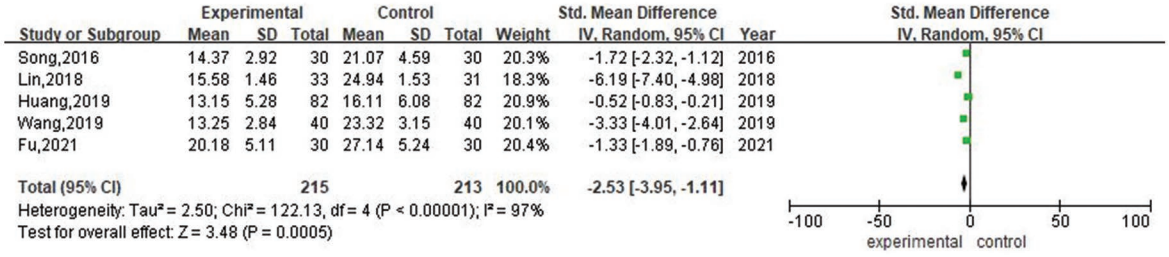

Figure 4. *Hospitalization Time.*

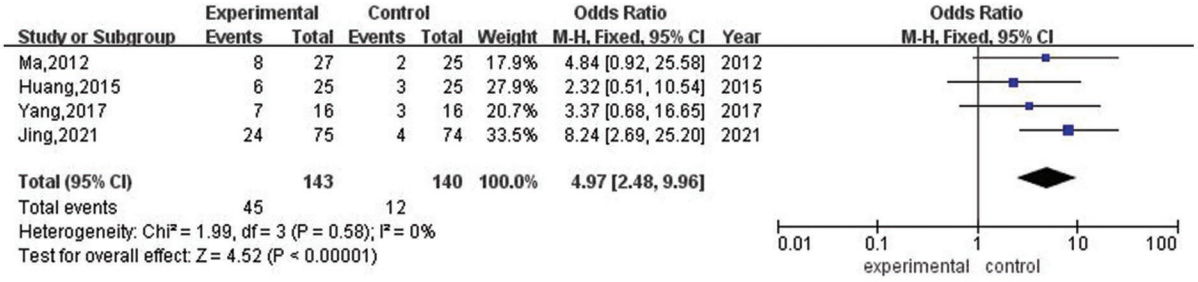

Figure 5. *Daily living ability.*

The effect of minimally invasive stereotactic puncture evacuation of intracranial hematoma on hospital stays in patients with cerebral hemorrhage

Five articles compared the effect of minimally invasive stereotactic puncture evacuation of intracranial hematoma (experiment group) with traditional craniotomy or treatment methods (control group) concerning the length of hospital stay among patients with cerebral hemorrhage. The heterogeneity evaluation showed a high degree of heterogeneity among studies (I^2 = 97%, p < 0.00001); therefore, the random effects model was used to calculate the pooled statistics. The meta-analysis showed that minimally invasive stereotactic puncture evacuation of intracranial hematoma could significantly shorten the length of hospital stay for patients with cerebral hemorrhage, compared with craniotomy or treatment modalities used in the control group (SMD = –2.53, 95% CI: –3.95, –1.11, p = 0.0005) as shown in figure 4. After excluding one study[19], the sensitivity analysis showed that heterogeneity among the

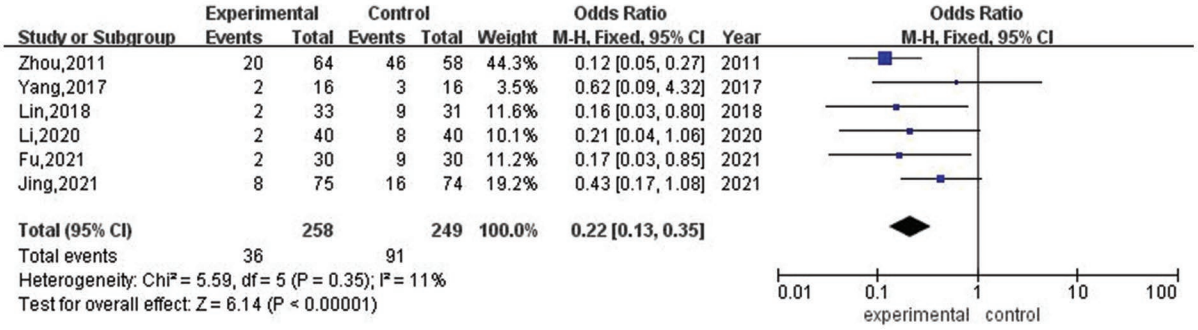

Figure 6. *Complications.*

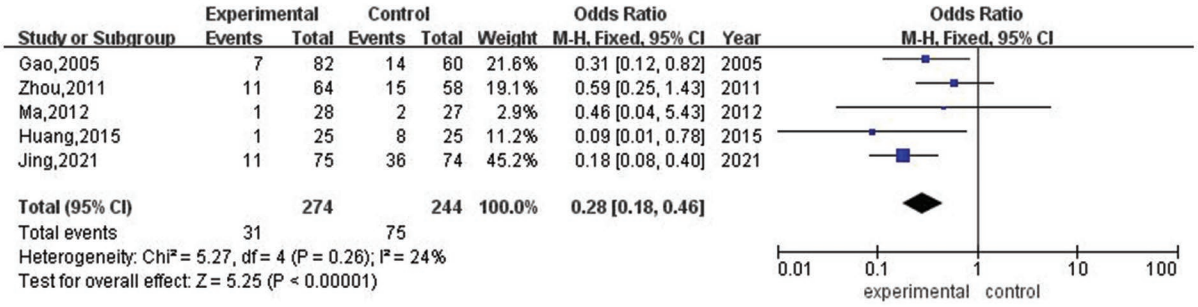

Figure 7. *Mortality.*

included studies had been reduced by 2%, and minimally invasive stereotactic puncture evacuation of intracranial hematoma could still significantly shorten the length of intensive care unit (ICU) stay for patients with cerebral hemorrhage (SMD = –1.70, 95% CI: –2.83, –0.56, p = 0.003).

The effect of minimally invasive stereotactic puncture evacuation of intracranial hematoma on the ADL in patients with cerebral hemorrhage

Five articles compared the effect of minimally invasive stereotactic puncture evacuation of intracranial hematoma (experiment group) with traditional craniotomy or treatment methods (control group) on the ADL of patients with cerebral hemorrhage. The heterogeneity evaluation showed good homogeneity among studies (I^2 = 0%, p = 0.58); accordingly, the fixed effects model was used to calculate the combined statistics. Patients in the experiment group had significantly higher levels of post-operative ADL compared with patients in the control group (OR = 4.97, 95% CI: 2.48, 9.96, p < 0.0001) as shown in figure 5.

The effect of minimally invasive stereotactic puncture evacuation of intracranial hematoma on complications for patients with cerebral hemorrhage

Six articles compared the effect of minimally invasive stereotactic puncture evacuation of intracranial hematoma (experiment group) with traditional craniotomy or treatment methods (control group) on complications for patients with cerebral hemorrhage. Because the heterogeneity evaluation showed low heterogeneity across studies (I^2 = 11%, p = 0.35), the fixed effects model was used to calculate the pooled statistics. Compared with patients in the control group, patients treated with minimally invasive stereotactic puncture evacuation of intracranial hematoma had a lower incidence rate of postoperative complications (OR = 0.22, 95% CI: 0.13, 0.35), and the difference was statistically significant (p < 0.00001) as shown in figure 6.

The effect of minimally invasive stereotactic puncture evacuation of intracranial hematoma on mortality among patients with cerebral haemorrhage

Five articles compared the effect of minimally invasive stereotactic puncture evacuation of intracranial hematoma (experiment group) with traditional craniotomy or treatment methods (control group) on the mortality of patients with cerebral hemorrhage. Because the heterogeneity evaluation showed low heterogeneity across studies (I^2 = 24%, p = 0.26), the fixed effects model was used to calculate the pooled statistics. Compared with patients in the control group, patients treated with minimally invasive stereotactic puncture evacuation of intracranial hematoma had a lower mortality rate (OR = 0.28, 95% CI: 0.18, 0.46), and the difference was statistically significant (p < 0.00001) as shown in figure 7.

Discussion

In this research, 15 studies evaluating the clinical efficacy of minimally invasive stereotactic puncture evacuation of intracranial hematoma in the treatment of patients with cerebral hemorrhage were included by systematically searching Chinese and English databases. The results of this study are summarized below.

Minimally invasive stereotactic puncture evacuation of intracranial hematoma has a higher clinical efficacy

The results of this study showed that minimally invasive stereotactic puncture evacuation of intracranial hematoma in patients with cerebral hemorrhage had a higher overall clinical response rate compared with traditional craniotomy or treatment (OR = 4.84 [95% CI: 3.30, 7.10, p < 0.00001]). A traditional craniotomy is invasive, the treatment takes too long to ensure the required therapeutic effect and damage can occur to the patient's brain tissue[25]. The CT-guided stereotactic minimally invasive technique has been widely used in clinical practice in recent years. Minimally invasive intracranial hematoma evacuation mainly uses biochemical and enzymatic techniques to liquefy the patient's hematoma, as well as liquid jet positive pressure to comminute the hematoma, followed by impact, washing and drainage of the hematoma. This allows for completely removing the intracranial hematoma in a short time. Therefore, minimally invasive stereotactic puncture evacuation of intracranial hematoma has also been widely used[26,27]. The procedure has the following advantages: CT-guided directional operation avoids blind actions, can more accurately determine the location of the hematoma and can locate the patient's bleeding and determine the surrounding tissue damage, thereby improving the success rate, accuracy, and safety of the puncture[28]. In addition, endoscopic assistance can make the surgical field clearer, allowing for the accurate and comprehensive detection and handling of intraluminal hematoma bleeding to facilitate its removal quickly and thoroughly[29]. Furthermore, the operation of the technique is simple and can be completed with only local anesthesia, causing less impact on the brain tissue; the drainage tube placement time is also short[30].

Minimally invasive stereotactic puncture evacuation of intracranial hematoma has little effect on postoperative activities of daily life in patients with cerebral hemorrhage

The results of this study showed that the level of postoperative ADL was significantly higher in the experiment group compared with the control group (OR = 4.97, 95% CI: 2.48, 9.96, p < 0.0001). Activities of daily life are intuitive and effective indicators for evaluating prognosis. The meta-analysis showed that patients with cerebral hemorrhage, who had been treated with minimally invasive stereotactic puncture evacuation of intracranial hematoma, had a higher proportion of complete recovery of ADL within 3 months after surgery, compared with patients who had been treated with traditional treatments or craniotomy, with better postoperative ADL and an overall better prognosis. The possible reasons were analyzed as follows: Minimally invasive stereotactic puncture evacuation of intracranial hematoma minimized the surgical trauma of patients, for example, less damage to brain tissue and intracranial surrounding tissue than other surgical methods[31]. This surgical method was not strictly limited by age, condition or anesthesia, and could effectively drain the hematoma and shorten the surgical duration[32].

Minimally invasive stereotactic puncture evacuation of intracranial hematoma in patients with cerebral hemorrhage has a lower incidence of complications and mortality

The results of this study showed that patients treated with minimally invasive stereotactic puncture

evacuation of intracranial hematoma had a lower incidence of postoperative complications (OR = 0.22, 95% CI: 0.13, 0.35, p < 0.00001) and a lower mortality rate (OR = 0.28, 95% CI: 0.18, 0.46, p < 0.00001) compared with patients in the control group. Studies have shown that iatrogenic injury is more serious when performing a conventional craniotomy, and the incidence of long-term complications, such as postoperative mortality and secondary epilepsy, is relatively high[33]. This has the limitations of a long surgical procedure, possible severe trauma, and a high risk of anesthesia; accordingly, its prognosis and clinical efficacy are unsatisfactory[34]. Severe pulmonary infections, such as respiratory failure caused by severe pneumonia, epilepsy, and stress ulcers in the thalamus and brainstem are common postoperative complications among patients with cerebral haemorrhage[35]. Minimally invasive stereotactic puncture evacuation of intracranial hematoma can effectively reduce iatrogenic blood loss in patients with cerebral hemorrhage, quickly puncture the hematoma, aspirate the fluid part of cerebral hemorrhage and reduce intracranial pressure in a very short time. The residual semisolid hematoma is dissolved by a fibrinolytic solvent, the effect of early hematoma evacuation is achieved and the effect on brain tissue is reduced[36]. Accordingly, the risk factors of related complications are also effectively suppressed, thereby reducing the incidence of postoperative complications. In addition, the surgical process and time required to perform minimally invasive stereotactic puncture evacuation of intracranial hematoma are controllable. A routine post-operative CT scan re-examination can monitor the dynamic changes of residual hematoma volume to determine the dosage and frequency of urokinase injection and achieve the purpose of a maximum evacuation of hematoma fluid mass, significantly reducing the mortality of patients and improving their prognosis level[37]. Moreover, a stereotactic puncture is less cost prohibitive than traditional medical conservative treatment due to shorter stays in the ICU and a greater clinical effect[38].

Conclusion

In summary, the meta-analysis results of this study showed that minimally invasive stereotactic puncture intracranial hematoma evacuation had higher clinical efficacy in the treatment of patients with cerebral hemorrhage, compared with traditional craniotomy or conservative treatment, which could improve the post-operative ADL and reduce the incidence of post-operative complications and mortality. However, the method's effect on neurological deficits remains unclear, which may be because the scoring criteria used in each study have not yet been unified. The degree of neurological deficit is primarily evaluated using scales and lacks strong objectivity. Furthermore, the current authors did not collect information about the size of the hematomas that each study included. Conventionally, it has been established that patients who are eligible for the evacuation of these collections by the stereotactic method are those that present smaller bruises, but some studies did not provide this information. Therefore, it is still necessary to carry out a large sample, multicenter study in the future, using standardized, unified and scientific methods to evaluate the postoperative indicators among patients with cerebral hemorrhage, thereby further verifying the comprehensive efficacy of minimally invasive stereotactic puncture intracranial hematoma evacuation in the treatment of patients with cerebral hemorrhage.

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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 no patient data appear in this article.

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

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ORIGINAL ARTICLE

The effect of platelet-rich plasma on intra-abdominal adhesions in rabbit uterine horn model

El efecto del plasma rico en plaquetas en las adherencias intraabdominales en modelo de cuerno uterino de conejo

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Abstract

Objective: *This study was carried out to investigate the effect of autologous platelet-rich plasma (PRP) on intra-abdominal adhesion at the cesarean section incision line in the uterus.* **Material and methods:** *As experimental animals 16 white New Zealand rabbits, 5-months-old, unmated, were used. Animals were divided into two groups the control group and PRP application group. In each group, a transverse incision was made to the uterus to mimic the cesarean section and sutured. Relaparotomy was performed 21 days after the first operation.* **Results:** *When the groups were evaluated in terms of inflammation, there was a significant difference between the two groups. When the groups were evaluated in terms of Mason's Trichrome staining and fibrosis, There was a significant difference between groups. When the groups were evaluated in terms of vascular endothelial growth factor-1, there was also a significant difference between the groups. In an experimental rabbit uterine horn adhesion model, PRP is effective in preventing post-operative adhesion formation.* **Conclusions:** *This result may guide clinical studies using autologous PRP to prevent post-operative adhesion formation after gynecological operations.*

Keywords: *Gynecological surgery. Platelet-rich plasma. Post-operative complications- Repeat cesarean sections. Surgical adhesions.*

Resumen

Objetivo: *Este estudio se llevó a cabo para investigar el efecto del plasma rico en plaquetas (PRP) autólogo sobre la adhesión intraabdominal en la línea de incisión de la cesárea en el útero.* **Material y métodos:** *Como animales de experimentación se utilizaron 16 conejos blancos de Nueva Zelanda, de 5 meses de edad, sin aparear. Los animales se dividieron en dos grupos como grupo de control y grupo de aplicación de PRP. En cada grupo, se hizo una incisión transversal al útero para imitar la cesárea y se suturó. La relaparotomía se realizó 21 días después de la primera operación.* **Resultados:** *Cuando los grupos se evaluaron en términos de inflamación, hubo una diferencia significativa entre los dos grupos. Cuando los grupos se evaluaron en términos de tinción MT y fibrosis, hubo una diferencia significativa entre los grupos. Cuando los grupos se evaluaron en términos de VEGF-1, también hubo una diferencia significativa entre los grupos. En un modelo experimental de adherencia al cuerno uterino de conejo, el PRP es eficaz para prevenir la formación de adherencias posoperatorias.*

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Conclusiones: *Este resultado puede guiar los estudios clínicos que utilizan PRP autólogo para prevenir la formación de adherencias postoperatorias después de operaciones ginecológicas.*

Palabras clave: *Cirugía ginecológica. Plasma rico en plaquetas. Complicaciones postoperatorias. Repita las cesáreas. Adherencias quirúrgicas.*

Introduction

Every year, millions of laparotomies are performed worldwide due to trauma, malignancies, acute abdomen syndrome, infections, vascular pathologies, and gynecological and urogenital diseases. Unfortunately, peritoneal adhesions inevitably occur after these operations. Peritoneal adhesions are fibrous tissues formed between the peritoneum and intra-abdominal organs such as the small intestine, colon, and uterus and play an essential role in post-operative morbidity. Adhesions after pelvic surgery are the leading cause of complications such as chronic abdominopelvic discomfort, pain, and infertility. The remarkable increase in morbidity and mortality due to pelvic adhesions has revealed the necessity of developing more safe and effective anti-adhesion auxiliary models[1-3]. Numerous pharmaceutical studies have recently investigated the trial of drugs with anti-inflammatory effects on various animal models and their usability in clinical settings[4-7].

Peritoneal adhesions begin to form on the peritoneal and visceral surfaces concerning post-operative trauma. The vascular permeability of the tissue increases, followed by the exudation of inflammatory cells. The fibrin matrix is gradually organized and replaced by tissue fibroblasts, macrophages, and giant cells. In the next step, fibrin bands are modeled, and connections are formed between the injured tissue and the peritoneum. The fibrinolytic system destroys fibrin bands, and peritoneal healing is achieved. If this system is insufficient, fibrin bands become permanent[8]. Tissue response may be exaggerated after surgical interventions, and tissue regeneration and remodeling may result in adhesion formation[9].

Platelet-rich Plasma (PRP) obtained from the patient's blood contains growth factors and biomolecules necessary for wound healing. Using autologous PRP eliminates the risks of cross-contamination, disease transmission, or immune reactions. Another significant advantage is that it is simple and fast to prepare, and the preparation cost is low (approximately 30 minutes from blood collection to administration). PRP is prepared from the centrifugation of autologous whole blood and combined with thrombin and calcium chloride to produce a viscous coagulation gel[7]. PRP contains many growth factors and various proteins that can stimulate the healing process. Therefore, it has widespread clinical use. PRP accelerates neovascularization and increases blood flow and nutrient flow required for cell regeneration in damaged tissues. It also stimulates the proliferation and differentiation of cells involved in the healing process[10].

Transverse incision on the uterus is applied in many surgical interventions such as myomectomy and cesarean section in surgical practice. This study was designed to investigate the effect of PRP on the healing process and intra-abdominal adhesion at gynecologic surgery.

Material and methods

Preparation of PRP

Locally applied PRP was used in this study. Three milliliters of blood collected from the rabbits' ear veins were slowly injected into a tube containing 10:1 sodium citrate. 0.5 ml of blood was taken into a separate tube, and platelet count (489.000/μl) was measured with a complete blood count panel (Mindray BC-6800). The blood was centrifuged at 160 G for 10 min. The blood components were divided into two: the clear supernatant forming PRP and the other part containing erythrocytes and leukocytes. A portion of the clear supernatant is centrifuged again at 300 G for 10 min. With the complete blood count, it was determined that the platelet count reached approximately three times (1463.000/μl). Calcium chloride (10:1) was added for platelet activation before injection[7].

Animal experiments

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

In the research within this project's scope, 16 adults, an average of 20 weeks old, unmated, female, 2500-3000 g

white New Zealand rabbits were used as experimental animals. Rabbits were left to acclimate to laboratory conditions for 1 week after purchase. Rabbits are kept as single individuals in a cage. The animals were kept in the laboratory's standard animal housing conditions with 12 h of light-dark, 21°C temperature, 50-60% humidity, and optionally standard pellet rabbit food and water. All rabbits fasted for 12 h before surgery.

Animals were randomly divided into two groups, 8 for each, as the control group and the PRP application group. Animals were anesthetized by intramuscular injection of 10 mg/kg xylazine (Rompun; Bayer, Turkey) and 30-35 mg/kg ketamine (Ketalar; Parke Davis, Turkey, Istanbul) and allowed to breathe spontaneously. A rectal tube was inserted into the animals and placed on a heating pad to maintain their body temperature at 37°C. All surgical procedures were performed by the same surgeon. Rabbits were fixed in the supine position. The surgery was limited to 10 min per rabbit to control the effect of tissue drying in room air, with care being taken to avoid large amounts of bleeding from the tissues. The midline lower abdomen of each rabbit was shaved and disinfected with an iodine solution. The abdomen was entered with an approximately 5 cm long midline vertical incision. In each group, a transverse incision was made on the uterus for wound healing and adhesion evaluation. The abdominal wall was opened, and a typical lesion was created by making a 10 mm long transverse incision on the antimesenteric face of one of the uterine horns with a scalpel. The uterus was duly closed with 4-0 vicryl. After the bleeding control was achieved with cautery, the PRP prepared on the wound lips was applied equally to the PRP group with an insulin syringe. Since we injected PRP into the sutured uterine incision, local injection with saline was applied as a placebo fluid for the control group, considering the damage that the injection needle would cause to the uterine tissue. Then, the abdominal wall was closed with two layers of 4/0 vicryl. Antibiotic prophylaxis was administered during and after the surgery. Relaparotomy was performed in both groups 21 days after the first operation. The uterine incision site was excised and preserved for histopathological examination.

Macroscopic adhesion scoring

Adhesions formed after relaparotomy on the 21st day were evaluated macroscopically by two independent researchers unaware of the applications. The mean score of both researchers was used for that rabbit.

Table 1. Macroscopic Adhesion Scoring[11]

Score	Definition
Adhesion prevalence (0-4)	
0	0%
1	< 25%
2	25-50%
3	50-75%
4	> 75%
Adhesion severity (0-4)	
0	Absent
1	Self detached
2	Separated by withdrawal
3	Separated by blunt dissection
4	Separated by sharp dissection
Total adhesion score (range 0–8)	Total adhesion prevalence and severity score

Grading of adhesions was evaluated in terms of adhesion prevalence and severity, with scores from 0 to 4. The total adhesion score (0-8) was found for each rabbit by summing the adhesion prevalence and severity scores[11] (Table 1).

Histopathological evaluation

The uterine incision site was excised 21 days after the first operation. These tissues were fixed in 10 % neutral buffered formaldehyde solution at room temperature for 24 h. In the 15-h follow-up process with the tissue tracking device (Sacura), dehydration, transparency, and tissue hardening processes were completed by passing through alcohol, xylene, and paraffin stages. Then, the tissues were made into blocks by embedding paraffin in a tissue embedding device (Thermo Shandon). After the blocks were cooled in the refrigerator, 3-micron-thick sections were taken on the microtome device (Leica). Some of these sections were taken from standard slides for hematoxylin-eosin (HE) and Mason's Trichrome (MT) staining, and some of them were taken on a positively charged slide for anti-vascular endothelial growth factor-1 (VEGF-1) immunohistochemistry staining. Sectioned preparations for HE (Facepath) staining were stained in an automatic staining-off device (Sacura) and closed. MT staining (Facepath) was applied to the slides manually with the kit. VEGF-1 antibody (Abcam, Clone: Y103, 1/100 dilution, 32 min incubation time) immunohistochemical staining was performed on the preparations taken on positively loaded slides in an automatic Ventana Benchmark XT device.

Then, the slides were closed by dripping entellan. After staining procedures, the samples were assessed in a blinded manner by two pathologists to avoid bias with a light microscope (Leica DM 750). Inflammation and fibrosis were evaluated in HE-stained preparations[9,12,13] (Table 2).

Statistical review

Count data were given with numbers and percentages, and measurement data with mean, standard deviation, minimum and maximum values. Mann–Whitney U test, a non-parametric test, was used to compare both groups. $p < 0.005$ was considered statistically significant.

Results

A veterinarian checked the rabbits daily, and no problems were encountered throughout the study. The total adhesion score of the control group was 38, and the total adhesion score of the PRP group was 32 (Table 3). A statistically significant relationship was found between the two groups regarding total adhesion score ($p = 0.005$) (Table 4). The histopathological findings of both groups were compared, and the results were scored (Table 5).

When the control group and PRP group were evaluated in terms of inflammation (Fig. 1), there was a significant difference between the two groups ($p = 0.041$). When the control and PRP groups were evaluated in terms of MT staining and fibrosis, There was a significant difference between groups ($p = 0.041$) (Figs. 2 and 3). When the control and PRP groups were evaluated in terms of VE GF-1, there was also a statistically significant difference between the groups ($p = 0.020$) (Table 6) (Figs. 4 and 5).

Table 2. Histopathological evaluation[9,12,13]

The degree of inflammation	
0	
1	No inflammation
2	Rarely presence of giant cells, lymphocytes, and plasma cells
3	Presence of giant cells, plasma cells, eosinophils, and neutrophils Presence of many inflammatory cells and microabscesses
The degree of fibrosis	
0	No fibrosis
1	Mild
2	Moderate
3	Severe
Percentages of VEGF-1 immunoreactive cells	
0	Negative for staining
1	33% positive staining
2	33-66% positive staining
3	66% recorded as positive staining

VEGF: vascular endothelial growth factor.

Table 3. Macroscopic adhesion scoring in groups

Macroscopic adhesion	Control group	PRP group
Adhesion prevalence	3, 3, 2, 3, 3, 2, 3, 2	2, 2, 2, 2, 2, 2, 1, 1
Adhesion severity	3, 3, 3, 3, 2, 2, 3, 3	2, 3, 2, 2, 3, 2, 2, 2
Total adhesion score	6, 6, 5, 6, 5, 4, 6, 5	4, 5, 4, 4, 5, 4, 3, 3

PRP: platelet-rich plasma.

Discussion

Adhesion development after abdominopelvic surgery is a common complication (60-93%). This situation forms the basis of many problems, such as intestinal obstruction, chronic pain, and infertility[14].

First of all, in this study, when PRP produced from the rabbits own blood was applied to the uterine incision, it was observed that adhesion was reduced in all the examined parameters, both macroscopically and histopathologically.

PRP is 3-5 times more concentrated than the amount of autologous rabbit platelets in whole blood. It contains growth factors and biomolecules that accelerate wound healing[15-19]. Using autologous PRP eliminates the risks of cross-contamination, disease transmission, or immune reactions. By accelerating neovascularization, PRP helps the proliferation and differentiation of cells involved in the healing process[10].

Many studies have been conducted on using PRP as a gel on the wound to accelerate wound healing. The common conclusion in these studies is that PRP contributes to wound healing[20-22]. After the acute inflammatory phase, wound healing occurs with increased fibroblastic activity. It continues for several weeks to months to restore tissue strength and maturation. During this continuity, the healing response may occur more than necessary. These results in delayed adhesion formation are related to the time of surgery because post-operative adhesions in the peritoneum most commonly become permanent within the 1st week and after the 2nd week[23]. Unlike previous

Table 4. Statistical comparison of macroscopic adhesion scoring

Macroscopic adhesion	Control group	PRP group	p-value
Adhesion prevalence	2.62 ± 0.51 (min-2, max-3)	1.75 ± 0.46 (min-1, max-2)	**0.009**
Adhesion severity	2.75 ± 0.46 (min-2, max-3)	2.25 ± 0.46 (min-2, max-3)	0.051
Total adhesion score	5.37 ± 0.74 (min-4, max-6)	4.00 ± 0.75 (min-3, max-5)	**0.005**

Results were given as mean ± standard deviation (n = 8 for each group).
PRP: platelet-rich plasma.

Table 5. Scoring of histopathological findings

Histopathological findings	Control group	PRP group
Inflammation	2, 1, 1, 2, 1, 1, 2, 1	1, 1, 1, 1, 1, 0, 1, 0
Fibrosis	1, 2, 1, 1, 2, 1, 1, 2	1, 1, 1, 1, 1, 0, 1, 0
MT	1, 2, 1, 1, 2, 1, 1, 2	1, 1, 1, 1, 1, 0, 1, 0
VEGF-1	3, 2, 3, 3, 3, 3, 3, 3	3, 2, 2, 2, 3, 2, 2, 2

PRP: platelet-rich plasma; MT: Mason's Trichrome staining; VEGF: vascular endothelial growth factor.

Table 6. Statistical comparison of histopathological scoring

Histopathological findings	Control group	PRP group	p-value
Inflammation	1.38 ± 0.51 (min-1, max-2)	0.75 ± 0.46 (min-0, max-1)	0.041
Fibrosis	1.38 ± 0.51 (min-1, max-2)	0.75 ± 0.46 (min-0, max-1)	0.041
MT	1.38 ± 0.51 (min-1, max-2)	0.75 ± 0.46 (min-0, max-1)	0.041
VEGF-1	2.88 ± 0.35 (min-2, max-3)	2.25 ± 0.46 (min-2, max-3)	0.020

Results were given as mean ± standard deviation (n = 8 for each group).
PRP: platelet-rich plasma; MT: Masson's trichrome staining; VEGF: vascular endothelial growth factor.

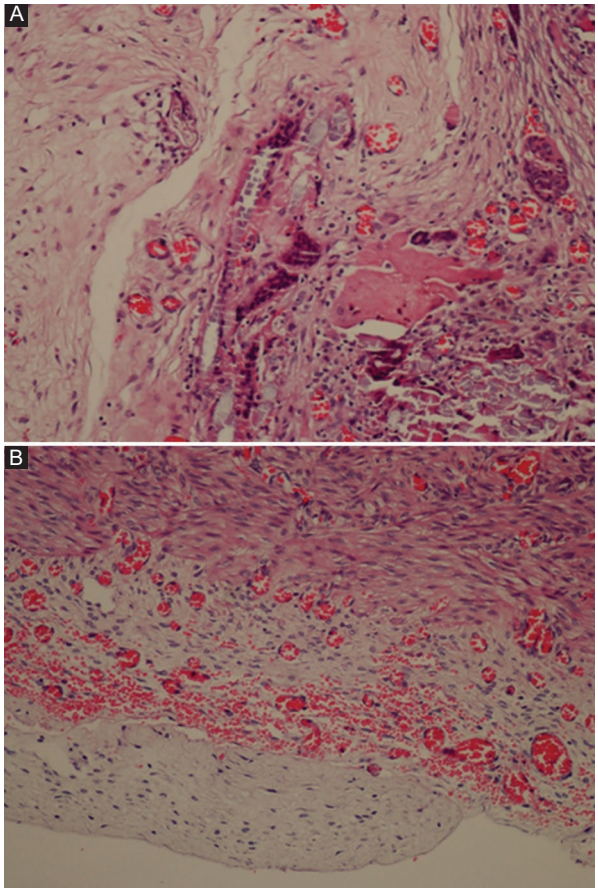

Figure 1. *Control group.* **A:** *moderate fibrosis, inflammation with giant cells and signs of increased vascularization (hematoxylin-eosin [HE] × 200).* **B:** *mild fibrosis (HE × 200).*

studies, in which the degree of adhesion was evaluated at day 7, 10, or 14 postoperatively[12,24,25], fibroblastic activity and degree of fibrosis were evaluated at day 21 in this study. When the adhesion scoring was performed macroscopically, it was determined that the extent of adhesion and the total adhesion score were significantly lower in the PRP group, and the adhesion severity was close to the significance level.

The first step in peritoneal adhesion formation is inflammation[26]. In our study, as expected, inflammation was detected significantly less in the PRP group compared to the control group.

Fibrosis score is another important parameter in the evaluation of peritoneal adhesions, and it is frequently used to evaluate the effectiveness of anti-adhesion studies[27]. A low fibrosis score is indicative of weak adhesions. Fibroblasts and many growth factors released from them increase during the healing process and contribute to wound healing. It has also been reported that PRP application increases fibroblast migration and proliferation[28,29]. This study detected a significantly reduced fibrosis score histopathologically in the PRP group compared to the control group.

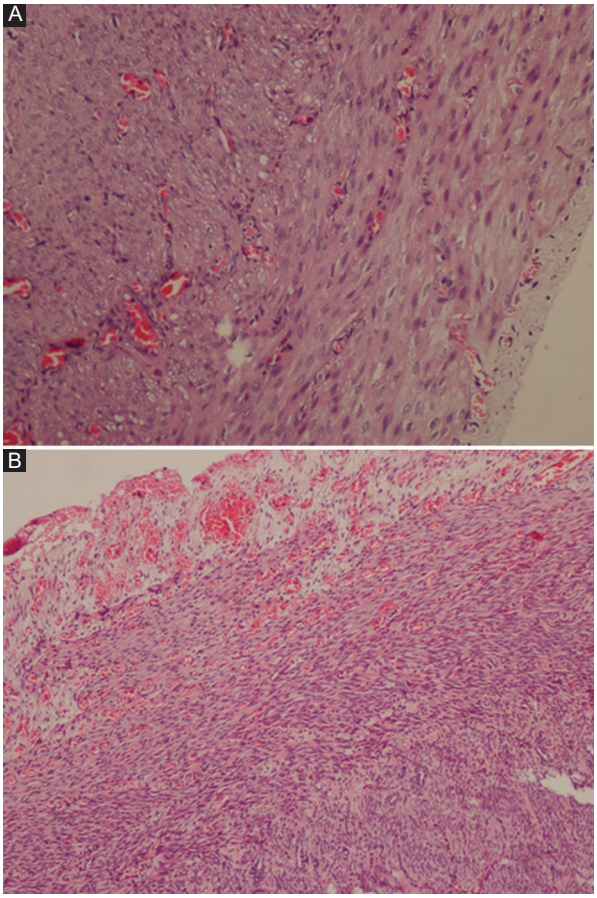

Figure 2. *Platelet-Rich Plasma group.* **A:** *no fibrosis (hematoxylin-eosin [HE] × 200).* **B:** *mild fibrosis, mild signs of inflammation (HE × 100).*

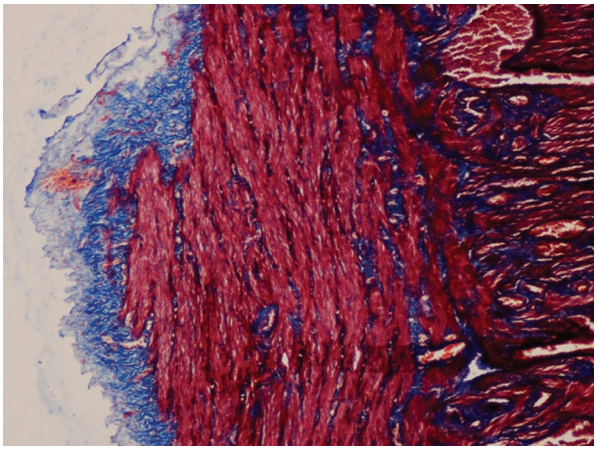

Figure 3. *Fibrosis with Mason's Trichrome staining (× 200).*

Another parameter examined immunohistochemically is VEGF-1. High expression levels of VEGF-1 are thought to stimulate angiogenesis and fibrosis. In addition, tissue expression of VEGF-1 will result in

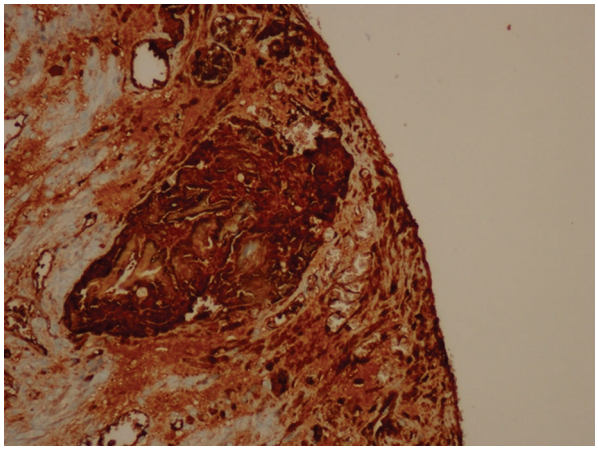

Figure 4. *Severe staining with vascular endothelial growth factor-1 in the control group (× 200).*

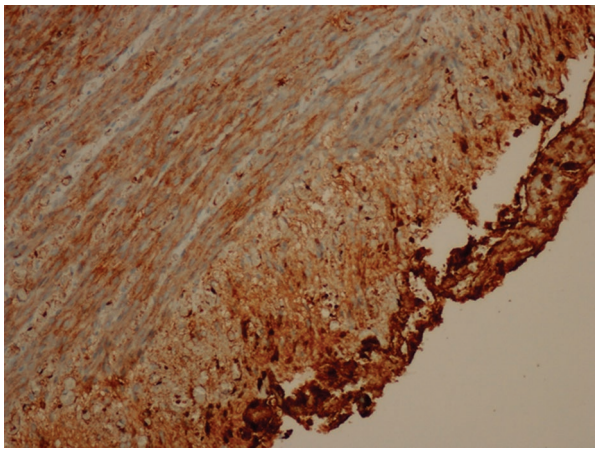

Figure 5. *Moderate staining with vascular endothelial growth factor-1 in the platelet-rich plasma group (× 200).*

adhesion formation secondary to tissue damage. VEGF-1 is a major factor in wound healing and is responsible for adhesion formation[30,31]. In this study, as in all other parameters, tissue expression of VEGF-1 decreased significantly with PRP application. The strength of this study is the autologous preparation and use of PRP.

Our study is the first to reveal the effect of autologous PRP on uterine wounds. In experimental rat models, the blood volume is too low to produce autologous PRP, so allogeneic preparations are preferred[9]. We chose rabbits in the study to use autologous PRP and test its effectiveness. Thus, risks such as cross-contamination, disease transmission, or immune reactions are eliminated. In the literature, there is no other intra-abdominal adhesion study using autologous PRP.

Conclusions

Our study concluded that using PRP in the experimental rabbit uterine horn adhesion model is effective in preventing post-operative adhesion formation and can guide clinical studies using autologous PRP to prevent post-operative adhesion formation after gynecological operations.

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Conflicts of interest

The authors declare no conflicts of interest for this article.

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.

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ORIGINAL ARTICLE

A model to determine factors influencing intraoperative complications in sleeve gastrectomy

Un modelo de determinantes de complicaciones intraoperatorias en gastrectomía en manga

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Abstract

Objective. *The study presents a logistic regression model describing the factors leading to intraoperative complications in laparoscopic sleeve gastrectomy (LSG) and a detailed description of the intraoperative complications that occurred in our operations.* **Material and methods.** *The study was designed as a retrospective and cohort study. It includes patients who underwent laparoscopic sleeve gastrectomy between January 2008 and December 2020.* **Results.** *The study included 257 patients. The mean (SD) age of all patients included in the study was 40.28 (9.58) years. The body mass index of our patients ranged from 31.2 to 86.6 kg/m^2. The Stepwise Backward model was used (Cox and Snell R^2 = 0.051, Nagelkerke R^2 = 0.072, Hosmer-Lemesxow χ^2 = 1.968, df = 4, p = 0.742, overall model accuracy of 70.4%). The model shows that pre-operative diabetes mellitus or hypertension Stage 3 significantly increases the probability or risk of intraoperative complications.* **Conclusions.** *The study shows which intraoperative complications occur in LSG, how they can be remedied and which factors can lead to them and influence the outcome of the operation itself. The recognition and successful treatment of intraoperative complications are very important as they reduce the number of reoperations and treatment costs.*

Keywords: *Bariatric. Laparoscopic. Sleeve gastrectomy. Complications.*

Resumen

Objetivo. *El estudio presenta un modelo de regresión logística que describe los factores que conducen a las complicaciones intraoperatorias en la gastrectomía en manga laparoscópica (LSG) y una descripción detallada de las complicaciones intraoperatorias que ocurrieron en nuestras operaciones.* **Material y métodos.** *Estudio de cohorte retrospectivo. Incluye pacientes que se sometieron a LSG entre enero de 2008 y diciembre de 2020.* **Resultados.** *El estudio incluyó a 257 pacientes. La edad media (DE) de los pacientes del estudio fue de 40.28 (9.58) años. El índice de masa corporal de nuestros pacientes osciló entre 31.2 y 86.6 kg/m^2. Se utilizó el modelo Stepwise Backward (Cox y Snell R^2 = 0.051, Nagelkerke R^2 = 0.072, Hosmer-Lemesxow χ^2 = 1.968, gl = 4, p = 0.742, precisión global del modelo del 70.4%). El modelo muestra que la diabetes mellitus o hipertensión preoperatoria en estadio 3 aumenta significativamente la probabilidad de complicaciones intraoperatorias.* **Conclusiones.** *El estudio muestra qué complicaciones intraoperatorias ocurren en la LSG, cómo se pueden remediar y qué factores pueden conducir a ellas e influir en el resultado de la operación en sí. El reconocimiento y el tratamiento exitoso de las complicaciones intraoperatorias son muy importantes ya que reducen el número de reintervenciones y los costos del tratamiento.*

Palabras clave: *Bariátrica. Laparoscópica. Gastrectomía en manga. Complicaciones.*

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Introduction

With the increase in obesity in the world, bariatric surgery is becoming increasingly important. At present, the most popular and frequently performed bariatric procedure worldwide is laparoscopic sleeve gastrectomy (LSG), accounting for 55.4% of all bariatric procedures[1].

Due to the low number of complications and the good results in the treatment of obesity and metabolic syndrome, it stands out as a procedure in its own right. LSG used to be used as the first measure in patients who had a body mass index (BMI) of more than 50 kg/m^2 and a high intraoperative risk of complications, which was followed by a new and additional procedure with a malabsorptive component[2-4].

Indications for laparoscopic bariatric surgery: in patients with a BMI $\geq$ 40 kg/m^2 and patients with a BMI $\geq$ 35-40 kg/m^2 and associated comorbidities where improvement through weight loss is expected, but also in patients with a BMI $\geq$ 30-35 kg/m^2 and Type 2 diabetes and/or arterial hypertension with poor control despite optimal medical therapy[5,6].

Barrett's esophagus is the only absolute contraindication to LSG. Some authors consider gastroesophageal reflux disease (GERD), liver cirrhosis, hiatal hernia, and uncontrolled diabetes to be contraindications, while others believe that there are no contraindications[7,8]. Although LSG is considered a safe procedure, there are still complications.

Bariatric surgery solves the problem of weight and comorbidities in the long-term, but the comorbidities also affect the complications. Complications in bariatric surgery are divided into intraoperative, early complications up to 30 days after surgery and late complications beyond 30 days after surgery[9]. The most common intraoperative complication of LSG is bleeding. Bleeding can occur from the staple suture or from injury to the short gastric arteries toward the upper pole of the spleen. To avoid subsequent revision surgery, it is necessary to treat these complications appropriately[10,11].

The study presents a logistic regression model describing the factors leading to intraoperative complications in laparoscopic sleeve gastrectomy and a detailed description of the intraoperative complications that occurred in our operations.

Materials and methods

The study was designed as a clinical and observational study in the form of a retrospective cohort study. It includes patients who underwent laparoscopic sleeve gastrectomy at the Institute of Pulmonary Diseases of Vojvodina in Sremska Kamenica between January 2008 and December 2020.

Patients of both sexes aged over 18 years were enrolled in the study. The patients were examined and treated by a multidisciplinary team (bariatric surgeon, anesthetist, psychologist, cardiologist, and endocrinologist). According to the classification recommended by the World Health Organization, patients with increased body mass are divided into the following categories: pre-obesity (BMI = 25.0-29.9 kg/m^2), Obesity I: degree (30.0-34.9 kg/m^2), Obesity II: grades (35.0-39.9 kg/m^2), Obesity III: Grades (40.0-49.9 kg/m^2), Obesity IV: degrees (50.0-59.9 kg/m^2), and Obesity V: degrees (> 60.0 kg/m^2). Patients with IV and V degrees of obesity are referred to as "superobese" and "super-superobese" in the surgical literature. According to the European Association of Preventive Cardiology, patients with preoperative hypertension are classified into three stages. The first stage is 140-159 and/or 90-99 mmHg, the second stage is 160-179 and/or 100-109 mmHg, and the third stage is $\geq$ 180 and/or $\geq$ 110 mmHg.

Antibiotic prophylaxis (2nd-generation cephalosporins) and thromboembolic prophylaxis (low molecular weight heparin) were given to all patients according to the same protocol. Patient data were taken from the medical history and surgical lists. Approval was obtained from the Expert Council (number: 76-XV/1) and the Ethics Committee of the Institute of Pulmonary Diseases of Vojvodina in Sremska Kamenica (number: 72/XIII/24) for the preparation of the study.

Surgical technique of laparoscopic sleeve gastrectomy

All operations were performed by one bariatric surgeon under the same conditions. The patient is placed on the operating table in a supine position with his legs extended and spread, and the surgeon takes a place between his legs while the assistant is on the left side of the patient. A typical sleeve gastrectomy is performed as standard with three or more laparoscopic openings, initially immobilizing the large curve of the stomach. All LGS resections were performed using the Ethicon® Echelon Flex™ 60 mm stapler. We place the first stapler 3 cm from the pylorus and always use a stapler with one "green" cartridge, in the corpus a stapler with three "gold" cartridges and in

the fundus one or two "blue" cartridges. A 38-42 Fr probe is used during the operation. The staple line is not sutured. The sleeve gastrectomy is controlled intraoperatively with 50 mL methylene blue.

The commercial program Statistical Package for the Social Sciences (v. 18.0; SPSS Inc. Chicago, IL, USA) was used for statistical processing of the data obtained.

A multivariable logistic regression model was used for intraoperative complications and the factors leading to them.

Results

The study included 257 patients, of whom 134 (52.1%) were female and 123 (47.9%) were male. The mean age (SD) of all those included in the study was 40.28 (9.58) years. The BMI of our patients ranged from 31.2 to 86.6 kg/m^2. The most common comorbidities among the patients were: hypertension (43.9%), diabetes mellitus (24.2%), dyslipidemia (17.9%), cardiovascular disease (7.8%), respiratory disease (7.4%), and depression (7.4%). Intraoperative complications as well as the occurrence of complications according to BMI groups are shown in the tables (Tables 1 and 2).

Binary logistic regression was performed for the dichotomous outcome of intraoperative complication. In the univariable analysis, statistically significant results were obtained for the variables diabetes mellitus preoperatively (Crude OR = 2.094, 95% CI = 1.152-3.809) and hypertension preoperatively Stage 3 (Crude OR = 12.457, 95% CI = 1.347-115.173). The model shows that pre-operative diabetes mellitus or elevated blood pressure at sSage 3 significantly increases the likelihood or risk of intraoperative complications (Table 3). With diabetes about two and with elevated blood pressure 3 stages almost 12 times.

A multivariable logistic regression model for intraoperative complications was used. The Step-wise Backward model was used (Cox and Snell R^2 = 0.051, Nagelkerke R^2 = 0.072, Hosmer-Lemesxow χ^2 = 1.968, df = 4, p = 0.742, overall model accuracy of 70.4%). The following variables were used in the construction of the model: age, BMI categories, preoperative hypertension levels, comorbidities, gender, pre-operative diabetes mellitus, preoperative cholesterol, pre-operative triglycerides, and smoking. Other variables used in the construction of the model are either confounding or independent, indicating that their influence on the occurrence of the observed outcome was also considered in the model.

Table 1. Intraoperative complications

Intraoperative complications	Frequency	Percentage (%)
Bleeding-stapler line	68	26.5
Spleen lesion	1	0.4
Deserosation of the stomach	1	0.4
Open-impossibility of laparoscopy	3	1.2
Splenectomy due to bleeding	1	0.4
Total	74	28.9

Discussion

Laparoscopic sleeve gastrectomy is a restrictive bariatric procedure consisting of a vertical subtotal gastrectomy in which the fundus, body and antrum of the stomach are resected while retaining the pylorus. In this way, a tubular channel is formed along the small curve of the stomach. About 80% of the stomach is removed by resection and the rest of the stomach has a capacity of about > 100 mL[1,12,13].

Among a variety of different procedures, LSG gradually gained acceptance and became the most popular and commonly performed method, both because of its technical simplicity and safety and because of the low number of complications and low mortality rate. This most common execution has led to a variety of variations, from surgical techniques to the use of different stapling devices and instruments. According to some authors, all of this was reflected and had an impact on the incidence of complications[14]. In addition to the division into intraoperative, early and late complications, complications in bariatric surgery are divided into other, less commonly used subdivisions, namely, surgical and non-surgical post-operative complications, and major and minor complications[10,11,15]. There are very few data on intraoperative complications in LSG. They are either not reported in the studies or the authors state that they did not exist.

Some studies show that they occur in about 14% of cases[16]. In our study, they occur in a much higher percentage, but there were no cases of gastric leakage.

The most common intraoperative complication in our study was bleeding from the staple suture at 26.5%.

Table 2. Intraoperative complications by BMI groups (kg/m²)

Intraoperative complications	30.0-34.9	35.0-39.9	40.0-49.9	50.0-59.9	> 60	Total
Bleeding-stapler line	4	10	33	15	6	68
Spleen lesion	1	0	0	0	0	1
Deserosation of the stomach	0	0	1	0	0	1
Open-impossibility of laparoscopy	0	1	0	1	1	3
Splenectomy due to bleeding	0	0	0	1	0	1
Total (%)	5 (2)	11 (4.4)	34 (13.2)	17 (6.6)	7 (2.7)	68 (28.9)

BMI: body mass index.

Table 3. Statistical significance for the variables diabetes mellitus preoperatively and hypertension stage 3 preoperatively

Independent variables	p	Exp (B)	95% confidence interval	
			Lower	Upper
Hypertension stage 3 preoperatively	0.030	11.816	1.264	110.459
Diabetes mellitus preoperatively	0.045	1.906	1.013	3.586

There is an opinion that bleeding depends on the surgical technique itself[14]. In our study, in all patients used a surgical technique in which the staple line was not sutured, and the bleeding itself was treated intraoperatively, mostly by placing a clip and in a few cases by suturing. This technique gives good results and reduces the length of hospital stay and thus the cost of surgical treatment[17].

Another intraoperative complication that occurred in three patients (1.2%) was conversion or open gastric sleeve resection due to inadequatue pneumoperitoneum. This complication occurred more frequently in "super-obese" and "super-super-obese" patients, which may be attributed to the difficulty of performing the surgery and the associated comorbidities. Considering that the pre-operative preparation took about 6 weeks and involved the whole team, the surgery was performed in these patients as it was expected that these patients were unlikely to be in a better state of preoperative preparation. Of the other intraoperative complications, there was one case of splenic lesion, one gastric deserosion, and one case of splenectomy.

The popularity of this procedure has also led to the development of various scores that can predict complications. One of these is the "SLEEVE BLEED" calculator, which is used to assess the risk of bleeding[18]. Logistic regression has been used to develop a risk calculator that is used to assess adverse events after LSG and can help the surgeon decide on surgical treatment, but also predicts the surgical risk for the patient[19].

Logistic regression was used to create our model with an accuracy of 70.4%. The model shows that the probability or risk of intraoperative complications increases significantly if the patient has preoperative diabetes or Grade 3 elevated blood pressure. For diabetes about 2 times (adjusted OR = 1.9) and for elevated blood pressure stage 3 almost 12 times (adjusted OR = 11.8).

Pre-operative treatment or improvement of comorbidities may reduce the risk of intraoperative complications.

This study also has some limitations. It is a retrospective study. Series with a larger number of patients are needed to gain an accurate insight into the incidence of intraoperative complications.

Conclusion

In summary, the study shows which intraoperative complications occur in LSG, how they can be resolved and which factors can lead to them and influence the outcome of the operation itself. The recognition and successful treatment of intraoperative complications are very important because they reduce the number of reoperations and the costs of treatment.

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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 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 and observational study.

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ORIGINAL ARTICLE

Clinicopathological features of colorectal cancer patients under 30 years of age

Características clinicopatológicas del cáncer colorrectal en pacientes menores de 30 años

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Abstract

Background: *Colorectal cancer (CRC) is the second cause of cancer death in the world and is estimated to have been responsible for almost 935,000 deaths during 2020.* **Objective:** *Describe clinicopathological features, overall survival (OS) and progression-free survival (PFS) in CRC patients under 30 years.* **Method:** *This is a retrospective cohort study in patients under 30 years diagnosed with CRC.* **Results:** *From 2017 to 2021, 1823 patients were diagnosed with CRC, of which 54 (2.96%) were under 30 years. The OS, during 4 years, was 41.5%. The clinical stage found IV (hazard ratio [HR]: 6.212; 95% confidence interval [95%CI]: 2.504-15.414; p < 0.001), giving neoadjuvant therapy (HR: 0.705; 95%CI: 0.499-0.996; p = 0.047) and no medical history of Lynch syndrome (HR: 3.925; 95%CI: 1.355-11.364; p = 0.012) are independent predictors of mortality. The PFS, during 4 years, was 21.3%. Clinical stage IV (HR: 2.418; 95%CI: 1.000-5.850; p < 0.050), and no diagnosis of Lynch syndrome (HR: 3.800; 95%CI: 1.398-10.326; p = 0.009) are independent predictors.* **Conclusions:** *Younger patients are usually diagnosed with CRC in advanced stages. Early symptoms and evaluation, irrespective of age, are crucial.*

Keywords: *Colon cancer. Rectum cancer. Young adult. Hereditary.*

Resumen

Antecedentes: *El cáncer colorrectal (CCR) es la segunda causa de muerte por cáncer en el mundo y se estima que fue responsable de casi 935,000 muertes durante el año 2020.* **Objetivo:** *Describir las características clinicopatológicas, la supervivencia global (SG) y la supervivencia libre de progresión (SLP) en pacientes con CCR menores de 30 años.* **Método:** *Estudio de cohorte retrospectivo en pacientes con diagnóstico de CCR menores de 30 años.* **Resultados:** *Entre 2017 y 2021 se diagnosticaron 1823 pacientes con CCR, de los cuales 54 (2.96%) eran menores de 30 años. La SG a 4 años fue del 41.5%. Se encontró que la etapa clínica IV (hazard ratio [HR]: 6.212; intervalo de confianza del 95% [IC95%]: 2.504-15.414; p < 0.001), recibir tratamiento neoadyuvante (HR: 0.705; IC95%: 0.499-0.996; p = 0.047) y no tener antecedente de síndrome de Lynch (HR: 3.925; IC95%: 1.355-11.364; p = 0.012) son predictores de mortalidad independientes. La SLP a 4 años fue del 21.3%. La etapa clínica IV (HR: 2.418; IC95%: 1.000-5.850; p < 0.050) y el no contar con diagnóstico de síndrome de Lynch (HR: 3.800; IC95%: 1.398-10.326; p = 0.009) son predictores independientes.* **Conclusiones:** *Los pacientes jóvenes son diagnosticados con CCR en etapas avanzadas. Los síntomas iniciales, junto con la evaluación, independientemente de la edad, son cruciales.*

Palabras clave: *Cáncer de colon. Cáncer de recto. Adultos jóvenes. Hereditario.*

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Introduction

Colorectal cancer (CRC) is the second leading cause of cancer death worldwide, estimated to be responsible for nearly 935,000 deaths in 2020. It is the third most frequent neoplasm in men and the second in women[1]. In Mexico, CRC ranks fourth in incidence, accounting for 7.6% (14,901 people) and 6245 deaths in 2020, placing it second in mortality[2].

The incidence and mortality of CRC have dropped from 1975 to 2006; however, this trend is mainly influenced by older age groups[3]. Between 2009 and 2013, the incidence of CRC decreased by 4.6% per year in people aged 65 and older, likely due to a combination of screening tests, changes in the distribution of risk factors (less smoking, more aspirin use), and treatment improvements. However, epidemiological studies show an alarming increase in incidence among people younger than 50 years, at a rate of 1.6% per year[4]. Similarly, CRC mortality rates for adults younger than 50 increased by approximately 1% per year from 2005 through 2014, while they dropped by 1% to 3% per year for older patients. For individuals aged 20 to 34 years, compared to 2010, the incidence is forecasted to increase by 90% and up to 124% by 2030[3,5]. Other studies report that for patients younger than 50 years, the incidence is projected to increase from 11% in 2010 up to 22% in 2030[6]. The specific cause of the increase in cases among young patients remains unknown. It is believed to be closely related to lifestyle changes over the past 45 years (sedentary behavior, diet, substance abuse, etc.) and an increase in the prevalence of chronic non-communicable diseases and hereditary origins[1,7].

Diagnosing CRC in people younger than 30 is challenging because most young adults do not have obvious risk factors (such as family history) and are categorized as average risk according to current CRC screening and management algorithms. Age and family history of cancer remain the cornerstone of CRC risk stratification algorithms. However, only a minority of early-onset CRC patients report having a first-degree relative with CRC, and even fewer have a predisposing condition (such as inflammatory bowel disease)[8-10]. The failure to consider the possibility of CRC by both patients and doctors contributes to delays in diagnosis in younger adults, even in the presence of warning symptoms (such as hematochezia or iron deficiency anemia), resulting in a substantial proportion of young patients having metastatic disease at diagnosis.

Hereditary syndromes play an important role in the development of CRC in young patients[11]; 20% have a family history of CRC, and up to 33% of cases in those younger than 35-40 years are related to hereditary syndromes, such as Lynch syndrome (hereditary CRC)[6]. This syndrome is caused by mutations in DNA mismatch repair genes (MLH1, MSH2, MSH6, and PMS2) and accounts for 1% to 2% of all CRC cases[12].

The objective of this study is to describe the clinicopathological characteristics, overall survival (OS), and progression-free survival (PFS) in patients younger than 30 years diagnosed with CRC.

Method

Data source

Data source was the physical and electronic health records of the National Cancer Institute, which provide demographic data (age at diagnosis, sex, tumor location, TNM staging according to the American Joint Committee on Cancer (AJCC) 8th edition, histological type, tumor grade, and number of lymph nodes evaluated), as well as dates of diagnosis, recurrence, and last consultation. We obtained permission to access the research data files with reference number 2022/106. The study did not involve interaction with human subjects nor the use of personally identifiable information, did not require informed consent, and was approved by the research committee of the National Cancer Institute.

Patient selection

We included patients with CRC who were younger than 30 years at the time of diagnosis, from January 2017 through December 2021. Patients older than 30 at diagnosis, those with TNM in situ, and those with incomplete information were excluded (Fig. 1).

Data analysis

Data analysis was conducted on patients younger than 30 years at the time of diagnosis. Clinicopathological characteristics, genetic disorders (microsatellite instability), type of treatment (resective surgery, palliative surgery, neoadjuvant, adjuvant, and palliative), and survival were

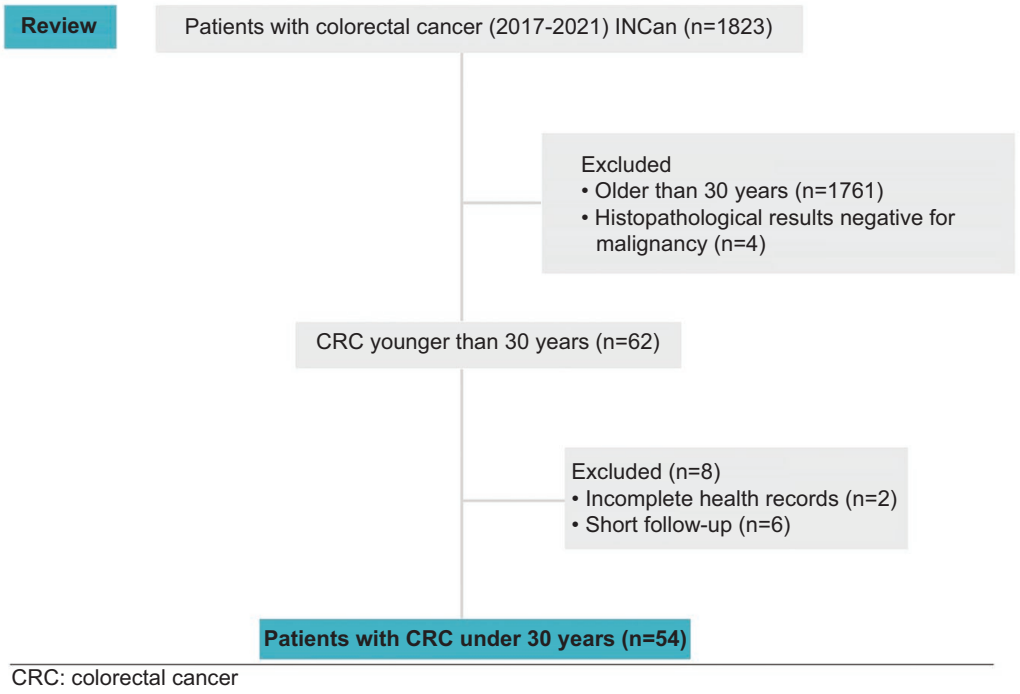


Figure 1. *STROBE diagram.*

evaluated. Anatomical location analysis included the right colon (cecum, ascending colon, hepatic flexure, and transverse colon), the left colon (splenic flexure, descending colon, and sigmoid colon), and the rectum (rectosigmoid junction and rectum). Staging was performed according to the criteria described in the 8th edition of the AJCC classification. Histological type was categorized into 3 classes: adenocarcinoma, mucinous adenocarcinoma, and signet ring cell adenocarcinoma. Tumor grade was categorized as well differentiated (G1), moderately differentiated (G2), and poorly differentiated (G3). Of note that patients with Lynch syndrome were diagnosed using the following guidelines: 1) clinical criteria, 2) molecular techniques for detecting microsatellite instability and immunohistochemistry, and 3) a combination of both. Deaths attributed to CRC were treated as events, overall survival (OS) was calculated from the date of diagnosis to the date of death or end of follow-up (cut-off date: December 2021), and progression-free survival (PFS) was calculated from the start date of treatment to the date of progression or end of follow-up (cut-off date: December 2021).

Statistical analysis

Continuous data were expressed as medians and standard deviations. Categorical data were compared using the chi-square test or Fisher's exact test. Survival curves were generated using Kaplan-Meier estimates, and differences between the curves were analyzed using the log-rank test. Cox univariate and multivariate regression models were developed to analyze the influence of each characteristic on survival. Data were summarized as hazard ratios (HR) and their 95% confidence intervals (CI95%). A p-value $\leq$ 0.05 was considered statistically significant. Data were analyzed using SPSS software version 26 (SPSS, IBM, Inc., Chicago, IL, United tates).

Results

From January 2017 through December 2021, a total of 1823 patients were diagnosed with CRC, 54 of whom (2.96%) were younger than 30 years (Fig. 1). Table 1 describes the general characteristics. The mean age at diagnosis was 24.7 years (range, 17-30). Notably, a low percentage of the population was overweight (12; 22.2%) or obese (4; 7.40%). A total of 27.80% of the patients had a family history of CRC. The most common initial symptoms were abdominal pain (38; 70.3%), weight loss (38; 70.3%), and hematochezia (32; 59.26%). The most frequent location of the primary tumor was the rectum (25; 46.3%). Simple adenocarcinoma was the most frequent histological subtype (37; 68.5%); however, signet ring cell

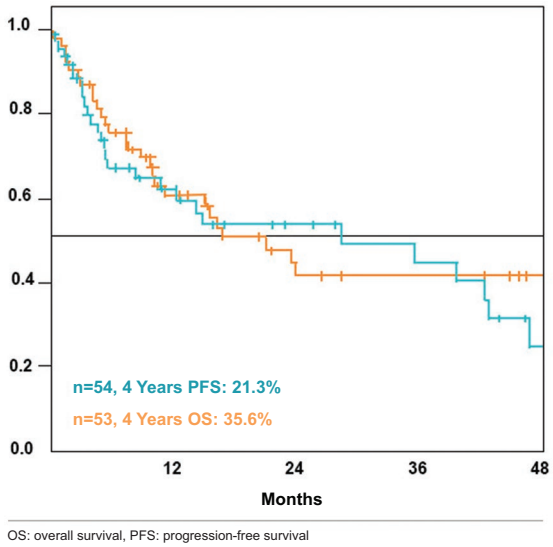
adenocarcinoma accounted for 25.9% (14), and the most common histological grade was poorly differentiated (31; 57.4%). Non-metastatic stages (I-III) predominated over metastatic stage (IV), with 34 (62.4%) and 20 (37%) patients, respectively. Lynch syndrome was diagnosed in 15 (27.8%) patients, with MLH1 being the most affected mismatch repair gene (7; 46.7%). Resective surgery prevailed over other initial treatments (30; 63.3%). The most widely implemented systemic treatment was neoadjuvant therapy (25; 68%).

Overall survival

The 4-year OS rate was 35.6% (Fig. 2). Using a stepwise logistic regression model, it was found that stage IV at diagnosis (HR, 6.212; 95%CI, 2.504-15.414; p < 0.001), having received neoadjuvant therapy (HR, 0.705; 95%CI, 0.499-0.996; p = 0.047), and not having been diagnosed with Lynch syndrome (HR, 3.925; 95%CI, 1.355-11.364; p = 0.012) are independent mortality predictors (Table 2).

Progression-free survival

The 4-year PFS rate was 21.3% (Fig. 2). Multivariate analysis found that stage IV at diagnosis (HR, 2.418; 95%CI, 1.000-5.850; p < 0.050) and not having been diagnosed with Lynch syndrome (HR, 3.800; 95%CI, 1.398-10.326; p = 0.009) are independent predictors of disease progression (Table 3).



OS: overall survival, PFS: progression-free survival

Figure 2. *Overall and disease-free survival.*

Discussion

Currently, an unequivocal definition of early-onset CRC in young adults is needed, as there is no clear consensus in the literature or guidelines. Therefore, direct comparisons among available studies are not possible due to differing age cutoffs (ranging from 30 to 50 years). However, this study is based on the Adolescent and Young Adult (AYA) guideline, which includes CRC patients diagnosed between the ages of 15 and 29 years[13].

Early-onset CRC predominantly affects racial and ethnic minorities vs non-Hispanic whites. Although 10% to 12% of all patients diagnosed with CRC are younger than 50 years, the proportion nearly doubles among non-Hispanic blacks (16%) vs non-Hispanic whites (9%)[14]. Early-onset CRC incidence rates have consistently been higher among blacks, though the gap with whites has recently narrowed[9]. Incidence rates have also rapidly increased among young Hispanics[15,16].

According to CRC records from the SEER (Surveillance, Epidemiology, and End Results) database of the National Cancer Institute, the incidence of this neoplasm in individuals younger than 35 years is 2.2%[17]. Özaydın et al.[18], in their study on CRC in individuals younger than 30, found an incidence of 3.59%. In our study, it was 2.96% (54/1823), with a slight male predominance (51.85% vs. 49.15%), but no statistically significant difference. These percentages show that the rate has increased in this population; according to data from the GLOBOCAN (2020) database of the Global Cancer Observatory, a significant increase in new cases in this population group has been documented in recent years[19].

The role of body mass index (BMI) in the OS of CRC patients is still unclear. Birmingham et al.[20] published on the possible negative effect of leptin on tumor progression and metastasis by stimulating vascular endothelial growth factor. On the other hand, studies by Ogino et al.[21] assert that a high BMI may positively influence survival, as it was reported higher in obese CRC patients with p27 gene alterations or increased STMN1 gene expression. García-Oria et al.[22] state in their study that BMI is not a prognostic factor for long-term survival in CRC patients. In our study, we observed that only a small percentage of individuals had a BMI categorized as overweight or obese. However, it should be considered that the weight used for

Table 1. Clinical characteristics of patients with colorectal cancer

Characteristic	n	%
Age, years	24.7 (17-30)	
Sex		
Male	28	51.85
Female	26	48.15
BMI		
Underweight	10	18.50
Normal	28	51.90
Overweight	12	22.20
Obesity	4	7.40
Family history of CRC		
Yes	16	29.60
No	38	70.37
Clinical presentation		
Abdominal pain	38	70.37
Weight loss	38	70.37
Hematochezia	32	59.26
Constipation	15	27.78
Fecaluria	1	1.85
Primary tumor location		
Right colon	13	24.07
Left colon	13	24.07
Rectum	25	46.30
Synchronous	3	5.56
Histological type		
Adenocarcinoma	37	68.50
Signet ring cell adenocarcinoma	14	25.90
Mucinous adenocarcinoma	3	5.60
Histological grade		
G1: Well-differentiated adenocarcinoma	4	7.41
G2: Moderately differentiated adenocarcinoma	19	35.19
G3: Poorly differentiated adenocarcinoma	31	57.41
TNM staging		
Stage 1	4	7.40
Stage 2	17	31.50
Stage 3	13	24.10
Stage 4	20	37.00
Lynch syndrome		
Yes	15	27.80
No	39	72.20
Type of MSI in patients with Lynch syndrome		
MLH1	7	12.96
MSH2	3	5.55
Combination of MSI*	5	9.25
None	39	72.2
Type of surgery		
Resective surgery	30	63.3
Palliative surgery	16	18.8
No surgery	8	37.5
Systemic treatment		
Adjuvant	16	25
Neoadjuvant	25	76
Palliative	13	15.4

CRC: colorectal cancer; BMI: body mass index; MSI: microsatellite instability.
*Including MLH1, MSH2, MSH6, and PMS2.

this study was the weight at diagnosis, after initial symptoms, and one of the most common symptoms prior to diagnosis is weight loss (a little more than 70% of the studied population had this symptom).

CRC in young patients tends to occur more frequently in the distal sigmoid or rectum[23,24]. According to our study, the location was similar in the right (24.07%) and left (24.07%) colon, and the most frequent was in the rectum (46.30%). In contrast, in patients older than 50, proximal colon cancer is more common[25].

At the time of diagnosis, most patients in our study were in stage IV (37%). In the study by Fu et al.[26], the age group of young patients had a higher percentage in clinical stages III and IV vs the group older than 35, in whom stages I and II predominated. Their survival analysis in clinical stages I-III was similar for both age groups, while in stage IV, being younger than 35 a poor prognosis factor. Similarly, a study of 32 patients younger than 30 with CRC showed a higher percentage in advanced clinical stages III (46.8%) and IV (31.2%)[18].

Regarding histological type, simple adenocarcinoma was present in most individuals (68.5%), followed by adenocarcinoma with a signet ring cell pattern (25.90%). The predominant histological grade in our study was G3 (poorly differentiated), at 57.41%. In the study by You et al.[27], the mucinous and signet ring cell pattern (12.6% vs 10.8%), as well as poorly or undifferentiated (20.4% vs 18%), were the most common findings and were also independent predictors. In a comparison between age groups 20-40 years and 60-80 years, O'Connell et al.[28,29] evidenced that tumors in younger populations often exhibit a mucinous and signet ring cell pattern, with low differentiation (27.3% vs 17.2%) vs an older group.

In the absence of distinctive biological characteristics, current treatment guidelines do not distinguish early-onset CRC from the disease in older adults. Surgical resection should meet the appropriate standards for the corresponding tumor site. Care should be taken to avoid overtreatment in these patients, despite the lower risk of morbidity and the years of life gained. In our sample, curative intent surgery was predominant, with 30 cases (63.3%), followed by palliative surgery with 16 cases (18.8%), and no surgical intervention in 8 cases (37.5%). These rates are similar to one of the largest studies of young adults with metastatic CRC, with more than 6700 patients, which reported surgical treatment outcomes, showing that 2653 (39.5%) underwent primary tumor resection only, 1547 (23.1%) underwent primary tumor resection plus

Table 2. Analysis of factors associated with overall survival in patients

Factor	Total (events)	Univariate analysis (48 months)	Multivariate analysis (48 months)
	n (%)	% (95%CI) p	HR (95%CI) p
Overall	54 (12)	67.4 (49.8-85.0)	
Sex		0.276	
Female	26 (11)	53.60 (31.45-75.69)	
Male	28 (18)	33.6 (14.39-52.8)	
BMI		0.112	
≤ 18.5	10 (8)	15.0 (11.65-41.65)	
> 18.5	44 (21)	47.5 (30.84-64.16)	
Family history of CRC		0.227	
Yes	16 (6)	50.10 (19.13-81.06)	
No	38 (23)	37.7 (20.64-54.65)	
Tumor location		0.53	
Right colon	13 (5)	39.60 (1.57-77.62)	
Left colon	13 (9)	33.70 (5.47-61.92)	
Rectum	25 (14)	42.5 (21.33-63.66)	
Synchronous	3 (1)	66.7 (13.38-120)	
Pathological stage		< 0.001	6.212 (2.504-15.414)
≤ III	33 (10)	69.10 (50.28-87.91)	< 0.001
IV	21 (19)	5.10 (4.7-14.9)	
Histological type		0.002	1.153 (0.651-2.042)
Adenocarcinoma	37 (19)	47.00 (29.16-64.83)	0.626
Signet ring cell adenocarcinoma	14 (10)	0 (0.0-0.0)	
Mucinous adenocarcinoma	3 (0)	0 (0.0-0.0)	
Tumor differentiation		0.268	
Poor-moderate	23 (12)	50.8 (29.82-71.77)	
Well	31 (17)	29.8 (8.24-51.36)	
Type of surgery		0.003	0.875 (0.500-1.529)
No surgery	8 (5)	25.00 (13.80-63.80)	0.638
Curative	30 (11)	62.20 (43.18-81)	
Palliative	16 (13)	15.50 (3.90-34.9)	
Systemic treatment		< 0.001	0.705 (0.499-0.996)
Adjuvant	16 (12)	22.50 (0.94-44.06)	0.047
Neoadjuvant	25 (6)	77.80 (75.72-79.87)	
Palliative	13 (11)	0 (0.0-0.0)	
Lynch syndrome		0.007	3.925 (1.355-11.364)
No	39 (25)	29.0 (12.53-45.46)	0.012
Yes	15 (4)	73.5 (47.04-99.96)	

CRC: colorectal cancer; HR: hazard ratio; 95%CI: 95% confidence interval; BMI: body mass index.

metastasectomy, 231 (3.4%) received metastasectomy without primary tumor resection, and 2277 patients (32.9%) had no surgery. Their results showed significant differences in OS: the median for patients who underwent primary tumor resection was 29 months vs13 months for those who did not[30]. Akinkuotu et al.[31] grouped individuals into ≤ 25 years and > 25 years and found that the first group had higher rates of total colectomy (8.9% vs 2.7%) and total proctocolectomy (5.0% vs 0.5%), higher rates of contiguous organ resection (12.9% vs 8.0%), external beam radiation treatment (3.9% vs. 1.9%), and chemotherapy treatment (76.6% vs 40.1%). Younger patients had significantly lower 30- and 90-day mortality (0.6% vs 4.2% and 2.1% vs 7.6%) vs those older than 25 years. Although colectomy was associated with a lower risk of death, contiguous organ resection associated with colectomy was linked to a higher risk of death[31]. Despite these results for sporadic early-onset CRC patients, extended

Table 3. Analysis of factors associated with progression-free survival in patients

Factor	Total (events)	Univariate analysis (48 months)	Multivariate analysis (48 months)	p-value
		% (95%CI) p	HR (95CI)	p
Overall	50 (12)	67.4% (49.7-85.0)		
Sex		0.065		
Female	26 (10)	30.50% (25.54-35.45)		
Male	28 (17)	14.7% (3.72-25.67)		
BMI		0.028	0.384 (0.138-1.069)	0.067
≤ 18.5	10 (8)	0.0% (0.0-0.0)		
> 18.5	44 (19)	26.6% (5.04-48.16)		
Family history of CRC		0.367		
Yes	16 (7)	38.70% (7.92-69.47)		
No	38 (20)	11.10% (7.52-29.62)		
Tumor location		0.885		
Right colon	13 (5)	31.30% (14.56-77.16)		
Left colon	13 (7)	30.80% (1.14-62.74)		
Rectum	25 (14)	14.30% (8.82-37.42)		
Synchronous	3 (1)	0.0% (0.0-0.0)		
Pathological stage		0.005	2.418 (1.000-5.850)	0.050
≤ III	33 (16)	27.10% (4.75-49.44)		
IV	21 (11)	24.00% (0.67-47.32)		
Histological type		0.185		
Adenocarcinoma	37 (21)	22.10% (3.48-40.72)		
Signet ring cell adenocarcinoma	14 (6)	0.0% (0.0-0.0)		
Mucinous adenocarcinoma	3 (0)	0.0% (0.0-0.0)		
Tumor differentiation		0.832		
Poor-moderate	23 (14)	12.60% (8.37-33.57)		
Well	31 (13)	32.20% (6.91-57.48)		
Type of surgery		0.068		
No surgery	8 (2)	0.0% (0.0-0.0)		
Curative	30 (13)	32.40% (6.72-58.07)		
Palliative	16 (12)	15.80% (4.19-35.79)		
Type of systemic treatment		0.005	0.899 (0.557-1.450)	0.662
Adjuvant	16 (7)	29.60% (1.76-60.96)		
Neoadjuvant	25 (10)	28.60% (2.14-55.06)		
Palliative	13 (10)	15.80% (4.46-38.26)		
Lynch Syndrome		0.005	3.800 (1.398-10.326)	0.009
Yes	15 (5)	17.70% (1.9-37.3)		
No	39 (22)	49.50% (16.18-82.82)		

CRC: colorectal cancer; HR: hazard ratio; 95%CI: 95% confidence interval; BMI: body mass index,

resections, such as total colectomy or proctocolectomy, have not shown any advantage in disease-free survival or OS[5].

Our results regarding systemic treatment indicate that neoadjuvant therapy was the most implemented, followed by adjuvant therapy and palliative treatment, with a statistically significant difference. In the study by Arhin et al.[30], 5552 (82.8%) patients received systemic chemotherapy and 1156 (17.2%) received radiotherapy, and they found that receiving chemotherapy and radiotherapy was significantly associated with better survival (HR, 0.65 and 0.88, respectively). However, in the study by Kneuertz et al.[32], it was found that the use of more aggressive systemic therapy did not lead to significant gains in survival. Over-treatment with multiple doses of chemotherapy, due to the maximum tolerated dose that can be administered, limits or perhaps eliminates any chemotherapy options at the time of relapse[31]. It is more likely that AYA patients in low-risk stage I or II will receive unindicated adjuvant

regimens, highlighting the risk of over-treatment faced by this population. Given the higher proportion of advanced-stage disease in early-onset CRC, along with the trend of over-treatment, multidisciplinary coordination of care is necessary to define individualized and appropriate treatment plans[5].

Hereditary syndromes play a very important role in the development of CRC; they cause 1% up to 3% of all CRC cases[33]. In young patients, it is estimated that 20% have a family history of CRC and up to 34.2% of cases in those younger than 35 years are related to hereditary syndromes, such as Lynch syndrome[12]. In our study, 27.8% of the population was diagnosed with Lynch syndrome, which is similar to the findings made by Schofield et al.:[12] a total of 1434 tumors in patients younger than 60 years, 33 of whom (2.30%) were younger than 30 years, 9 (27.3%) with microsatellite instability, and 24 (72.7%) without instability[12]. The most widely affected mismatch repair gene was MLH1 (n = 9, 60.3% of all Lynch syndrome cases). In the study by Durhuus et al.[6], in their group younger than 40 years, the most widely affected mismatch repair gene was MSH2 (39.4%), followed by MLH1 (33%). Additionally, 36.2% were diagnosed in clinical stages III and IV, with a 5-year OS rate of 55%, and in clinical stages I and II, a 5-year OS rate of 97%. Similar results regarding OS in early stages were obtained by Domínguez et al.[34], who reported that tumors related to Lynch syndrome in clinical stages I, II, and III have a 10-year survival of over 82%. Our results, when categorizing clinical stages into 2 groups in patients with Lynch syndrome, considering clinical stage IV and clinical stages I-III, show 1 (6.7%) and 14 (93.3%) cases, respectively, indicating a clear predominance of early stages that positively influence the OS of patients in this group. All patients with Lynch syndrome had resective surgery as their initial treatment with adjuvant therapy. It is obvious that this group benefited from early-stage diagnosis and initial resective surgery treatment.

The descriptive nature, small sample size, and having been conducted in a single center are all limitations of our study; however, it is the first national study addressing this topic.

Conclusions

As far as we know, this is the largest series to date examining the clinical and histological characteristics of people diagnosed with CRC up to 30 years of age in Mexico.

CRC in young patients is a public health problem as they have pathological characteristics leading to late diagnosis (advanced clinical stages) and worse prognosis. Alarm symptoms, along with evaluation regardless of age, family history, and genetic syndromes, are crucial.

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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

Biliary microhamartomas (von Meyenburg complexes), liver metastasis simulators: a series of eight cases

Microhamartomas de los conductos biliares (complejos de Von Meyenburg), simuladores de metástasis hepáticas: una serie de ocho casos

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Abstract

Background: *Von Meyenburg complexes are benign hamartomatous lesions, they are part of the spectrum of ductal plate malformations. They are rare, reported in 0.35-5.6% of the general population, predominantly in adults, with no clear predilection for sex.* **Objective:** *To present the clinical characteristics of Von Meyenburg complexes in our region.* **Method:** *We searched all cases with diagnosis of Von Meyenburg complexes in a period from 2012 to 2022, in our institutions.* **Results:** *We identified eight cases, with an average age of 59.25 years, with a predominance of females and with one case associated with gastric carcinoma.* **Conclusions:** *It is important to adequately recognize this entity, since due to its multifocal nature it can easily simulate metastasis, additionally, and its presence does not rule out other synchronous neoplasms.*

Keywords: *Hamartomas. von-Meyenburg. Bile ducts. Metastasis. Gastric carcinoma.*

Resumen

Antecedentes: *Los complejos de Von Meyenburg son lesiones hamartomatosas benignas que forman parte del espectro de las malformaciones de la placa ductal. Son poco frecuentes, se reportan en un 0.35-5.6% de la población general, predominantemente en adultos, sin clara predilección por un sexo.* **Objetivo:** *Presentar las características clínicas de los complejos de Von Meyenburg en nuestro medio.* **Método:** *Se buscaron todos los casos con diagnóstico de complejos de Von Meyenburg en nuestras instituciones entre 2012 y 2022.* **Resultados:** *Identificamos ocho casos, con un promedio de edad de 59.25 años, con predominio por el sexo femenino y con un caso asociado a carcinoma gástrico.* **Conclusiones:** *Es importante reconocer y diagnosticar adecuadamente esta afección, ya que por su naturaleza multifocal fácilmente puede simular metástasis, y además su presencia no descarta otros procesos neoplásicos sincrónicos.*

Palabras clave: *Hamartomas. Von Meyenburg. Conductos biliares. Metástasis. Carcinoma gástrico.*

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Introduction

Bile duct microhamartomas or von Meyenburg complexes were first described in 1918 as benign hepatic malformations of the embryonic ductal plate, placing them within the spectrum of ductal plate lesions (such as congenital hepatic fibrosis and Caroli disease)[1]. These are small hamartomatous lesions affecting the smallest intrahepatic bile ducts. They are composed of bile duct elements, often with well-demarcated, open lumens, containing thick bile inside. Although their etiology is unclear, they can be observed in livers with and without cirrhosis, in children and adults. They have occasionally been associated with cirrhosis due to chronic viral hepatitis, alcohol-related liver disease, and adult polycystic liver disease[2].

They are rare and can be confused with or associated with malignant neoplasms or metastases, making it important to have a good understanding of them.

Method

Cases diagnosed as bile duct microhamartomas or Von Meyenburg complexes were identified from the archives of Hospital General de México Dr. Eduardo Liceaga and the Institute of Medical Biological Research at the Universidad Veracruzana, over a 10-year period (2012-2022). A basic analysis was conducted using descriptive statistics.

Results

We identified a total of 8 cases, with an age range of 21 to 71 years (mean, 59.25 years). 62.5% of the cases occurred in women and 37.5% in men, with a 1.6:1 ratio. In 7 (87.5%) patients, lesions were incidental findings during surgeries for cholecystitis, and 1 (12.5%) was associated with diffuse gastric adenocarcinoma (Table 1). In all cases, a liver biopsy was performed to rule out the presence of metastases, as the lesions were identified as multifocal on the liver surface (Fig. 1). Microscopically, diagnosis was established by observing proliferative lesions in all patients, composed of ducts with cuboidal epithelium, cytologically without atypia, with some bile plugs inside, surrounded by fibrous stroma (Fig. 2).

Discussion and Conclusions

Von Meyenburg complexes have a variable frequency. In series of liver needle biopsies, an incidence of 0.35%[3] up to 0.6%[4] has been reported, and in autopsy series, 0.49%[5] up to 2.8%[4], and up to 5.6%, being more common in adults, as in children they only represent 0.9% of total cases[6].

They do not have a clear gender predilection, and although the age range of presentation is broad, from 17 to 76 years, they are most frequently diagnosed in the fourth and fifth decades of life[3,4]. In our series, although the age range is similar to that reported in the literature, the mean age is slightly higher, corresponding to the sixth decade of life.

Macroscopically, they appear as small nodules, generally < 1.0 cm, grayish-white in color, usually distributed both in the subcapsular regions and throughout the hepatic parenchyma, making them visible from the liver external surface, as was the case in our patients. Microscopically, they look like well-demarcated lesions composed of bile ducts with dilated, anastomosed lumens with bile plugs. Epithelium is cytologically soft, without atypia or mitosis, and with a very low proliferative rate when marked with Ki-67. They are associated with stroma that can be loose, myxoid, or densely fibrous; most have mild lymphoid infiltrate and are found adjacent to portal tracts[2,4,7].

In general, they do not present symptoms or abnormalities in liver function tests, making them incidental findings in most cases, although they have sometimes been associated with abdominal pain, infectious processes such as cholangitis, hepatic abscesses[8], fatigue, jaundice[3], and biliary colic[9].

Differential diagnoses include bile duct adenomas and, more rarely, cholangiocarcinomas[2]; sometimes they can be mistaken for hepatic metastases. It is important to emphasize that their diagnosis does not exclude the synchronous presence of malignant neoplastic processes[10], as seen in one of the patients in our series.

Although they generally have a benign clinical course, they can rarely progress to cholangiocarcinomas, as epithelial cells may present mutations in tumor suppressor genes, such as TP53, APC, PTEN, or p16[11].

In conclusion, bile duct microhamartomas or Von Meyenburg complexes are rare and generally asymptomatic lesions that are important to recognize, as

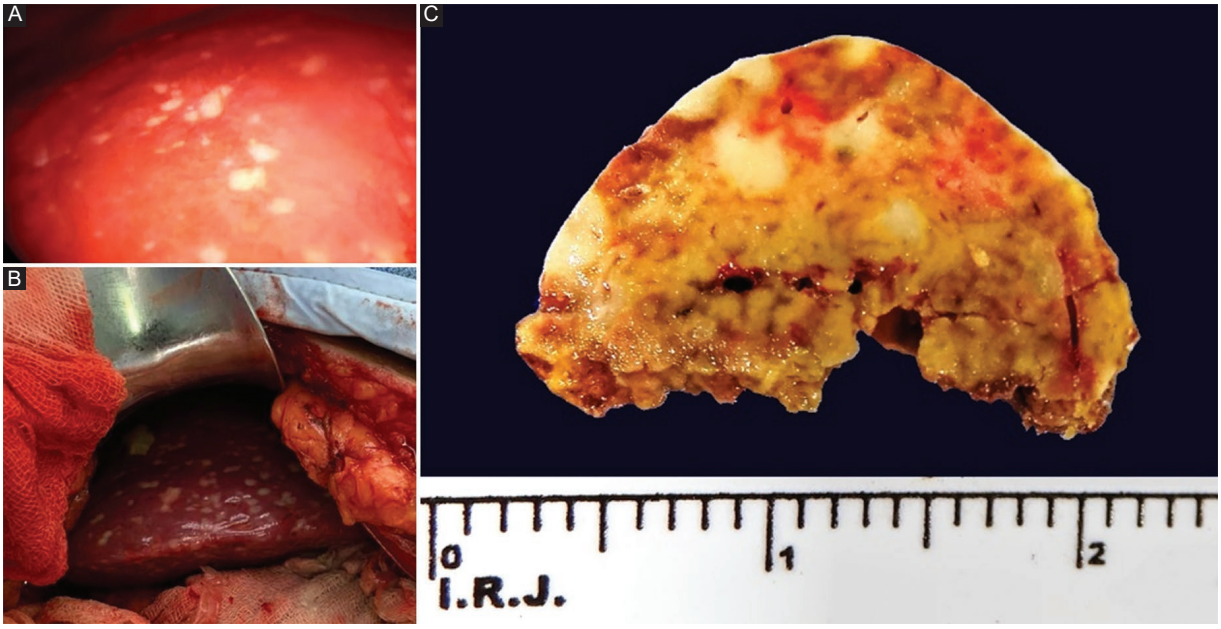

Figure 1. A: *multiple nodular lesions on the liver surface observed during laparoscopic surgery.* **B:** *similarly, diffuse lesions are observed on the liver surface in open surgery.* **C:** *Cut surface of a liver biopsy fixed in 10% formalin, showing multiple grayish-white nodular lesions affecting the capsular and subcapsular regions of the liver, as well as deeper areas of the parenchyma.*

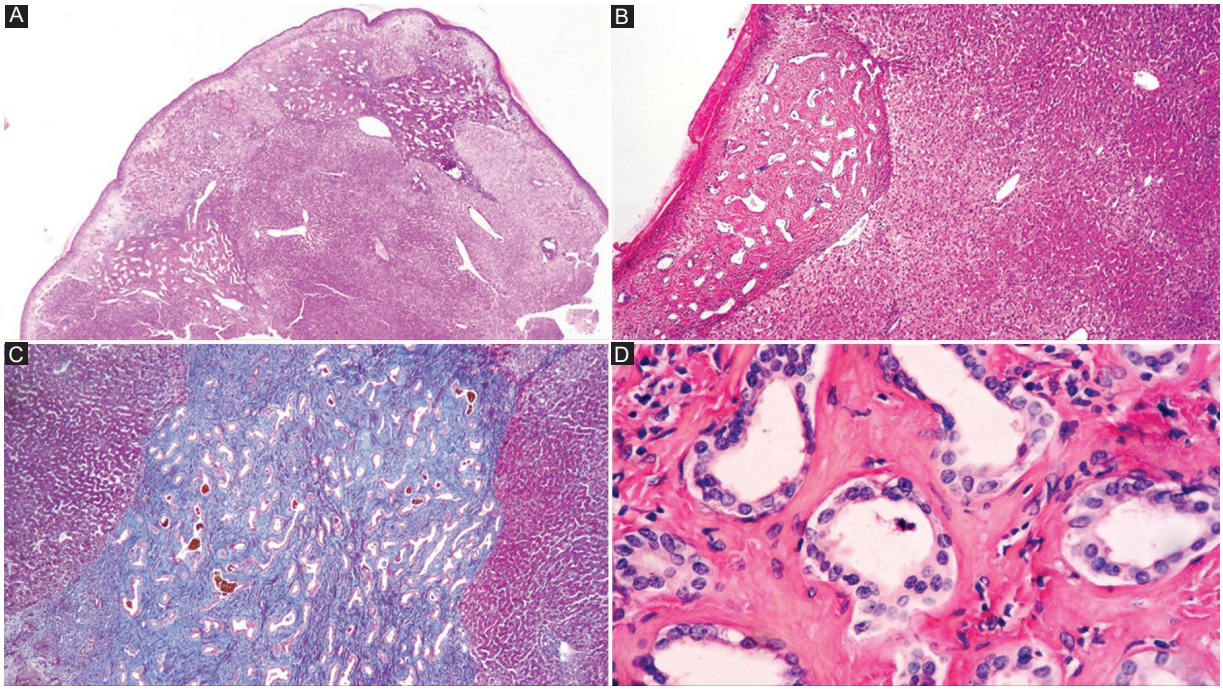

Figure 2. A: *at low magnification, the lesions appear multifocal with normal interposed hepatic parenchyma (hematoxylin and eosin, 40×).* **B:** *at medium magnification, the lesions are well-demarcated, composed of ducts embedded in fibrous stroma (hematoxylin and eosin, 100×).* **C:** *the stroma surrounding the ducts consists of collagen fibers stained blue. Bile is also observed in some ducts (Masson's trichrome, 100×).* **D:** *at high magnification, the epithelium lining the ducts is cytologically bland, with no cellular atypia (hematoxylin and eosin, 400×).*

they can mimic metastases, can rarely progress to cholangiocarcinoma (warranting consideration for long-term follow-up), and their presence does not rule out other synchronous processes (so their diagnosis should not discourage a protocol for investigating a suspected malignant neoplasm).

Table 1. Characteristics of patients with Von Meyenburg complexes

Case No.	Age (years)	Sex	Other Findings
1	21	Female	Microvesicular steatosis, liver regeneration
2	71	Male	Diffuse gastric adenocarcinoma (poorly cohesive), with signet ring cells
3	69	Female	Chronic and acute cholecystitis, hemorrhagic, ulcerated
4	67	Female	Chronic and acute abscessed cholecystitis, cholecystolithiasis
5	68	Male	Chronic cholecystitis, cholecystolithiasis
6	50	Female	Chronic cholecystitis
7	65	Male	Chronic cholecystitis
8	63	Female	Chronic cholecystitis, cholecystolithiasis

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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 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

Intense craving for eat: standardization of the Food Cravings Questionnaire-State in Mexico

Deseo intenso de comer: estandarización del Food Cravings Questionnaire-State en México

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Abstract

Background: *Food craving is an intense-compulsive response to eating highly appetizing foods. The Food Cravings Questionnaire-State (FCQ-S) is the most used instrument for its diagnosis. It is a multidimensional instrument, sensitive and adaptable to contextual and cultural changes.* **Objective:** *To standardize the FCQ-S in the adult population of Mexico City.* **Method:** *Non-experimental, cross-sectional, at convenience design, with 1059 adults of both sexes, aged 18-84 years. It is highlighted that 71.9% of the participants were women.* **Results:** *A reliability coefficient of 0.95 was obtained, the correlations between the items were from r = 0.598 to r = 0.793. With the exploratory factorial analysis, an MKO of sampling adequacy of 0.943 was obtained, and with the Bartlett sphericity test a p = 0.000. The factors explain 78.61% of the total variation of the data. The RMSEA was 0.068, which indicates an acceptable fit. The CFI was 0.974, considered good, and NNFI was 0.969, good fit. The correlations ranged from p < 0.05 to p < 0.01, showing a connection between the different dimensions.* **Conclusions:** *The FCQ-S is valid and adaptable in the Mexican population.*

Keywords: *FCQ-S. Validation. Standardization. Food craving. Obesity.*

Resumen

Antecedentes: *El food craving es un deseo intenso y compulsivo de comer alimentos altamente apetecibles. El Food Cravings Questionnaire-State (FCQ-S) es el instrumento más utilizado para su diagnóstico. Es un instrumento multidimensional, sensible y adaptable a cambios contextuales y culturales.* **Objetivo:** *estandarizar el FCQ-S en población adulta de la Ciudad de México.* **Método:** *Diseño no experimental, transversal y a conveniencia por método de bola de nieve, con 1059 adultos ambos sexos y de 18-84 años. Se destaca que el 71.9% de los participantes fueron mujeres.* **Resultados:** *Se obtuvo un coeficiente de fiabilidad de 0.95 y las correlaciones entre los ítems fueron de r = 0.598 a r = 0.793. Con el análisis factorial exploratorio se obtuvo una MKO de adecuación de muestreo de 0.943, y con la prueba de esfericidad de Bartlett una p = 0.000. Los factores explican el 78.61% de la variación total de los datos. La RMSEA fue 0.068, lo cual indica ajuste aceptable. El CFI fue 0.974, considerado bueno, y el NNFI fue 0.969 (buen ajuste). Las correlaciones fueron de p < 0.05 a p < 0.01, lo que muestra una conexión entre las diferentes dimensiones.* **Conclusiones:** *El FCQ-S es válido y adaptable en población mexicana.*

Palabras clave: *FCQ-S. Validación. Estandarización. Food Craving. Obesidad.*

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Introduction

Food craving is a psychophysiological response of intense desire towards consuming highly palatable foods[1-3]. It is a component of addiction to fatty, sweet, or salty foods and is also related to overeating, and therefore, to overweight and obesity[4]. To identify and establish diagnostic criteria, Cepeda-Benito et al.[5] designed the Food Cravings Questionnaire-State (FCQ-S) and -Trait (FCQ-T) in the United States, which the following year were validated in a Spanish population[6] in a sample of 271 college students. Both instruments demonstrated high internal consistency and appropriate fit for all factors.

The next validation took place in the Netherlands[7] in a sample of 227 undergraduate students, yielding an overall α of 0.92, with subscales ranging from 0.80 up to 0.91. The factor analysis showed a Kaiser-Meyer-Olkin (KMO) measure of 0.87, and Bartlett's test of sphericity found $p < 0.001$. Similar to the Spanish validation, this study also retained the 5 factors of the original version, the 15 items, with an explained variance of 80.02%. In Germany, the FCQ-S was validated with 133 college students, but it was designed in 2 phases, including food deprivation at the beginning and end of the semester; a reliability coefficient of $\alpha = 0.94$ was found.[8]

The first study conducted in South America was in Brazil[9], again among undergraduate students (n = 611). In this validation, they obtained an $\alpha = 0.82$, maintaining the 5 subscales. In a different study, 2 phases were conducted, with the first involving 492 university students responding to both questionnaires (FCQ-T-r and FCQ-S), but with items related to chocolate. Specifically, in the FCQ-T, they found $\alpha = 0.94$, with 2 subscales identifying lack of control over chocolate intake ($\alpha = 0.91$) and thoughts related to chocolate ($\alpha = 0.91$). In the FCQ-S, they obtained $\alpha = 0.87$ with 2 subscales, one for the desire to eat chocolate ($\alpha = 0.90$) and the other for hunger level ($\alpha = 0.85$). The scores positively correlated with self-reported chocolate consumption frequency and scores on the Chocolate Attitudes Questionnaire, indicating that the FCQ-S has convergent validity. In the second phase, participants (n = 76) were exposed to chocolate, which generated high scores on both instruments and positively correlated with salivation. The authors concluded that the instruments represent reliable and valid self-report measures for assessing chocolate craving[8-10].

However, despite the diversity of validations around the world, all the samples in the studies described involved fewer than 1000 participants, were conducted in university populations, and lacked confirmatory analyses. Notably, of the few standardizations done worldwide, we conducted one for the FCQ-T[11], but not for the FCQ-S. Therefore, the objective of this research was to validate and standardize the FCQ-S in the Mexican population. Our hypothesis is that α will be > 0.90, with good fit in the confirmatory analyses, allowing its standardization in the Mexican population, similar to the FCQ-T.

Method

The design was non-experimental, cross-sectional, and convenience-based, conducted in 2018-2019 with 1059 adults attending first- and second-level clinics of the Secretaría de Salud de la Ciudad de México, aged 18-84 years.

Instrument

We used the original version of the FCQ-S[6], with a reliability coefficient of 0.94, and subscales ranging from 0.74 up to 0.88. It includes 5 factorial dimensions: 1) intense desire to eat, 2) anticipation of positive reinforcement that may result from eating, 3) anticipation of relief from negative states and feelings as a result of eating, 4) lack of control over eating, and 5) craving as a physiological state. It consists of 15 items rated on a Likert scale, with 1 = strongly disagree, 2 = slightly disagree, 3 = neutral, 4 = slightly agree, and 5 = strongly agree.

Procedure

We collected the overall sample from March 2018 through February 2019. Within the first few months of 2018, we conducted a pilot test with 50 adult subjects from the open population of Instituto Politécnico Nacional, Unidad Lázaro Cárdenas, using a convenience sampling method. We asked them to provide feedback on the wording of the items. Subsequently, we conducted a reliability analysis and adapted the wording to Mexican regionalisms. In the second phase, another group of participants responded to the modified questionnaire, and we again performed a reliability analysis, resulting in the final version of the questionnaire in its Mexican version. In a third

phase, we randomly selected three out of 16 boroughs in Mexico City for the application of the questionnaire: Miguel Hidalgo, Azcapotzalco, and Cuauhtémoc, where health centers from the Secretary of Health are located. We administered the questionnaire in the outpatient clinic area with prior authorization from the authorities of the Secretary of Health of Mexico City. The interviewers approached clinic attendees and invited them to participate; those who agreed were read the informed consent form and proceeded to sign it. This is how we gathered 1059 participants.

We entered the data into Excel, reviewed for errors and inconsistencies, and transferred the database to SPSS version 26.0 (IBM).

Ethical criteria

This research was conducted in full compliance with the Ethical Principles for Medical Research Involving Human Subjects and posed minimal risk to the participants.

Statistical analysis

Various statistical tests were used to verify reliability and validity. The former was assessed using Cronbach's alpha test to evaluate the internal consistency of the test. The latter was assessed with exploratory and confirmatory factor analyses with orthogonal varimax rotation.

Results

Statistical analysis

A total of 1059 participants were included, 71.9% of whom were women, with a mean age of 39.9 years (range, 18-84). The reliability coefficient was 0.951, and the item correlations ranged from r = 0.598 up to r = 0.793, indicating high association. For the exploratory factor analysis, we obtained a KMO sampling adequacy of 0.943, and Bartlett's test of sphericity found p = 0.000.

Factor extraction was performed using the variance percentage criterion, which indicated that they explain 78.61% of the total data variation. The varimax method was used with a fixed number of four factors that explain the total variability. The items were distributed in these factors:

- Pleasurable emotions: evidence that food consumption is associated with pleasurable states, emotions, and an increased sense of well-being.
- Loss of control: the intense desire to consume highly palatable foods triggers a search and ends in uncontrolled consumption.
- Intense desire: urgency and desire to consume one or several specific foods are experienced.
- Physiological response: craving arises as a conditioned physiological response to physical stimuli, or the evocation of memories related to consumption.

It is important to note that the original questionnaire contains 15 items, but in this analysis, item #4 loaded onto two factors with similar factor loadings, so it was decided to eliminate it. We redid both the reliability and factor analysis (Table 1), which showed that the KMO sampling adequacy was 0.935, and Bartlett's test of sphericity found p = 0.000. Also, the percentage of variance increased up to 81.5% of the total data. We redid the reliability analysis, and the results, both for the total and for each factor, are also shown in Table 1.

We conducted the confirmatory factor analysis using IBM SPSS Amos 26.0 software, based on the results obtained in the exploratory factor analysis, to identify the model fit with the four correlated latent factors. Factor 1, "Pleasurable Emotions," consists of five items; Factor 2, "Loss of Control," consists of three items; Factor 3, "Intense Desire," consists of three items; and Factor 4, "Physiological Response," consists of two items. Figure 1 illustrates a diagram of the factor structure. The confirmatory factor analysis was performed using the maximum likelihood estimation method and applying Structural Equation Modeling (SEM) methodology to assess construct validity. To determine how well the observed covariance matrix was predicted, we considered the root mean squared error of approximation (RMSEA), which was 0.068, indicating an acceptable fit. The analysis also included the comparative fit index (CFI), which was 0.974, considered good. The non-normed fit index (NNFI) analysis yielded 0.969, which is considered a good fit. All correlations were significant at the 0.05 level, with many at the 0.01 level, demonstrating a connection between the different dimensions. In summary, the model presented very adequate levels of fit to the data, confirming the factor structure obtained in the exploratory analyses.

Table 1. Rotated component matrix for 14 items and general and factor-specific reliability results

Items	Factors			
	Pleasurable emotions	Loss of control	Intense desire	Physiological response
1) I have an intense desire to eat one or more specific foods			0.778	
2) I'm craving one or more specific foods			0.782	
3) I have an urge for one or more specific foods			0.644	
5) If I were to eat what I am craving, I am sure my mood would improve	0.768			
6) Eating one or more specific foods would feel wonderful	0.705			
7) If I ate something I wouldn't feel so sluggish and lethargic	0.750			
8) Satisfying my craving would make me feel less grouchy and irritable	0.698			
9) I would feel more alert if I could satisfy my craving	0.699			
10) If I had one or more specific foods, I could not stop eating them		0.817		
11) My desire to eat one or more specific foods seems overpowering		0.854		
12) I know I'm going to keep on thinking about one or more specific foods until I actually have it		0.785		
13) I am hungry				0.856
14) If I ate right now, my stomach wouldn't feel as empty				0.839
Factor reliability	$\alpha = 0.910$	$\alpha = 0.913$	$\alpha = 0.903$	$\alpha = 0.861$
Overall reliability	$\alpha = 0.945$			

Results of confirmatory factor analysis.

Discussion

The internal consistency in this validation varies little compared to the reliability coefficients reported in other countries: in the original version $\alpha = 0.94$[5], in the Spanish version $\alpha = 0.94$[6], in the Netherlands $\alpha = 0.92$[7], in Germany $\alpha > 0.901$[2], and in Brazil $\alpha = 0.86$[9]. Therefore, the coefficient obtained from the analyses confirms that this instrument is adaptable and sensitive to contextual and cultural changes.

For the factorial analysis of this questionnaire, it can be observed that, while previous validations have maintained the 15 original items and factors, this particular validation eliminated one item (the fourth) and regrouped the items into different factors, similar to the German version: Desire/lack of control, Hunger, and Reinforcement[12].

The Desire/lack of control factor in this validation included six items, sharing items 10, 11, and 12 with the original and Spanish versions, although items 1, 2, and 3 were not included in this version[5,6]. On the other hand, the Hunger factor in the German version and the Intense desire to eat factor obtained in this study have items 13 and 14 in common. However, this factor includes the same items as the original and Spanish versions.

In the study conducted by Meule et al.[12], the subscales Anticipation of positive reinforcement that may result from eating and Anticipation of relief from negative states and feelings as a result of eating were merged, resulting in a final subscale called Reinforcement. In both studies, the same items were included after rotation: 4, 5, 6, 7, 8, and 9. However, in this specific validation, the factor Anticipation of relief from negative states and feelings as a result of eating included item 15 ("I feel weak for not eating"), while the subscale Anticipation of positive reinforcement that results from eating included the items as in the original and Spanish versions. It is important to note that item 4 was not included in the final version of this study.

In summary, the four factors identified in this validation (pleasant emotions, loss of control, intense desire, and physiological response) provide a suitable explanation of food craving as a state in the Mexican population.

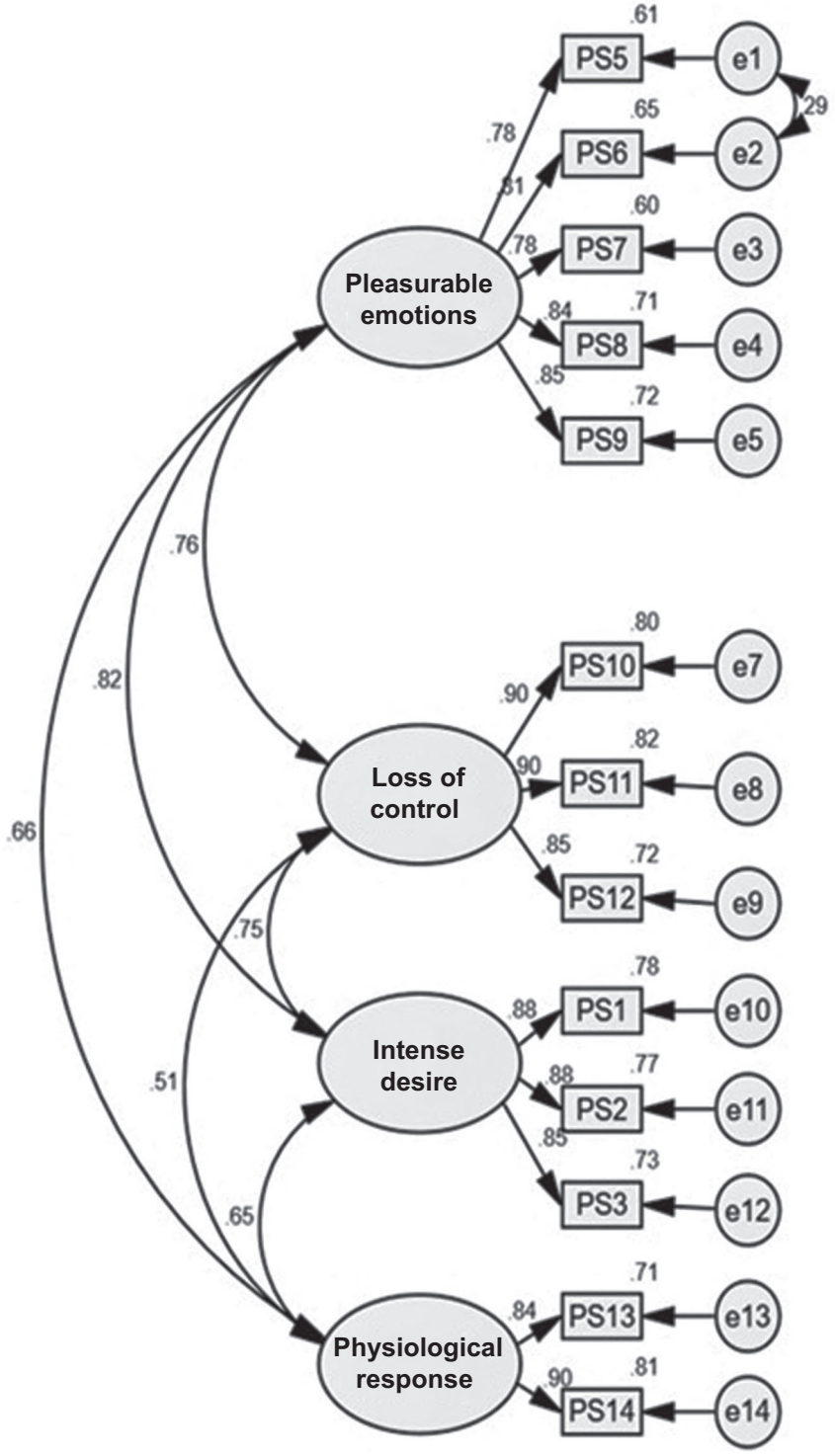

Figure 1. *Confirmatory analysis.*

Conclusions

The FCQ-S, which measures the intensity of the desire to consume a specific food, is an adaptable, valid, and reliable instrument for the Mexican population. The 4 factors it comprises help explain food craving as a state. It has been confirmed that the FCQ-S is suitable for use in both clinical and research

settings within the adult Mexican population. For future research, it is suggested to correlate it with other instruments that measure food craving and to conduct validations in child and adolescent populations.

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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

Gallbladder stones during pregnancy: are we doing the right thing in Mexico?

Litiasis vesicular durante el embarazo y el puerperio: ¿estamos haciendo lo correcto en México?

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Abstract

Objective: *To present the treatment of choice and approach in pregnant and postpartum women with a diagnosis of gallstones in Mexico and to compare it with the recommendations of international guidelines.* **Method:** *Observational, descriptive, and retrospective study based on information from the 2019 Dynamic Cubes database of pregnant women diagnosed with cholecystitis and/or cholelithiasis who had undergone cholecystectomy.* **Results:** *During 2019, 937 patients with cholelithiasis and cholecystitis were registered, 516 (55%) pregnant and 421 (45%) in puerperium. 91.47% of cases were managed with medical treatment and 8.53% with cholecystectomy, with predominance in the open approach in 63.75% of cases. Mortality was nil in both groups.* **Conclusions:** *Despite current international guidelines recommending early laparoscopic cholecystectomy in pregnant or puerperal women, in Mexico medical treatment, delayed cholecystectomy and its open approach are still privileged.*

Keywords: *Cholelithiasis in pregnancy. Cholecystitis in pregnancy. Cholecystectomy in pregnancy. Laparoscopic cholecystectomy in pregnancy. Abdominal pain in pregnancy.*

Resumen

Objetivo: *Determinar el tratamiento de elección, el abordaje y la mortalidad en mujeres embarazadas y en puerperio con diagnóstico de litiasis vesicular en México, y compararlo con las recomendaciones de las guías internacionales.* **Método:** *Estudio observacional, descriptivo y retrospectivo basado en la información de la base de datos Cubos Dinámicos del año 2019 de mujeres embarazadas con diagnóstico de colecistitis o colelitiasis que se hubieran realizado colecistectomía.* **Resultados:** *En 2019 se registraron 937 pacientes con colelitiasis y colecistitis, 516 (55%) embarazadas y 421 (45%) en puerperio. El 91.47% de los casos se manejaron con tratamiento médico y el 8.53% con colecistectomía, con predominio del abordaje abierto en el 63.75% de los casos. La mortalidad fue nula en ambos grupos.* **Conclusiones:** *A pesar de que las guías internacionales actuales recomiendan la colecistectomía laparoscópica temprana en embarazadas y puérperas, en México todavía se privilegian el tratamiento médico, el retraso de la colecistectomía y su abordaje abierto.*

Palabras clave: *Litiasis vesicular en el embarazo. Colecistitis en embarazo. Colecistectomía en embarazo. Colecistectomía laparoscópica en embarazo. Dolor abdominal en embarazo.*

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Introduction

Cholecystectomy is the second most common non-obstetric surgery performed during pregnancy[1,2]. For many years, non-operative management has been the treatment of choice for cholecystitis and cholelithiasis[3]. However, current clinical practice guidelines published by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) recommend avoiding delaying surgical treatment, as this leads to a worse prognosis for both the mother and the fetus. This is due to the risk of symptom recurrence, complication rates, longer lengths of stay, and higher likelihood of low birth weight, preterm birth, and the need for C-section[4,5].

Moreover, clinical practice guidelines consider laparoscopic cholecystectomy to be a safe procedure in any trimester of pregnancy[4-6]. A meta-analysis published in 2017 comparing laparoscopic vs open cholecystectomy found that maternal, fetal, and surgical complications were lower when minimally invasive approaches were used[7]. The trend in other countries has been toward increasing cholecystectomies in pregnant patients with this biliary disease, with fewer days at the hospital when laparoscopic approaches are chosen[8].

In Mexico, clinical practice guidelines on the diagnosis and treatment of cholecystitis and cholelithiasis do not specify the preferred management[9]. Since 2008, when SAGES guidelines were published, only 4 studies have addressed the treatment of acute cholecystitis in pregnant patients in Mexico[10]. This situation justifies examining whether the management of this disease in obstetric patients has changed.

The objective of this work is to determine the treatment of choice (whether medical or surgical), approach (open or laparoscopic), and the mortality rate in pregnant and postpartum women with a diagnosis of gallbladder lithiasis in Mexico in 2019, and compare it with the recommendations of international guidelines. The study design, epidemiological in nature, aims to describe how clinical practice guidelines (as public health policies) are applied and to determine if the health needs of relevant groups (such as pregnant women) are met by the national health system in the case of individuals without social security or health services[11].

Method

We conducted an epidemiological, observational, descriptive, and retrospective study of national records. The source of information was the public database "Cubos Dinámicos," from the General Directorate of Health Information of the Mexican Ministry of Health, available at www.salud.gob.mx/cubos. The information recorded corresponds to all hospital discharges from public hospitals in Mexico (patients without IMSS, ISSSTE, SEDENA, SEMAR, PEMEX, or private hospital affiliation) in 2019 according to the International Classification of Diseases 10th edition (ICD-10) codes. Records from that year were selected because they are definitive and clinical-surgical activities were not affected by the COVID-19 pandemic.

The method for obtaining information involved filtering with the variables allowed by the Cubos Dinámicos platform and the ICD-10 codes. First, in the 2019 discharges section, information was sought as a woman of childbearing age, selecting pregnancy and postpartum. Afterward, in the main condition section, diagnoses of cholelithiasis (code K80) and cholecystitis (code K81) were filtered. Finally, these data were compared with those from the Procedures section of the year 2019, where the main condition was filtered by diseases of the digestive system complicating pregnancy, childbirth, and postpartum (code O996), and in Procedures, cholecystectomy (code 5122), laparoscopic cholecystectomy (code 5123), partial laparoscopic cholecystectomy (code 5124), and other partial cholecystectomy (code 5121) were selected.

Information was obtained in aggregate form based on the mentioned variables and filters for each recorded hospitalization episode. This means that data cannot be disaggregated by trimester of pregnancy or by diagnostic method used. Although cholecystitis code includes diagnoses of acute, chronic, and chronic aggravated cholecystitis, the platform does not allow identification of which specific diagnosis was made. Cases registered as other gallbladder diseases, which were also included, correspond to variants like hydrops, pyocyst, and Mirizzi syndrome, but the specific diagnosis for each case cannot be identified.

The recorded diagnoses are generally based on an ultrasound that confirms them. In a much smaller proportion, specific clinical criteria (such as the 2018 Tokyo Guidelines for acute cholecystitis) are used, but the database does not allow identification of the proportion of clinical criteria or diagnostic studies used. Finally, the platform does not allow identification of the reasons why laparoscopic procedures were converted to open approaches. Although determining the trimester of pregnancy, diagnostic method, reason for conversion, and cause of death is very important, publicly

available data through this platform does not provide this information specifically. Although this information falls outside the scope and objective of this work, some considerations are presented at the end to help interpret the findings.

Results

In 2019, public health institutions in Mexico recorded a total of 937 cases of pregnant and postpartum patients with cholelithiasis and cholecystitis as hospital discharges (Table 1). The mean age was 25.3 years, and the most common diagnosis was acute cholecystitis. Of these, 516 (55%) were pregnant, and 421 (45%) were postpartum. There were 61,900 cholecystectomies in the general population, 80 of which (0.001%) were in pregnant and postpartum patients (Table 2).

Medical management, and thus deferral of cholecystectomy, was the predominant treatment at 91.47%. There were a total of 80 (8.53%) cases of cholecystectomy, with the open approach predominating, accounting for 51 (63.75%) cases, 28 (35%) by laparoscopic approach, and 1 (1.25%) as partial cholecystectomy without specifying whether it was open or laparoscopic (Table 2). It was not recorded whether open cholecystectomies were conversions from laparoscopic surgeries or the reasons for such conversions. The length of stay was 15.78 days for open cholecystectomy cases and 8.66 days for laparoscopic cholecystectomy cases. Mortality was nil in both groups. The recorded information did not allow identification of whether the procedures were elective or emergency procedures.

For the correct interpretation of the previous records, it is important to make some specifications. After a hospital medical care episode, the main condition, which may be "suspected" or "questionable," if there is no further information or clarification, is coded as "confirmed."

It is likely that patients coded as cholelithiasis had one of the following situations: biliary colic clinical picture, cholelithiasis as an incidental finding when the reason for consultation or admission was another (e.g., prenatal checkup), or other diagnoses categorized as cholelithiasis (polyp or biliary sludge). Finally, it should be considered that the same patient may have been recorded more than once if she required multiple hospital medical care for biliary, maternal-fetal, or other disease; however, cholecystectomy records indicate only 1 procedure of this type per case.

Table 1. Cholelithiasis and cholecystitis in pregnant and postpartum women during 2019 in Mexico

Registered disease	Discharges n (%)
Pregnant women	
Cholelithiasis	301 (32.12%)
Cholecystitis	210 (22.41%)
Other gallbladder diseases†	5 (0.53%)
Subtotal	516 (55.06%)
Postpartum women	
Cholelithiasis	239 (25.50%)
Cholecystitis	180 (19.21%)
Other gallbladder diseases†	2 (0.21%)
Subtotal	421 (44.93%)
Total	937 (100%)

*Neoplasms of the gallbladder and diseases of the main bile ducts not included: acquired anatomical disorders of the gallbladder or bile ducts, choledocholithiasis, cholangitis, neoplasms, structural anomalies of prenatal development of the gallbladder or bile ducts.

†Includes obstruction, hydrops, perforation, fistula, gallbladder cholesterolosis, and other specified and unspecified gallbladder diseases.

Table 2. Treatment of pregnant women with gallbladder diseases during 2019 in Mexico

	n	%
Pregnant women with cholelithiasis, cholecystitis, and other gallbladder diseases	937	100.00
Medical therapy	857	91.46
Cholecystectomy	80	8.54
Open cholecystectomy	51	63.75
Laparoscopic cholecystectomy	28	35.00
Other partial cholecystectomy	1	1.25

The tables show the distribution of diagnoses and treatments among pregnant and postpartum women with gallbladder diseases in Mexico during 2019. Most patients were treated medically, while a small proportion underwent cholecystectomy, with open surgery being more common than laparoscopic surgery.

Discussion

The results show that, in Mexico, the management of pregnant patients with cholelithiasis and cholecystitis is contrary to what current evidence[1,7] and international clinical practice guidelines4 suggest. In national public centers, the treatment of choice is medical management, and surgical management is deferred until the patient has completed her pregnancy. This also contrasts with trends[8] and preferred approaches in other countries[12], as in the few cases that undergo cholecystectomy, the open approach predominates over the laparoscopic one.

In Mexico, the delay in surgical management occurs in 91.47% of pregnant patients with cholecystitis and cholelithiasis. This figure contrasts with the 36% reported by Chen et al.[8] in 2020 in the United States. Although SAGES recommendation on cholecystectomy during pregnancy is considered weak[4], it is noteworthy that there were no deaths in either case in Mexico, unlike reports from other countries[7]. Maternal-fetal complications (both in medical and surgical management) are beyond the scope of this study, so an analysis and discussion of the associated morbidity to determine if there was any difference cannot be performed. Despite this, in light of current evidence, it is important to discuss some arguments still used to delay cholecystectomy.

The first group of arguments relates to fetal outcomes: spontaneous abortion, preterm birth, and teratogenesis. Chen et al.[8] found that laparoscopic approaches were significantly associated with lower rates of preterm birth, preterm labor, or abortion (OR, 0.410; $p < 0.001$) vs non-operative management[8]. It should be considered that up to 30% of pregnancies within the first trimester end in spontaneous abortion, and while there is a risk of uterine contractions after surgery, these rarely result in preterm birth. In fact, these complications are more associated with other severe maternal diseases that are inadequately managed and can be exacerbated by delays in surgical management[13].

Regarding the risk of teratogenesis due to cholecystectomy or the use of anesthetics, the American College of Obstetricians and Gynecologists (ACOG) has issued an opinion since 2011. While it mentions that consultation with obstetricians is necessary for any non-obstetric surgery in pregnant women, it also states that the anesthetic agents currently in use have not been shown to have teratogenic effects in humans when used at standard concentrations at any stage of pregnancy. In fact, they state that a pregnant woman should never be denied justifiably indicated surgery, in any trimester of pregnancy[14].

Other arguments for delaying cholecystectomy have been maternal or surgical complications. However, it has been demonstrated that these occur in 4.3% of pregnant patients undergoing laparoscopic cholecystectomy[15], which is similar to those reported in non-pregnant women (0.5% up to 6%)[16-18]. Silvestri et al.[19] compared 32,479 non-pregnant women to 436 pregnant women, and found that the rates of major and minor complications within 30 days were similar in both groups, suggesting that pregnancy does not increase postoperative maternal morbidity; however, pregnant women underwent emergency and open procedures more frequently, likely due to delays in diagnosis, reluctance of surgeons to perform laparoscopic approaches, or initial attempts at medical management. In the same vein, the few reported intraoperative maternal complications have been categorized as minor[7,20].

On the other hand, the medical management of this biliary disease has some consequences. Approximately 80% of pregnant women with symptoms of cholecystitis will experience recurrence, and in 20% up to 40% of cases, the recurrences occur before delivery; the number of recurrent episodes ranges from one to three. Preterm labor has also been reported in 4% of cases, and there is a need to induce labor to control biliary colic in 15% of cases[21]. Up to 9% may require an emergency C-section due to fetal distress, leading to preterm birth, low birth weight, and the need for critical neonatal care[22].

The outcome of laparoscopic approach has also been proven better than that of the open approach in this population[23]. Demonstrated advantages include early return of bowel function, early ambulation, a short length of stay, quick return to normal activity, low frequency of surgical site infection and hernia, and less postoperative pain[24]. It is also associated with less fetal depression due to the reduced use of narcotics in the postoperative period and minimal manipulation of the uterus for adequate exposure. This leads to less uterine irritability, lower rates of spontaneous abortion, less preterm labor, and less preterm delivery[25].

In this study, the hospital stay was shorter (8.66 days) with the laparoscopic approach than with the open approach (15.78 days). It has been shown that the length of stay resulting from cholecystectomies in pregnant women is generally longer, although the surgeon's experience was the most important variable for this and for complications. In Mexico, experience with laparoscopic cholecystectomy has increased significantly in recent years[26], which may represent an advantage (among other variables) in shortening the length of stay. Finally, the laparoscopic approach in cases of acute abdomen is a strong recommendation, meaning the benefits clearly outweigh the risks[5].

There are situations that may explain why the open approach has predominated over the laparoscopic

one; among them, that the open approach is considered safer by the treating surgeons[27], that the surgeries were emergencies, limiting the availability of the laparoscopic approach, and that there were risk factors or intraoperative complications that required conversion[28].

Although this study did not determine the trimester of the recorded cases, cholecystectomy is currently considered the treatment of choice at any stage of pregnancy[5]. Previously, weeks 26-28 were considered the period of least maternal and fetal risk for surgical management[4], and most cases had been reported during this period[8]; however, although current evidence indicates that there is no difference by trimester[29,30] it has been observed that as pregnancy progresses, the length of stay increases[7,8] and technical difficulty increases[31].

In Mexico, the feasibility and impact on the safety and efficacy profile of performing early cholecystectomies in patients with symptomatic gallbladder stones or acute cholecystitis is unknown to this date. It is also unknown whether surgeons would be willing to implement this practice and whether legal implications would play a determining role in such decisions. Therefore, it is necessary to develop studies comparing the approach by trimester, the conversion rate, surgical complications, and maternal-fetal morbidity and mortality.

What is certain is that delays in the diagnosis and treatment of a surgical abdomen during pregnancy, due to fear of unnecessary studies and procedures, contribute to increased complications[31]. Sufficient clinical knowledge, systematic evaluation, greater diagnostic suspicion, and the development of sufficient surgical experience are necessary to avoid maternal complications and unnecessary fetal losses.

Conclusions

Despite current international guidelines recommending early laparoscopic cholecystectomy in pregnant and postpartum women, in Mexico, medical treatment, delayed cholecystectomy, and the open approach are still preferred. No difference in mortality has been found between patients managed medically and those who underwent cholecystectomy.

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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

Extremity soft tissue sarcoma: does surgical margin impact survival?

Sarcomas de tejidos blandos en las extremidades: ¿el margen quirúrgico impacta la sobrevida?

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Abstract

Objective: *To define the impact of surgical margins on local recurrence (LR), distant recurrence (DR) and overall survival (OS) in patients with soft tissue sarcomas of the extremities (eSTS).* **Method:** *Patients treated for a primary eSTS from 2006 to 2010 were analyzed. Rates of local recurrence, distant recurrence, and overall survival were estimated using the KaplanMeier method. The association of possible prognostic factors such as local recurrence, metastasis, and survival was performed using the Cox proportional hazards model.* **Results:** *128 patients were analyzed. The surgical margins were positive (R1 resection) in 22.7% and negative in 77.3%. The LR was 27%, the DR was 13% (70% of the population was free of disease at 5 years) and OS at 5 years was 84%. The prognostic factors for OS at 5 years were clinical stage, type and histological grade. The surgical margin had no impact on OS.* **Conclusions:** *Although an adequate oncological resection cannot be underestimated, this should be considered in the decision of the optimal treatment of eSTS when amputation or significant functional impairment of the limb is required to obtain negative surgical margins.*

Keywords: *Extremities soft tissue sarcoma. Surgical margins. Overall survival.*

Resumen

Objetivo: *Definir el impacto de los márgenes quirúrgicos sobre la recurrencia local (RL), la recurrencia a distancia (RD) y la supervivencia global (SG) en pacientes con sarcomas de tejidos blandos de las extremidades (STBe).* **Método:** *Se analizaron pacientes tratados por un STBe primario desde 2006 hasta 2010. Las tasas de recurrencia local, recurrencia a distancia y sobrevida global se estimaron mediante el método de Kaplan-Meier. La asociación de posibles factores pronósticos como recidiva local, metástasis y supervivencia se realizó mediante el modelo de riesgos proporcionales de Cox.* **Resultados:** *Se analizaron 128 pacientes. Los márgenes quirúrgicos fueron positivos (resección R1) en el 22.7% y negativos en el 77.3%. La RL fue del 27% y la RD fue del 13% (el 70% de la población está libre de enfermedad a 5 años) y la SG a 5 años fue del 84%. Los factores pronósticos para la SG a 5 años fueron el estadio clínico, el tipo y el grado histológico. El margen quirúrgico no tuvo impacto en la SG.* **Conclusiones:** *Aunque no se puede subestimar una resección oncológica adecuada, esto se debe considerar en la decisión del tratamiento óptimo de los STBe cuando se requiere una amputación o un deterioro funcional significativo de la extremidad para obtener márgenes quirúrgicos negativos.*

***Palabras clave*:** *Sarcoma de tejidos blandos de extremidades. Márgenes quirúrgicos. Sobrevida global.*

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Introduction

Soft tissue sarcomas (STS) are a heterogeneous group of rare solid tumors of mesenchymal origin with variable clinical and pathological characteristics, representing 1% of malignant tumors in adults. It is estimated that in the United States, approximately 13,130 new cases were diagnosed in 2020, and 5350 people died from the disease (2870 men and 2480 women)[1].

There are more than 100 different histological subtypes of soft tissue tumors, most of which are STS. The most common histotypes are liposarcoma, leiomyosarcoma, and undifferentiated pleomorphic sarcoma[2]. The most frequently affected anatomical sites are the extremities (43%), followed by the viscera (19%), retroperitoneum (15%), trunk (10%), and head and neck (9%)[3].

Surgery is the primary treatment for extremity STS (ESTS). It is necessary to circumferentially resect healthy tissue around the tumor because the surgical margin is the reference for defining the quality of the surgery and has a clear impact on local recurrence (LR), although the impact on overall survival (OS) remains controversial[4-7].

In a study conducted by Bonvalot et al.[8], margin status and local recurrence were not correlated with survival, while in a retrospective study by Zagars et al.[9], it was demonstrated that a negative margin improved disease-specific survival.

The known predictive factors that affect OS are histological grade, age, tumor size, and histological subtype[10]. Ten-year OS ranges from approximately 96% for grade 1 tumors down to 60% for grade 3 tumors[11].

Although adequate oncological resection cannot be overemphasized, it is also important to balance the negative surgical margin with functional outcomes, making it essential to have a better understanding of what is adequate in the local treatment of ESTS and its impact on OS. Therefore, we decided to conduct this retrospective analysis to determine whether patient and tumor characteristics, as well as LR, have an impact on OS in patients with intermediate and high-risk eSTS treated at a single institution in Mexico.

Method

Data were collected from patients with primary ESTS treated at the oncology hospital of Centro Médico Nacional Siglo XXI in Mexico from January 2006 through December 2010. All patients had histological confirmation of ESTS, no metastasis at the time of diagnosis, and were initially treated with surgery. Patients with recurrent or metastatic disease, those treated outside our hospital, and those on neoadjuvant chemotherapy or radiotherapy were excluded. The data retrieved included tumor size, histological type, surgical margin, and grade.

LR, distant recurrence (DR), and OS rates were estimated using the Kaplan-Meier method. The association of potential prognostic factors, such as LR, metastasis, and survival, was analyzed using the Cox proportional hazards model. Multivariate analysis was initially performed on all potential risk factors, such as sex, age, histology, grade, stage according to the American Joint Committee on Cancer, tumor size, and margin. LR and DR were analyzed as risk factors for decreased OS, incorporating these results into the Cox model as time-dependent covariates.

Results

A total of 128 patients were analyzed, with a sex ratio of 1:1. The lower extremities were the most affected location (85.2% of cases). The most frequent histology was liposarcoma (43.8%), followed by myxofibrosarcoma (14.1%), undifferentiated pleomorphic sarcoma (11.7%), synovial sarcoma (10.9%), malignant peripheral nerve sheath tumor (6.3%), and others (13.3%).

Regarding size, 53.9% of the tumors were > 16 cm, 33.6% were between 11 cm and 15 cm, 8.6% were between 6 cm and 10 cm, and 3.9% were < 5 cm. Lymphovascular invasion was present in only 4.7% of cases. Histological grade 1 was found in 45.3% of cases, grade 2 in 24.2%, and grade 3 in 25%; histological grade could not be determined in 5.5% of cases. Regarding clinical stage, the most frequent were IB, with 44.5%, and IIB, with 26.6%. Surgical margins were positive (R1 resection) in 22.7% of cases and negative in 77.3%. All patients underwent surgery; 36 patients (28.1%) also received adjuvant radiotherapy, and only 1 received adjuvant chemotherapy and radiotherapy.

The characteristics of the patients are summarized in Table 1.

Local recurrence

Lymphovascular invasion (odds ratio [OR], 15.333; p = 0.014), grade 3 histology (OR, 4.804; p = 0.002), and surgical margin (OR, 15.937; p = 0.000) were significant factors for LR. In grade 3 histology, the risk is up to 3.8 times higher, and for lymphovascular invasion or positive surgical margin, up to 14 times higher.

Table 1. Patient characteristics

	n	%
Sex		
Female	64	50
Male	64	50
Course of the disease		
< 3 months	4	3.1
3-6 months	17	13.3
> 6 months	107	83.6
Affected Limb		
Upper	19	14.8
Lower	109	85.2
Histological type		
Liposarcoma	56	43.8
Myxofibrosarcoma	18	14.1
Malignant peripheral nerve sheath tumor	8	6.3
Synovial sarcoma	14	10.9
MFH	15	11.7
Others	17	13.3
Treatment		
Surgery	91	71.1
Surgery and radiotherapy	36	28.1
Surgery, radiotherapy, and chemotherapy	1	0.8
Size (cm)		
1-5	5	3.9
6-10	11	8.6
11-15	43	33.6
> 16	69	53.9
Lymphovascular Invasion		
Present	6	4.7
Absent	122	95.3
Histological grade		
1	58	45.3
2	31	24.2
3	32	25
Undetermined	7	5.5
Surgical margin (mm)		
< 5	28	21.9
5.1-10	36	28.1
11-20	22	17.2
> 20	13	10.2
Positive	29	22.7
CS		
IA	5	3.9
IB	57	44.5
IIA	5	3.9
IIB	34	26.6
III	24	18.8
IV	3	2.3
DFI		
< 60 months	39	30.5
> 60 months	89	69.5
Local recurrence		
No	93	72.7
Yes	35	27.3
Distant recurrence		
No	111	86.7
Yes	17	13.3
Five-year survival		
Yes	108	84.4
No	20	15.6

CS: clinical stage; MFH: malignant fibrous histiocytoma; DFI: disease-free interval.

Distant recurrence

Risk factors for DR are similar to those for LR: lymphovascular invasion (OR, 16.769; p = 0.002), grade 3 histology (OR, 12.727; p = 0.002), and surgical margin (OR, 5.119; p = 0.003). Synovial sarcoma was found to be a high-risk histological subtype (OR, 13.250; p = 0.001).

Overall survival

Five-year OS was affected by the same risk factors as DR, except for positive surgical margin (OR, 2.105; p = 0.157). Statistical significance was observed in histological subtypes, malignant peripheral nerve sheath tumor (OR, 16.20; p = 0.007), synovial sarcoma (OR, 15.00; p = 0.003), and undifferentiated pleomorphic sarcoma (OR, 18.00; p = 0.001); also, when adjuvant radiotherapy was administered (OR, 3.504; p = 0.014), when lymphovascular invasion was present (OR, 13.250; p = 0.004), and with histological grade 2 (OR, 6.720; p = 0.025) or 3 (OR, 14.667; p = 0.001).

Overall survival analysis

In the statistical analysis, patients treated and followed for 5 years had an LR rate of 27% (35 cases), with 80% of these occurring within the first 2 years of follow-up, and a DR rate of 13% (17 cases), leaving only 70% of patients disease-free at 5 years. The 5-year OS was 84% (Fig. 1). Surgical margin did not affect OS, as shown in Fig. 2.

Univariate analysis

We found that clinical stage, histological grade, and R1 resection are prognostic factors for LR, as shown in Fig. 3. For DR, surgical margin, histological grade,

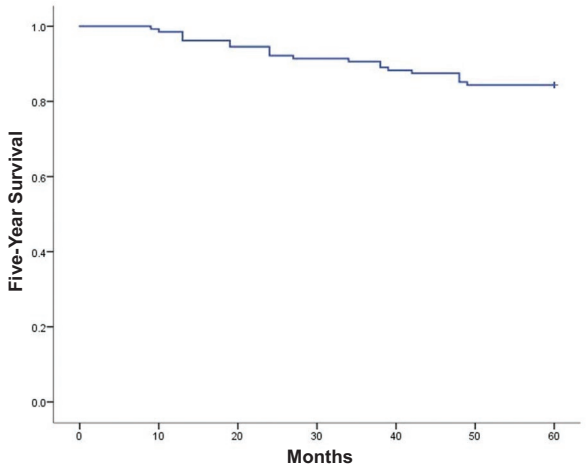

Figure 1. *5-year survival.*

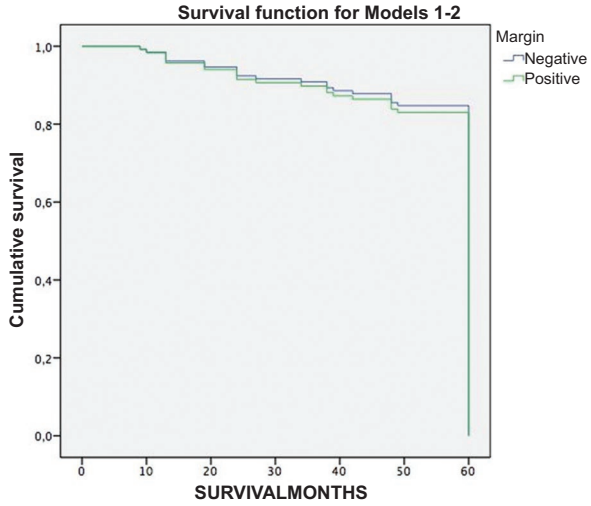

Figure 2. *5-year survival for patients with positive and negative surgical margins.*

and subtype were the prognostic factors found in our analysis (Fig. 4). The prognostic factors for 5-year OS were clinical stage, grade, and histological type (Fig. 5).

Discussion

The diagnosis of ESTS can be challenging. The most common presentation is a palpable tumor, and time from symptom onset to treatment usually exceeds 6 months, which clearly impacts the achievement of a negative surgical margin, which was achieved in 78% of cases due to the size and depth of the tumor (in 71.1% of cases, the tumor was located deep to the fascia). In more than 80% of our population, the lower limb was affected, which could explain why 53.9% presented with tumors > 16 cm.

The LR rate was 27.3%, higher than the 20% usually reported in the literature[12,13], with 80% of these recurrences occurring within the first 2 years after surgery. The DR rate was 13.3%, lower than reported in other studies[14], with a disease-free survival of 69.5%, well below the 85%-90% reported by Weitz et al.[15] in their study.

Histological subtypes such as epithelioid sarcoma and myxofibrosarcoma, and a surgical margin < 1 mm, are well-known predictors of LR, as previously demonstrated[16-19]; in our analysis, histological grade 2, lymphovascular invasion, and R1 resection were factors associated with LR.

We found that high-grade tumors, synovial sarcoma, and positive surgical margin were predictors of DR, unlike previous studies where tumor size was not a predictive factor, suggesting that it may be a less important predictor[9,15,20].

In a study conducted by Pisters et al.[21], factors such as tumor size ≥ 10 cm, high histological grade, deep location, local recurrence, and positive microscopic surgical margin were found to affect disease-specific mortality[21]. The predictors of OS found in this study were histological type (malignant peripheral nerve sheath tumor, synovial sarcoma, undifferentiated pleomorphic sarcoma), lymphovascular invasion, and histological grades 2 and 3. Surgical margin status did not affect OS.

We cannot retrospectively conclude that achieving negative margins would improve OS. Despite a 27% LR rate, 5-year OS was 84%, which could be influenced by the relatively small sample size, the limited number of deaths, and the short follow-up time in our study. Nevertheless, we found that high histological grade and lymphovascular invasion are factors that can increase the risk of LR, DR, and poor OS.

We cannot retrospectively conclude that achieving negative margins would have improved the OS. When the goal of obtaining negative surgical margins requires amputation or significant functional impairment, decisions should be made on a case-by-case basis, considering the disease biology, the patient's health status, and their informed decision.

Understanding the characteristics and biology of ESTS is complex due to the wide variety of histological subtypes. However, to establish a unified criterion, various centers have worked to identify prognostic factors that healthcare professionals can rely on to guide

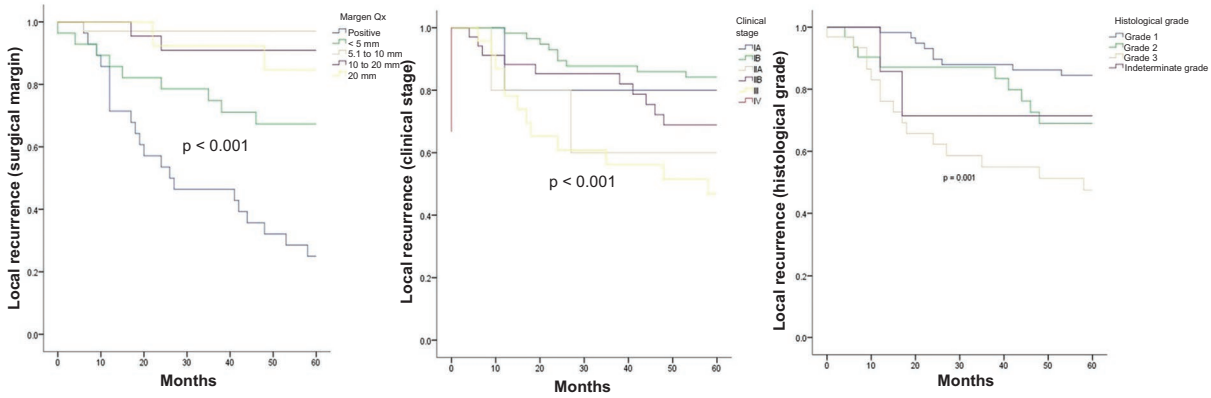

Figure 3. *Prognostic factors for local recurrence.*

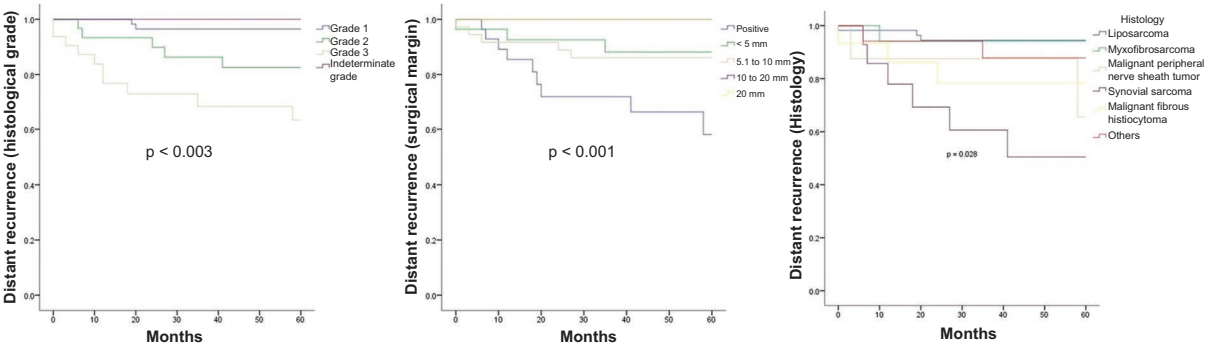

Figure 4. *Prognostic factors for distant recurrence.*

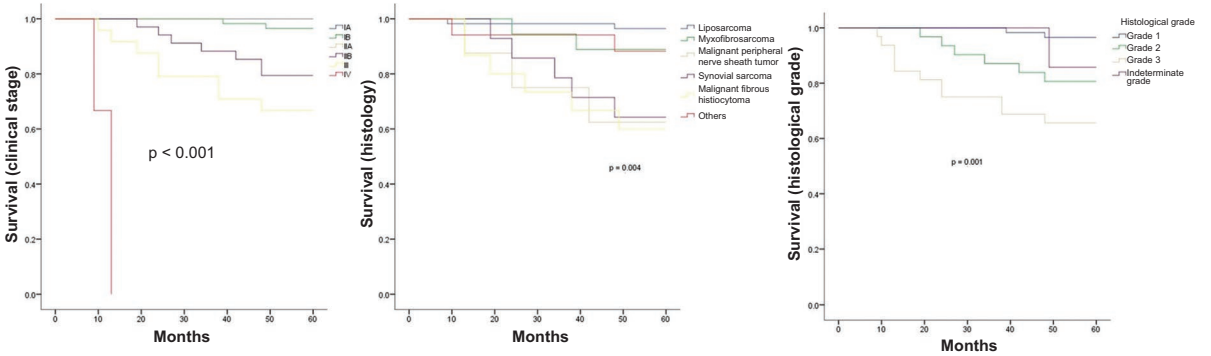

Figure 5. *Prognostic factors for overall survival.*

treatment. Among these factors, the surgical margin is controversial; in our study, it did not impact OS, which should be the primary goal of cancer treatment. We believe this is because the margin directly affects disease-free survival (DFS), which is not the same as overall survival. In our results, the surgical margin did not affect survival but did influence LR, DR, and DFS, which in turn affect OS. The therapeutic principle of limb preservation will remain important, and future research should focus on impacting OS.

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

Hearing results with combination steroid therapy for sudden sensorineural hearing loss

Resultados auditivos con terapia combinada esteroidea para la hipoacusia neurosensorial súbita idiopática

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Abstract

Background: *Sudden Sensorineural Hearing Loss was described by Mc. Cabe in 1979 and, since then, many authors have tried to define, explain and correctly treat this disease. The National Institute on Deafness and Other Communication Disorders defines it as sudden sensorineural hearing loss of at least 30 dB in three contiguous audiometric frequencies in a period of 72 hours. Among the therapeutic strategies, corticosteroids have been shown to have the greatest benefit due to their anti-inflammatory and anti-cellular stress effects.* **Objective:** *To determine the hearing results with combined steroid therapy in patients with sudden sensorineural hearing loss (SSHL), according to the Siegel recovery criteria scale.* **Method:** *Study carried out in the otorhinolaryngology and head and neck surgery service of the Centro Médico Naval, Ciudad de México, where 150 patients diagnosed with SSHL and who received combined therapy with intratympanic dexamethasone and systemic prednisone were included.* **Results:** *Therapeutic effectiveness was demonstrated by correlating therapeutic success in 82% of cases and therapeutic failure in 18% of cases, by correlating it with the Siegel recovery criteria scale. When evaluating the general average of the pure tone average levels at the beginning and 6 weeks after treatment, a statistically significant difference was obtained (p = 0.001). The average of the speech audiometry at the beginning and 6 weeks later had a statistically significant difference (p = 0.001).* **Conclusions:** *Initial combined steroid treatment for SSHL has been shown to have beneficial results according to Siegel recovery criteria scale.*

Keywords: *Hearing loss. Sudden. Treatment. Steroid. Results.*

Resumen

Antecendentes: *La Hipoacusia Neurosensorial Súbita Idiopática fue descrita por Mc. Cabe en 1979 y, desde entonces, muchos autores han tratado de definir, explicar y tratar correctamente esta enfermedad. El Nacional Institute on Deafness and Other Communication Disorders la define como pérdida auditiva neurosensorial brusca de al menos 30 dB en tres frecuencias audiométricas contiguas en un periodo de 72 horas. Entre las estrategias terapéuticas, los corticosteroides han demostrado tener mayor beneficio por sus efectos antiinflamatorios y antiestrés celular.* **Objetivo:** *Determinar los resultados auditivos con la terapia de esteroides combinados en pacientes con hipoacusia neurosensorial súbita idiopática (HNSI), de acuerdo a la escala de criterios de recuperación de Siegel.* **Método:** *Estudio realizado en el servicio de otorrinolaringología y cirugía de cabeza y cuello del Centro Médico Naval, en Ciudad de México, en el que se incluyeron 150 pacientes con diagnóstico de HNSI y que recibieron terapia combinada con dexametasona intratimpánica y prednisona sistémica.* **Resultados:** *Se demostró una efectividad terapéutica al correlacionar el éxito terapéutico en el 82% de los casos y un fracaso terapéutico en el 18% de*

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los casos según la escala de criterios de recuperación de Siegel. Al evaluar el promedio general de los niveles de promedio de tonos puros al inicio y 6 semanas posterior al tratamiento se obtuvo una diferencia estadísticamente significativa (p = 0.001). El promedio de las logoaudiometrías al inicio y 6 semanas posterior al tratamiento tuvo una diferencia estadísticamente significativa (p = 0.001). **Conclusiones:** *El tratamiento combinado con esteroides de manera inicial para la HNSI ha demostrado tener resultados benéficos de acuerdo con la escala de criterios de recuperación de Siegel.*

Palabras clave: *Hipoacusia. Súbita. Tratamiento. Esteroideo. Resultados.*

Introduction

According to the National Institute on Deafness and Other Communication Disorders[1,2], sudden idiopathic sensorineural hearing loss (SISNHL) is defined as a sensorineural hearing loss of generally sudden onset, with rapid or abrupt progression of, at least, 30 dB across 3 contiguous audiometric frequencies within a 72-hour period, with no identifiable etiology in most cases.

The approximate incidence of SISNHL is between 5 and 20 cases per 100,000 inhabitants per year and affects individuals of any age, though it is most widely observed in the fifth decade of life. It occurs equally in both sexes, presenting unilaterally in up to 96% of cases and bilaterally in 4% (of these, more than half do not occur simultaneously)[3].

The etiological factors can be determined in 10% up to 15% of cases; for the remaining sudden hearing losses, the term "idiopathic" is used[4]. There are various theories regarding the mechanisms involved based on case series studies, including cochlear inflammation due to viral infection, bacterial infections, autoimmune diseases, microvascular events, ototoxic substances, neoplasms, and trauma[5]. The viral theory is the most documented, both anatomopathologically in necropsies with findings related to herpes simplex virus type 1 infection and due to the frequent history of upper respiratory tract infections; however, specific serological profiles and a single response to antiviral treatments have not been demonstrated[6]. Another theory is changes the microcirculation of the inner ear, presenting transient ischemia phenomena in the inner ear, with a certain genetic predisposition to thrombosis in patients with cardiovascular risk, particularly those with mitral prolapse or antiphospholipid syndrome, as well as during general anesthesia or an episode of intralabyrinthine hemorrhage, demonstrated by magnetic resonance imaging[7,8]. It often goes unnoticed or presents a delay in diagnosis for being painless, with nonspecific symptoms, and symptoms are often attributed by the patient to everyday causes, such as respiratory infections, allergies, or cerumen impaction, among others[9]. The diagnosis of sudden hearing loss is suspected in a patient with concordant clinical findings and absence of identifiable causes based on history and normal otolaryngological physical examination; therefore, a detailed clinical and paraclinical assessment should be performed, sometimes requiring imaging or serological studies[10,11]. Audiometry is required for all these patients, as it not only confirms the diagnosis but also establishes the severity, prognosis, and follow-up[12]. The most frequent associated symptoms are aural fullness and tinnitus, in more than 90% of cases; vestibular symptoms have been described in 20% up to 60% of cases, and less frequently otalgia or paresthesias[13].

Treatment remains controversial due to the lack of solid scientific evidence clearly supporting any of the proposed options, with widely varying doses[14]. Oral corticosteroid administration is recommended for initial management, while intratympanic administration is traditionally reserved as a bailout therapy or in the presence of contraindications to high-dose systemic corticosteroids[15]. The use of intratympanic corticosteroids is based on increasing cochlear blood flow after ischemia induced by injury[16], stabilizing cellular and lysosomal membranes, inhibiting prostaglandins and proinflammatory cytokines (tumor necrosis factor-alpha, interleukins 2 and 6, and interferon-gamma), inhibiting chemotactic factors and factors that increase capillary permeability, and inhibiting the recruitment of inflammatory cells to the affected regions[17]. The benefit of intratympanic corticosteroids has been observed in patients with moderate.to-severe hearing loss, excluding cases of profound hearing loss[18]. Antiviral therapy has been proposed as a complement to conventional treatment due to the debated role of viral agents in its pathogenesis[19]. The use of hyperbaric oxygen therapy has been debated[20]. The use of oral magnesium and antioxidants (vitamins E and C) has shown some benefit in small studies[21].

Various scales have been used to assess patient improvement[22]. The most common and recommended

by consensus on the diagnosis and treatment of sudden hearing loss established by the Madrid Society of Otolaryngology in 2010 are the Siegel scale, the Furuhashi scale, and the recovery rate[23]. The Siegel scale is a graded scale proposed in the 1970s to assess the degree of recovery in patients with sudden hearing loss based on two parameters: the number of decibels recovered in the pure tone average (PTA) and the final PTA. It is the strictest scale, making it more difficult to consider a patient successful in therapy[24] (Table 1).

Sudden hearing loss usually has a good prognosis, especially in patients with isolated high or low-frequency loss[25]. Conversely, patients with profound hearing loss across all frequencies have a reserved prognosis[26]. Clinical criteria such as advanced age and the presence of vertigo are notable predictors of poor prognosis[27].

The present study evaluates the auditory outcomes of combined steroid therapy based on systemic prednisone and intratympanic dexamethasone in patients with SISNHL, according to the Siegel recovery criteria scale.

Table 1. Siegel recovery scale criteria

Siegel criteria		
Complete recovery	Final PTA ≤ 25 dB regardless of dB gained	Therapeutic success
Partial recovery	Improvement > 15 dB and final PTA: 25-45 dB	
Slight recovery	Improvement > 15 dB and final PTA > 45 dB	Therapeutic failure
No recovery	Improvement < 15 dB or final PTA > 75 dB	

PTA, pure tone average

Method

We conducted an observational, analytical, retrospective, and cross-sectional study in the otolaryngology and head and neck surgery service of the Naval Medical Center in Mexico City, Mexico. It included a total of 150 patients diagnosed with SISNHL through an audiological profile that included tonal audiometry and speech audiometry, who agreed to be treated with combined therapy of intratympanic dexamethasone (with prior informed consent, as it is an invasive procedure) and systemic prednisone, from January 2009 through November 2021. Patient records that met the inclusion criteria were reviewed: diagnosis of SISNHL confirmed by a complete audiological profile, initial combined treatment with prednisone at a dose of 1 mg/kg per day for 30 days and dexamethasone 8 mg/2 mL (after applying 5 drops of tetracaine, 5 mg/mL, in the external auditory canal of the affected ear and aspirating it after 20 minutes, with the support of a microscope to apply 1 mL of dexamethasone previously loaded in an insulin syringe with a 24-gauge needle in the posteroinferior quadrant for deposition in the tympanic cavity, and after completing the infiltration, the patient's head is turned to the opposite side of the application to maximize exposure of the solution in the middle ear on the round window membrane for 50 minutes, with a cotton plug placed at the entrance of the external auditory canal, avoiding swallowing, speaking, and performing Valsalva maneuver during the procedure to prevent drug leakage through the Eustachian tube), performed once daily for 5 consecutive days, with clinical follow-up at 6 weeks after treatment by conducting a second follow-up audiological profile. Clinical records of patients with Meniere's disease, trauma, fluctuating hearing loss, radiation-induced hearing loss, noise-induced hearing loss, or any other identifiable cause of sensorineural hearing loss, chronic pre-existing conditions in the affected ear, pregnancy or lactation, or comorbidities that would prevent steroid treatment were excluded. Records of patients who did not complete the steroid therapy regimen or had incomplete information were also excluded.

Initial and collective audiometry was assessed by obtaining the PTA and speech audiometry prior to combined steroid treatment and its controls at 6 weeks after treatment, categorizing the degree of hearing loss and affected frequencies before and after treatment. Variables such as sex, age, laterality of hearing loss, presence of tinnitus, and comorbidities were determined, as well as the association of the therapeutic window by evaluating the days elapsed from the onset of symptoms to the start of combined steroid treatment, and therapeutic success and failure according to the Siegel recovery criteria scale, where success was defined as a PTA < 25 dB or a hearing gain > 15 dB and a PTA 25-45 dB after treatment, while failure was defined as a hearing gain > 15 dB and PTA > 45 dB, or a hearing gain < 15 dB and PTA > 45 dB.

The study was conducted in full compliance with the bioethical principles for clinical research in humans, considering the confidentiality of patient information and the autonomy of participating subjects,

and taking into account the considerations of the Declaration of Helsinki, the Nuremberg Code, and the General Health Law of the United Mexican States. It was authorized by the Local Committee on Bioethics and Research and received permission from the Medical Directorate of the Naval Medical Center for access to documents and information from regulatory authorities.

Audiometric studies and clinical information from the electronic health records of the HIS (Hospital Information System) of target patients with code H912 from the ICD-10, corresponding to the diagnosis of SISNHL, were used. Additionally, a laptop was used to capture the database with the Office software package and perform statistical analysis using Graph Pad Prism 8.

Descriptive statistics were performed to summarize variables, using percentages, means, and ranges. Data distribution was then analyzed. Given the normality of measurements, parametric tests were used. ANOVA was employed to determine whether there was a statistical difference between the different groups, Pearson correlation test was used to correlate numerical variables and determine the existence of a negative or positive relationship between these variables, and paired Student t-test was used to find differences between PTA and speech audiometry figures at baseline and 6 weeks after treatment, with the patient serving as their own control.

Results

A total of 150 electronic health records of patients diagnosed with idiopathic sudden sensorineural hearing loss (ISSHL) on combined therapy with intratympanic dexamethasone and systemic prednisone from January 2009 through November 2021 at the otolaryngology and head and neck surgery department of the Naval Medical Center were included. Among these, 64 (43%) were women and 86 (57%) were men. The mean age of the patients was 52.31 ± 16.23 years, with a minimum of 19 years and a maximum of 87 years (Fig. 1).

Regarding recorded comorbidities, 39 (26%) patients had 1 disease at the time of their initial assessment, 5 (3.3%) had 2 concurrent diseases, and 2 (1.3%) had 3 concurrent diseases. Among the comorbidities found, 26 (17.3%) patients had a diagnosis of systemic arterial hypertension (which could be related to the vascular etiology of ISSHL), 10 (6.6%) had a diagnosis of type 2 diabetes mellitus, 5 (3.3%) had a diagnosis of dyslipidemia, 3 (2%) had a diagnosis of some form of heart disease, 1 (0.6%) had hypothyroidism, 1 (0.6%) had systemic lupus erythematosus, and 1 (0.6%) suffered from chronic kidney disease (Fig. 2).

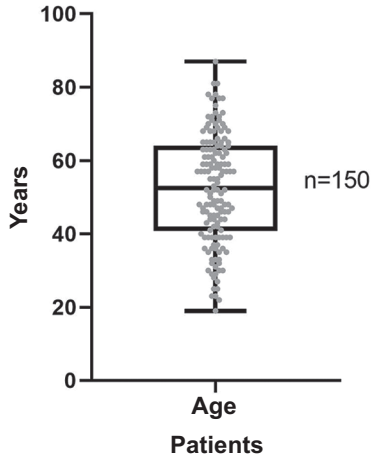

Figure 1. *Age distribution of patients represented individually in years.*

Regarding the affected ear's laterality, 79 (53%) patients had left ear involvement and 71 (47%) had right ear involvement.

On the presence of tinnitus, 67 (44.6%) reported having tinnitus at the time of their initial assessment, and 83 (55.3%) reported no tinnitus.

In terms of individual dB gain, according to the therapeutic goals of the Siegel recovery criteria scale, 110 (73.3%) patients showed an improvement > 15 dB, and 40 (26.7%) showed an improvement < 15 dB, with a mean dB gain of 20.22 dB and a standard deviation of 7.39 dB, ranging from a minimum of 1 dB to a maximum of 42 dB.

On the mean affected audiometric frequencies before treatment, the greatest involvement was observed in high frequencies in 58 (38.6%) patients, followed by low frequencies in 52 (34.6%) and mid frequencies in 40 (26.6%), with a pattern of decreased damage in each frequency after treatment, resulting in a mean 59 (39.33%) patients with no damage in any frequency.

Initial evaluation of hearing loss degrees according to the World Health Organization showed that 23 (15.3%) patients had mild hearing loss, 100 (66.6%) had moderate hearing loss, 26 (17.3%) had severe hearing loss, and 1 (0.6%) had profound hearing loss.

Regarding the correlation between the therapeutic window and hearing outcomes expressed in PTA, the

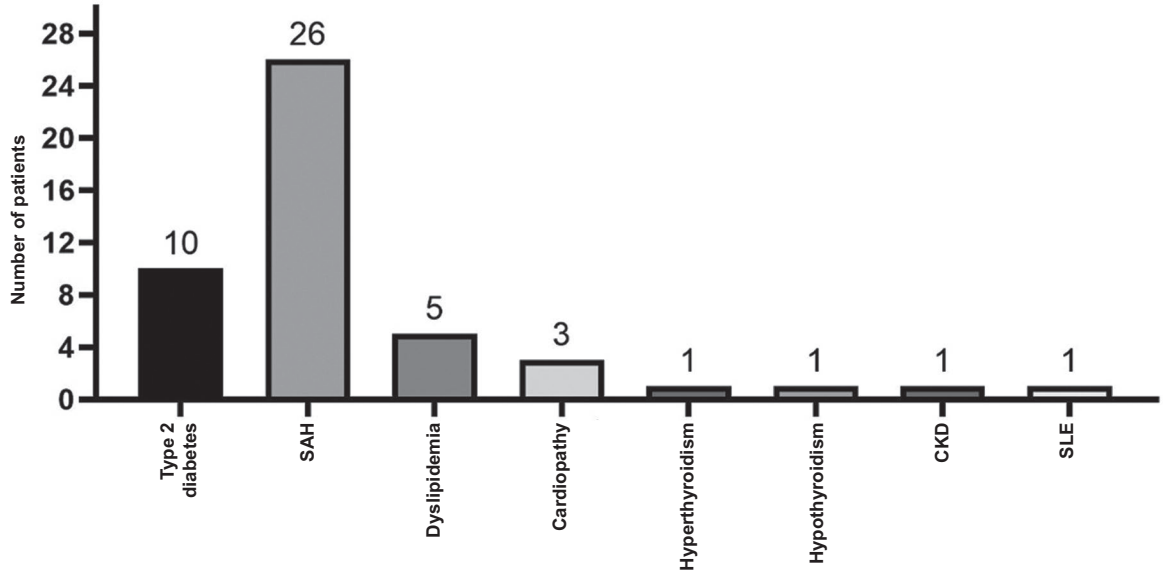

Figure 2. *Distribution of associated comorbidities. DM2: type 2 diabetes mellitus; CKD: chronic kidney disease; SAH: systemic arterial hypertension; SLE: systemic lupus erythematosus.*

population was categorized into 4 groups: > 1 to < 7 days, 75 cases (50%); > 8 to < 14 days, 40 cases (26.6%); > 15 to < 21 days, 26 cases (17.3%); and > 22 to < 28 days, 9 cases (6%). The mean time from symptom onset to diagnosis was 9.36 days, with no statistically significant relationship or relevance found ($p = 0.2557$; $R = 0.015$) (Fig. 3).

Correlation between patient age and hearing outcomes expressed in PTA using Pearson's test revealed no statistically significant relationship or relevance ($p = 0.779$; $R = 0.02$) (Fig. 4).

Regarding the overall PTA average in audiometry before and after treatment, the mean was 57.87 dB with a standard deviation of 14.59 dB before treatment, and after the same test at 6 weeks, the mean was 35.65 dB with a standard deviation of 10.01 dB, showing a statistically significant difference ($p = 0.001$) (Fig. 5).

In terms of the overall results of the logoaudiometry before and after treatment, a mean of 42.63 dB with a standard deviation of 19.36 dB was observed before treatment, and after the same test at 6 weeks, a mean of 32.3 dB with a standard deviation of 15.14 was found, representing a statistically significant difference ($p = 0.001$) (Fig. 6).

When evaluating the average degree of auditory recovery according to the Siegel recovery criteria scale, 107 (71%) patients had partial recovery, 16 (11%) had complete recovery, and 27 (18%) had slight recovery.

Regarding therapeutic success versus failure according to the Siegel recovery criteria, success was observed in 123 patients (82%) and failure in 27 (18%).

Discussion

The main objective of this study was to determine the auditory changes recorded in audiometries of patients diagnosed with ISSHL who underwent combined treatment with intratympanic dexamethasone and systemic prednisone, and to correlate these changes according to the Siegel recovery criteria scale to assess therapeutic success or failure. To this end, a total of 150 electronic health records of patients meeting the selection criteria and their characteristics were analyzed to assess differences between them and the homogeneity of the sample.

The evaluation of the overall PTA average in audiometry before and after treatment showed a mean of 57.87 dB with a standard deviation of 14.59 dB before treatment, and after the same test at 6 weeks, a mean of 35.65 dB with a standard deviation of 10.01 dB, representing a statistically significant difference ($p = 0.001$).

The results obtained suggest therapeutic effectiveness, with therapeutic success in 82% of cases and

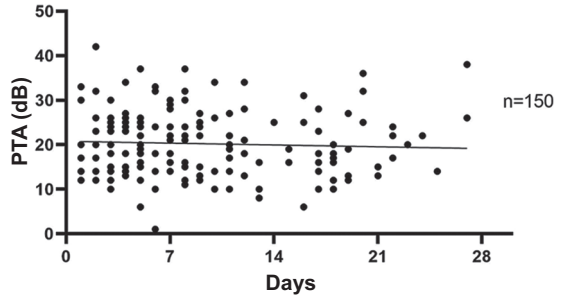

Figure 3. *Pearson correlation test with linear regression between the therapeutic window and auditory outcomes measured with PTA.*

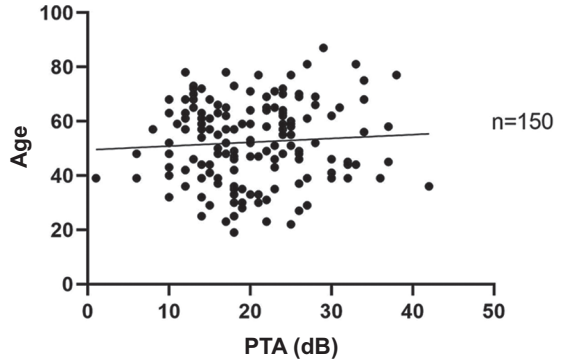

Figure 4. *Pearson correlation test with linear regression between age and auditory outcomes measured with PTA.*

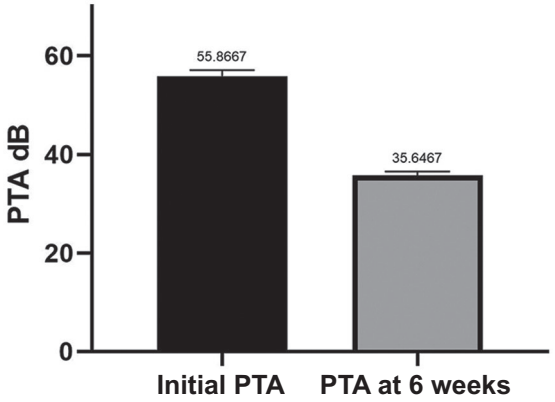

Figure 5. *Paired Student t-test to determine significant differences in the average PTA before and after treatment.*

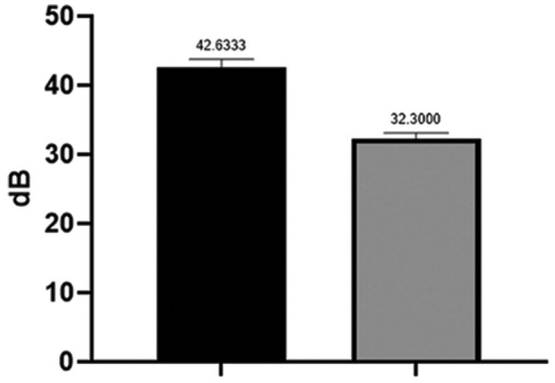

Figure 6. *Paired Student t-test to determine significant differences in the average logoaudiometry before and after treatment.*

therapeutic failure in 18%, correlating the results with Siegel's criteria.

Given the significant auditory improvement with pharmacological treatment and knowing that some studies demonstrate that the timing of treatment initiation is a crucial prognostic factor, we analyzed the results using Pearson's test to establish a correlation between the therapeutic window and hearing outcomes expressed in PTA, categorizing the population into 4 groups: > 1 to < 7 days, 75 cases (50%); > 8 to < 14 days, 40 cases (26.6%); > 15 to < 21 days, 26 cases (17.3%); and > 22 to < 28 days, 9 cases (6%). The mean time from symptom onset to diagnosis was 9.36 days, with no statistically significant relationship or relevance found ($p = 0.2557$; $R = 0.015$). However, the difference in values between the groups was not large enough to rule out the possibility that the lack of correlation was due to random sampling variability. Similarly, correlating patient age with hearing outcomes expressed in PTA using Pearson's test revealed no statistically significant relationship or relevance ($p = 0.779$; $R = 0.02$). This correlation is important, as numerous studies have shown that advanced age can be a negative prognostic factor.

There are many risk factors for ISSHL, including cardiovascular disease, diabetes, hypertension, dyslipidemia, and smoking[28]. Among the 150 patients studied, 39 (26%) had 1 disease at the time of assessment, 5 (3.3%) had 2 concurrent diseases, and 2 (1.3%) had 3 concurrent diseases. Among the comorbidities found, 26 (17.3%) patients had a diagnosis of systemic arterial hypertension (which could be related to the vascular etiology of ISSHL), 10 (6.6%) had a diagnosis of type 2 diabetes mellitus, 5 (3.3%) had a diagnosis of dyslipidemia, 3 (2%) had a diagnosis of some form of heart disease, 1 (0.6%) had hypothyroidism, 1 (0.6%) had systemic lupus erythematosus, and 1 (0.6%) had chronic kidney disease. These risk factors have not shown correlation with the degree of patient recovery in most studies.

Conclusions

Tonal audiometry is a good indicator of patient progress with ISSHL and has shown evident changes with the administered treatment[29]. The correlation of PTA results and logoaudiometry results before and at 6 weeks after treatment demonstrates statistically significant improvement.

Combined steroid treatment initially for ISSHL has shown an 86% success rate at 6 weeks according to the Siegel recovery criteria scale.

The therapeutic window plays an important role in hearing recovery; some studies demonstrate that early treatment influences therapeutic success, but in our study, we did not find a statistically significant correlation, likely due to our sample size[30].

Patient age appears to be an important factor in recovery after treatment, as numerous studies have demonstrated that advanced age can be a negative prognostic factor, although this effect could not be correlated in our study[31].

Most cases of sudden sensorineural hearing loss are idiopathic, involving primarily infectious, autoimmune, and vascular processes. Correlating these conditions in our studied population is challenging due to the low percentage of patients with comorbidity, with a predominance of cardiovascular and metabolic origins.

Acknowledgments

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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

Effectiveness of endoscopy in cochlear implantation

Efectividad de la endoscopía en la implantación coclear

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Abstract

Objective: *Determine the effectiveness of endoscopy in cochlear implantation as compared to microscopy.* **Method:** *Study comparing microscopy and endoscopy in cochlear implant placement in 34 patients (23 endoscopic implants and 20 implants via microscopy), between 2014 and 2019, at the Centro Medico Naval, Mexico City. The study was performed under informed consent and according to the Council for International Organizations of Medical Sciences (CIOMS).* **Results:** *Of the 34 patients, 12 were children or adolescents and 22 were adults. The visualization of the round window classified via microscopy per St. Thomas Hospital's classification showed that type IIB prevailed in 30.2% of patients, and type III in 41.9%, and when using the endoscope, the round window was observed in full in 82.6% of patients (type I), and type IIA was only observed in 17.4% (four patients). The number of attempts made to place the cochlear implant was greater with the microscope. The time to insertion of the electrode was 1.6 minutes. No differences were observed (p > 0.05) in the number of inpatient days. Cochleostomy was more frequent when using the microscope.* **Conclusions:** *Endoscopy is an effective resource in cochlear implantation for posterior tympanotomy, with no complications observed, offering greater safety in inserting the electrode through the round window.*

Keywords: *Ear. Cochlear implant. Endoscopy. Microscopy. Ear surgery.*

Resumen

Objetivo: *Determinar la efectividad de la endoscopía en la implantación coclear en comparación con la técnica microscópica.* **Método:** *Se comparó la microscopía frente a la endoscopía en la colocación de implante coclear en 34 pacientes (23 endoscópicos y 20 microscópicos), del año 2014 al año 2019, en el Centro Médico Naval de la Ciudad de México. El estudio se realizó bajo consentimiento informado y apegado a las normas del Council for International Organizations of Medical Sciences.* **Resultados:** *De los 34 pacientes, 12 eran niños o adolescentes y 22 eran adultos. La visualización de la ventana redonda fue clasificada con microscopio según la clasificación del St. Thomas Hospital, predominando la tipo IIB (30.2%) y la III (41.9%), y al utilizar el endoscopio se observó completa en el 82.6% (tipo I) y tipo IIA en tan solo el 17.4% (cuatro pacientes). El número de intentos en la colocación del implante coclear fue mayor con el microscopio. El tiempo en el que se insertó el electrodo fue de 1.6 minutos. No hubo diferencias (p > 0.05) en la estancia hospitalaria. Fue más frecuente la cocleostomía cuando se uso el microscopio.* **Conclusiones:** *La endoscopía es un instrumento efectivo en la implantación coclear por timpanotomía posterior, sin presentarse complicaciones y dando mayor seguridad para insertar el electrodo por la ventana redonda.*

Palabras clave: *Oído. Implante coclear. Endoscopía. Microscopía. Cirugía de oído.*

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Introduction

Endoscopy continues to evolve and expand its applications in otology; its use is well-established in procedures such as stapedectomy, tympanoplasty, ossiculoplasty, cholesteatoma removal, and chronic ear management[1,2]. Endoscopy is an innovative tool that enhances visualization and identification of anatomical structures that are difficult to observe with a microscope[3,4].

Recently, options for cochlear implantation have been described, such as the transcanal approach, but the transmastoid approach remains the most widely used technique, requiring optimal mastoidectomy with posterior tympanotomy[4], where the facial nerve may be at risk, requiring electrophysiological monitoring for its localization[5].

In our study, we compared endoscopy and microscopy in 43 ears, defining an effective endoscopic procedure as performing the surgery in a single attempt with complete electrode insertion through the round window without the need for cochleostomy in 1 or 2 attempts, no associated electrode complications, and hospital discharge within 48 hours.

Research question

What is the effectiveness of endoscopy vs microscopy for cochlear implant placement in patients treated at the Naval Medical Center?

Hypothesis

Endoscopy in cochlear implant placement is more effective than the microscopic technique, as it shows a lower frequency of complications associated with electrode insertion and cochleostomy, higher complete insertion rates, fewer implant placement attempts, and shorter lengths of stays.

Objective

To determine the effectiveness of endoscopy in cochlear implantation compared to the microscopic technique.

Study type

Observational, cross-sectional, ambispective, and comparative.

Method

This study was conducted at the Naval Medical Center in Mexico City between 2014 and 2019, through a systematic review of health records and surgical video recordings of patients who underwent cochlear implant surgery by the otorhinolaryngology and head and neck surgery department, where all patients were operated on by the same neuro-otologist.

To determine the effectiveness of endoscopy in implant recipients, 2 groups were created: Group #1 (23 ears), where the cochlear implant was placed endoscopically, and Group #2 (20 ears), where microscopy was used.

All patients in both groups underwent mastoidectomy with optimal posterior tympanotomy with microscope support, preserving anatomical references. The round window was described using the St. Thomas Hospital classification (Type I: complete round window exposure; Type IIa: exposure of more than 50% of the round window; Type IIb: exposure of less than 50% of the round window; Type III: round window not visible)[4] in all patients, and for the group in which endoscopy was used (0°, 3 mm, 6 cm), the visibility of the round window was reevaluated using the same classification. Attempts for implant placement, complete insertion, complications associated with electrode insertion through the round window, and insertion time (quantified from the appearance of the electrode in the endoscope view range of the round window entry until complete insertion, measured in min/s) were reported.

Means and standard deviations, frequencies, and percentages were determined, and Student t-tests, chi-square tests, and Fisher's exact tests were used. Data analysis was conducted using SPSSv23 and GraphPad Prism v5. A p-value ≤ 0.05 was considered statistically significant.

Results

The study included a total of 34 patients who received cochlear implants, treated at the otorhinolaryngology and head and neck surgery service of the Naval Medical Center. Of these, 38.24% (13) were women and 61.76% (21) were men.

There were 12 children or adolescents and 22 adults in this research. The mean age of those younger than 18 years was 6.33 ± 5.56 years, with a minimum age of 1 year and a maximum of 17 years, while the adult population had a mean age of 48.36 ± 16.23 years, with a minimum of 23 years and a maximum of 78 years.

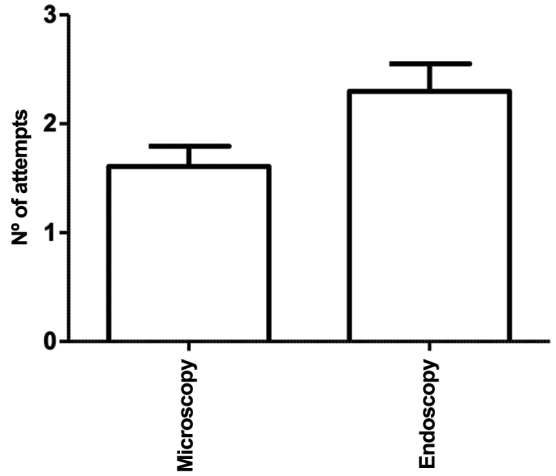

Figure 1. *Comparison of the mean number of attempts for cochlear implant placement in surgeries using endoscopy and microscopy.*

A total of 43 cochlear implants were performed. Most bilateral implants were done in children (9) ($p < 0.05$). Regarding surgical management, 53.5% (23) of the implants were performed using the endoscopic technique, and 46.5% (20) were performed using microscopy.

In the classification of the round window observed in surgeries performed with endoscopy, Types I and IIA predominated, unlike those performed with microscopy (Table 1).

The effectiveness of each type of surgery for cochlear implant placement was compared in terms of the presence of surgical complications, the need for cochleostomy, whether the insertion was complete, implant placement attempts, and length of stay.

No differences ($p > 0.05$) were observed in the frequencies of surgical complications between endoscopic and microscopic surgeries (Table 2).

The number of attempts for cochlear implant placement was higher in patients with surgical complications (3.5 ± 2.12 vs 1.85 ± 0.96; Student t-test, $p = 0.02$), and the insertion time was also longer in patients with surgical complications (5.0 ± 0.72 vs 1.64 ± 1.14 min/s; Student t-test, $p = 0.0001$).

Figure 1 illustrates the comparison of the mean number of attempts for implant placement in surgeries using endoscopy and microscopy. The mean number of attempts for endoscopic surgery was 1.6 ± 0.89 vs 2.3 ± 1.12 for the microscopy group, with the difference being statistically significant (Student t-test, $p = 0.03$).

Table 3 shows the comparison of cochleostomy outcomes with endoscopy and microscopy. In 22 patients, cochleostomy was not required ($p < 0.05$), being more frequent in patients treated with microscopy. Also, 100% of patients who required 5 attempts for implant placement underwent cochleostomy, a finding that was statistically significant ($p < 0.05$).

Table 1. Categorization of the round window in surgeries with endoscopy and microscopy

Round window classification	Microscopy (n = 43)	Endoscopy (n = 23)
Type I	11.6% (5)	82.6% (19)
Type IIA	16.3% (7)	17.4% (4)
Type IIB	30.2% (13)	-
Type III	41.9% (18)	-

Table 2. Comparison of the frequencies of intraoperative complications based on the type of surgery used for cochlear implant placement

Intraoperative complications	Type of surgery		Total
	Endoscopy (n = 23)	Microscopy (n = 20)	
Yes	0	10% (2)	4.6% (2)
No	100% (23)	90% (18)	95.3% (41)

Fisher's exact test, p = 0.21.

Table 3. Comparison of the frequencies of cochleostomy results based on the type of surgery used for cochlear implant placement

Cochleostomy	Type of surgery		Total
	Endoscopy (n = 23)	Microscopy (n = 20)	
Yes	4.3% (1)	70% (14)	34.9% (15)
No	95.7% (22)	30% (6)	65.1% (28)

Fisher's exact test, p = 0.0001.

Discussion

Mastoidectomy with posterior tympanotomy is the most widely used surgical procedure for cochlear implantation, and it requires a microscope. With the development of endoscopy as a tool, its use has expanded over the years, initially in sinonasal surgery and now in ear procedures, such as tympanoplasty, stapedectomy, cholesteatoma removal, and ventilation tube placement, and it is now considered an optional tool in cochlear implantation[1-3].

The visibility provided by the microscope is a straight and "tubular" line of sight, while the endoscope offers a wide field of view[1]. The microscope requires constant angling and repositioning of the patient to expose the anatomical structures being worked on, which limits the adequate anatomical identification of the round window and consequently increases the need for cochleostomies (11% up to 22% of patients)[4]. In the free-hand endoscopy technique, free manipulation is allowed without having to move the patient, with a wide field of view and clear images, achieving precise identification of the anatomical references of the middle ear[2,5].

This research compared microscopy and endoscopy in 43 ears of 34 patients (children, adolescents, and adults). Men and the adult population predominated, differing from documented international series.

Regarding surgical management, all patients underwent mastoidectomy with optimal posterior tympanotomy, supported by Tarabichi et al.[1] who concluded that posterior tympanotomy provides the most direct route to the round window for implant placement. Implantation was performed with a microscope in 20 ears, and in the rest with the support of an endoscope (23 ears). Regarding patient age and technique used for electrode placement, no difference was found, ruling out possible anatomical differences due to development and physiological growth that might prevent the use of endoscopy; this was described by the same authors mentioned previously, who found no significant trends related to age in the cochlear basal turn or the orientation of the round window[1].

The round window was classified using the St. Thomas Hospital microscopic classification[4] in all cases studied, with Types IIB (30.2%) and III (41.9%) predominating. With the endoscope, the visibility of the round window niche improved significantly, with complete observation in 82.6% (Type I) and Type IIA in only 17.4% (four patients). In these last cases, it may have been due to bony prominences limiting the niche. The improvement in visualization and identification with the endoscope of the window itself was evident. These results align with those reported by Jain et al.[2], who describe improved visualization of the round window region with better St. Thomas Hospital classification using the endoscope.

No differences ($p > 0.05$) were observed in the frequencies of complications associated with implant insertion between endoscopy and microscopy, although no complications were presented with endoscopy, while 2 were reported with microscopy: 1 false track (outside the tympanic ramp) and 1 perilymphatic fistula. Complications described in other reports were due to the approach route for cochlear implantation, such as damage to the tympanic membrane, facial nerve injury, and cerebrospinal fluid fistula, among others[6,7]. On the other hand, Carner et al.[8], in 25 cases with ear malformations implanted with endoscopy, had no complications; this supports the use of the endoscope. However, there is no historical record of studying complications associated with implant insertion as was done in this work.

The number of attempts for cochlear implant placement was recorded and analyzed for each group, requiring more attempts with the microscope than with the endoscope, with insertion achieved on the first or second attempt in most cases where endoscopy was used; insertion was also more challenging in patients with complications. The time for complete electrode insertion was measured, which was 1.6 minutes in those without complications.

Cochleostomy was more frequent in the group where implantation was performed under microscopic vision: 70% vs 4.3% with endoscopic vision, and the need for the only cochleostomy performed with the latter was due to a special cochlear condition (intracochlear bands), in the same patient who had difficulty with electrode insertion (greater number of attempts and longer time for implant insertion).

The length of stay was documented and no differences ($p > 0.05$) were observed between endoscopy and microscopy. Patients who were hospitalized longer were due to decompensation of their own comorbidity.

Endoscopy is effective in posterior tympanotomy as no surgical complications were presented, significantly improved visibility of the round window, did not require cochleostomy, and allowed complete electrode insertion through the round window, with minimal manipulation (1 or 2 attempts) and within an appropriate time, without extending the length of stay. Our results are similar to those reported by Jain et al.[2], who used endoscopy in the transmastoid approach with excellent results. Previously, Marchioni et al.[7] reported the use of endoscopy but via the transcanal approach without posterior tympanotomy, and later Dia et al.[3] and Migirov et al.[9] suggested that endoscopy could be a viable, safe, and feasible alternative or complement in standard open transmastoid cochlear implantation.

Conclusions

Endoscopy is an effective, feasible, and safe instrument in cochlear implantation through posterior

tympanotomy. No complications were presented, and it offered greater safety in electrode insertion through the round window into the cochlea. Visualization and identification of the round window niche were improved, avoiding the need for cochleostomy, and allowing verification of all electrode insertions through the round window.

Therefore, it is recommended to perform cochlear implant placement with endoscopy to achieve a safe insertion through the round window without complications and potentially greater auditory gain. Additionally, endoscopy reduces morbidity in cochlear implant recipients and can be used as a review tool in cases where insertion is done with a microscope.

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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 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

Management of post-ERCP duodenal perforations: experience at Hospital Juárez de México

Manejo de las perforaciones duodenales post-CPRE: experiencia en el Hospital Juárez de México

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Abstract

Background: *Endoscopic retrograde cholangiopancreatography (ERCP) is an endoscopic study in which the duodenum is observed laterally, and the bile duct is instrumented. There are several indications and complications in the procedure.* **Objective:** *To determine the incidence of duodenal perforations, using the Stapfer classification in the Hospital Juárez de Mexico over a period of 5 years, as well as the management implemented in such cases.* **Method:** *The study was carried out at the Hospital Juárez de Mexico of the Ministry of Health. All patients who underwent ERCP between January 1, 2017, to May 30, 2022 were included.* **Results:** *485 ERCP were performed in the study period. Incidence of 1.6% post-ERCP duodenal perforation. The average age of the subjects 56.37 years. In-hospital stay of post-ERCP perforations averaged 9.37 days. The time of the endoscopic study at the time of the surgical procedure is 10 h on average.* **Conclusions:** *Post-ERCP duodenal perforation is a complication that occurs with a low incidence, it tends to increase the number of days of in-hospital stay and increases morbimortality of patients; therefore, it is important to be always alert.*

Keywords: *ERCP. Perforation. Duodenum. Complication.*

Resumen

Antecedentes: *La colangiopancreatografía retrógrada endoscópica (CPRE) es un estudio endoscópico en el cual se observa lateralmente el duodeno y se instrumenta la vía biliar. Existen diversas indicaciones y complicaciones en el procedimiento.* **Objetivo:** *Determinar la incidencia de perforaciones duodenales utilizando la clasificación Stapfer para ubicación anatómica en el Hospital Juárez de México en un periodo de 5 años, así como el manejo implementado en dichos casos.* **Método:** *El estudio se realizó en el Hospital Juárez de México de la Secretaría de Salud. Se incluyeron todos los pacientes sometidos a CPRE entre el 1 de enero de 2017 y el 30 de mayo de 2022.* ***Resultados:*** *Se realizaron 485 CPRE en el periodo de estudio. Hubo una incidencia del 1.6% de perforación duodenal post-CPRE. El promedio de edad de los sujetos fue de 56.37 años. La estancia hospitalaria de los pacientes con perforación post-CPRE fue en promedio de 9.37 días. El tiempo del estudio endoscópico al momento de realizar el procedimiento quirúrgico fue de 10 h en promedio.* **Conclusiones:** *La perforación duodenal post-CPRE es una complicación que ocurre con una baja incidencia, suele aumentar los días de estancia intrahospitalaria y aumenta la morbimortalidad de los pacientes, y por ello es importante estar siempre alerta.*

***Palabras clave*:** *CPRE. Perforación. Duodeno. Complicación.*

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Introduction

Perforation during endoscopic retrograde cholangiopancreatography (ERCP) can occur at an incidence of less than 1%, leading to various injuries that increase morbidity and mortality[1]. Perforations during ERCP typically occur during sphincterotomy, guide placement, or due to inadequate manipulation of the endoscope during bile duct stone extraction[2]. Duodenal wall perforation results from improper positioning of the endoscope during bile duct drainage[3]. Mortality rate for duodenal perforation ranges from 16% up to 18%, which is associated with delays in diagnosis and treatment, as it can lead to sepsis and multiple organ failure[4].

Stapfer categorized endoscopic procedural perforations into 4 categories based on severity:

- Type I: corresponds to perforation of the lateral or medial portion of the duodenal wall, which can cause leak of a large volume of intestinal content. This occurs due to incorrect manipulation of the endoscope or migration of the bile duct stent. Type I lesions typically cause persistent leakage of pancreatic juice into the retroperitoneum or abdominal cavity, requiring early diagnosis and treatment.
- Type II: refers to ampullary perforations that usually occur during sphincterotomy. The retroperitoneum is usually the site where leaked material deposits. Depending on the lesion and nature of the leak, it is decided whether surgical treatment is necessary or conservative management is sufficient.
- Type III: refers to bile duct perforations that occur during guide placement or procedures for stone extraction from the bile duct. These lesions are generally small and require medical management with appropriate drainage.
- Type IV: refers to microperforations into the retroperitoneum that occur during sphincterotomy, with leak of material or gas into the retroperitoneal space. Most of these lesions are managed conservatively with medical care[5-8].

The severity of ERCP-related perforations can be categorized based on symptoms:

- Minor perforations are those with leaks of intestinal secretions that require hospitalization for at least 3 days.
- Moderate perforations require 4 to 10 days of hospitalization with conservative treatment.
- Severe perforations are those where the patient requires more than 10 days of hospitalization with conservative, radiological, or surgical treatment[9,10].

Various risk factors increase the likelihood of perforation during endoscopic procedures, such as advanced age, Oddi sphincter dysfunction, papillary stenosis, anatomical abnormalities, difficult cannulation, or multiple cannulation attempts[11,12].

Clinically, post-ERCP perforations can range from asymptomatic to acute abdomen. In the initial stages, patients may be asymptomatic or only exhibit mild abdominal pain, and such lesions may easily go unnoticed[13]. Therefore, continuous observation is essential for patients suspected of perforation or those with multiple above-mentioned risk factors[14,15].

Method

This is a descriptive, observational, retrospective, and cross-sectional study that includes all cases of ERCP-related perforation during the study period. Inclusion criteria were all patients undergoing ERCP at Hospital Juárez de México from January 1st, 2017 through May 1st, 2022, who experienced procedure-related perforations. Diagnosis of duodenal perforation was established through direct visualization during an endoscopic procedure or as a post-study tomographic finding. Exclusion criteria were patients who requested voluntary discharge during hospitalization and those who had ERCP performed at another health institution. Patients with incomplete records and minors were excluded.

A database was created to identify patients admitted with a diagnosis of choledocholithiasis or cholangitis. Once the health records were identified, they were reviewed to determine the endoscopic procedure performed, the complications encountered, and the type of injury following Stapfer's classification, the clinical status of the patients, the management implemented by the service, and the patients' outcomes. An Excel database was compiled including the patient's name, record No., age, sex, diagnosis, type of injury, clinical status, and outcomes.

Data analysis was performed using SPSS. The mean age of patients with post-ERCP complications, sex distribution, the percentage of most common conditions associated with post-ERCP complications, the frequency of lesions according to Stapfer's classification and their correlation with admission pathologies, the percentage of patients with inflammatory response syndrome at the time of diagnosis of post-ERCP complications, the mean time until treatment for these complications at Hospital Juárez de México, the most common anatomical location, and the most common comorbidity associated with post-ERCP complications were obtained.

Results

During the study period, a total of 485 ERCPs were performed. In 2017, 112 procedures were performed (23.09%), 67 of which were performed in women (59.82%) and 45 in men (40.17%). In 2018, a total of 69 procedures were performed (14.22%), 50 in women (72.46%) and 19 in men (27.53%). In 2019, 142 procedures were performed (29.27%), 82 in women (57.74%) and 60 in men (43.66%). In 2020, 67 procedures were performed (13.81%), 44 in women (65.67%) and 23 in men (34.32%). In 2021, 87 procedures were performed (17.93%), 61 in women (70.11%) and 26 in men (29.88%). In 2022, a total of 8 procedures were performed (1.64%), 6 in women (75%) and 2 in men (25%). Therefore, of the 485 ERCPs, 310 were performed in women (63.91%) and 175 in men (36.09%). A total of 84 cases of duodenal perforation were recorded during the same period. Records with a history of ERCP and duodenal perforation were evaluated, and 8 cases were found (Fig. 1).

Of these cases, 50% were men and 50% were women. The participants' mean age was 56.37 years (standard deviation [SD], 18.59) (Fig. 2). Regarding comorbidities, 25% had none, 25% had diabetes mellitus, 12.5% had systemic arterial hypertension, and 37.5% had both diabetes mellitus and hypertension.

Regarding the length of stay of patients with post-ERCP perforations, the mean length was 9.37 days (SD, 3.46). Of the cases studied, 25% developed pneumonia and 75% had no additional morbidities. The most common indication for ERCP was choledocholithiasis, in 87.5%, while only 12.5% were indicated for jaundice syndrome.

Endoscopic findings were as follows: pancreatic head cancer in 12.5%, Klatskin bile duct cancer in 12.5%, severe Oddi sphincter dysfunction in 12.5%, choledocholithiasis in 37.5%, contrast medium leak in 12.5%, and duodenal perforation in 12.5%. The procedures performed during the study were: bile duct stent placement in 25%, sphincterotomy plus stenting in 12.5%, sphincterotomy plus balloon sweep in 25%, and sphincterotomy alone in 37.5% (Fig. 3).

The endoscopic lesions reported were: Stapfer I in 37.5%, Stapfer II in 12.5%, no Stapfer III cases, and Stapfer IV in 50%. The anatomical location of duodenal perforation post-ERCP was the second portion of the duodenum in 50% of cases; in the remaining 50%, the lesion could not be identified. Of these patients, 25% had inflammatory response syndrome and 75% did not. It was observed that 37.5% of cases did not require additional studies for the diagnosis of duodenal perforation, and 62.5% underwent computed tomography.

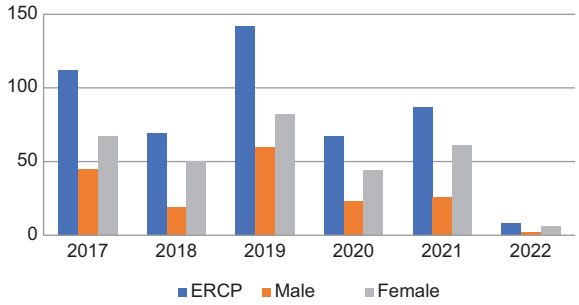

Figure 1. *Endoscopic retrograde cholangiopancreatographies performed from 2017 through 2022, distribution by year and sex.*

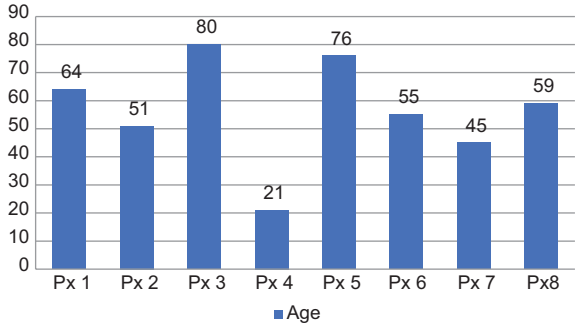

Figure 2. *Ages of patients. The mean age was 56.37 years.*

Of the cases presented, a total of 37.5% required surgical management while 63.5% were managed conservatively. For surgical management, primary closure of the duodenal perforation was performed in 100% of cases. The mean time from the endoscopic procedure to surgical intervention was 10 hours (SD, 11.26).

Discussion

Post-ERCP duodenal perforations have incidence rates from 0.8% up to 1.6%. At Hospital Juárez de México, the incidence rate of post-ERCP perforation during the study period was 1.6%, which falls within global statistics[10].

Several risk factors for post-ERCP duodenal perforation include older age, prolonged endoscopic procedure time, Oddi sphincter dysfunction, papillary stenosis, and anatomical disorders. Notably, in the perforations that occurred among the 485 procedures performed, there was no difference between sexes.

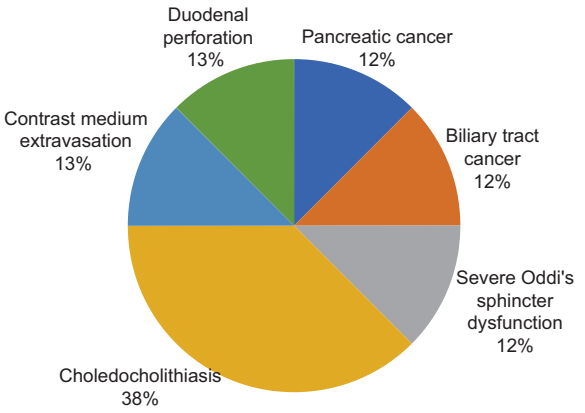

Figure 3. *Endoscopic findings of Endoscopic retrograde cholangiopancreatographies associated with subsequent perforation.*

The mean age described in the literature for presenting post-ERCP perforation is 51.3 years (SD, 15.8). In the study presented here, the mean age was 56.37 years (SD, 18.59), which can be considered within the risk age range for this complication[7]. Risk factors described by Retuerta et al.[5] indicate that female sex and advanced age were not criteria in this study, as there was no difference between sexes and the mean age was 56 years. Other risk factors, such as bilirubin levels, post-ERCP pancreatitis, and Oddi sphincter dysfunction, were not included in the study variables, suggesting the need for further research including special tests to evaluate sphincter function prior to endoscopy, and monitoring post-ERCP pancreatitis, which may impact perforation risk[4].

Post-ERCP duodenal perforations increase the length of stay depending on the type of injury, ranging from 3 days in mild cases to more than 10 days[8]. In the cases presented in this study, the mean length of stay was 9.37 days, with only 2 patients developing pneumonia during this stay. Further studies are needed to observe long-term morbidity in these patients.

Duodenal perforations during ERCP most commonly occur during sphincterotomy, guide placement, or endoscope manipulation. In this case, this is confirmed, as 75% of the perforations are related to the sphincterotomy procedure as a common factor, combined with balloon sweep or stent placement, and 25% occur with stent placement[1].

Post-ERCP duodenal injuries follow the classification established by Stapfer, and based on this, along with the patient's clinical status, a decision is made to perform either surgical or conservative treatment. The most common injury was Stapfer IV, characterized by microperforations to the retroperitoneum and presenting asymptomatically, which was managed conservatively. Of Stapfer I perforations, 100% required surgical intervention with primary closure of the injury[2,3]. Laforgia et al.[3] state that surgical intervention should be performed within a matter of 2 to 8 hours if there is no improvement and within 24 hours of the procedure. At Hospital Juárez de México, the mean time from the study to surgical intervention is 10 hours[2]. Although the terms for early and late diagnosis are not yet established, the first 28 hours are considered crucial for diagnosing perforations. Based on this, it can be determined that at Hospital Juárez de México, duodenal perforations post-ERCP are not only diagnosed in a timely manner but also receive timely treatment[1]. Cirocchi et al.[6] describe that early surgical treatment is defined within the first 24 hours for Stapfer I perforations and late when surgical treatment occurs > 24 hours. Therefore, it is confirmed that at Hospital Juárez de México, early surgical treatment is achieved for Stapfer I perforations[5].

During ERCP, duodenal perforation may or may not be diagnosed, and therefore, 37% of cases did not require additional studies for diagnosis. The usefulness of computed tomography is significant, as it diagnosed 63% of cases where there was suspicion of injury, and patients were asymptomatic[10].

Surgical treatment that can be implemented for these perforations may include primary closure or primary closure plus omental patch as diversion. At Hospital Juárez de México, 100% of cases that required surgery received primary closure of the perforation[2].

Of note that 30% of cases intervened within the first 24 hours require multiple surgeries; this study only evaluated the first surgical procedure performed during the initial surgical event, leaving room for longer-term follow-up[5].

Of note that Hospital Juárez de México is a teaching hospital, and most endoscopic procedures are performed by residents in training, under the supervision of an expert in the procedure. However, the prevalence of post-ERCP perforation is comparable to the statistics of other national and international centers. It should also be mentioned that during the study period, Hospital Juárez de México was a referral center during the COVID-19 pandemic, and as a result, endoscopic procedures were fewer compared to other years.

Conclusions

Duodenal perforation post-ERCP is a complication feared by surgeons and endoscopists alike, though it

has a low incidence rate. When it occurs, it increases the length of stay and patient morbidity and mortality, making it crucial to always remain vigilant.

The slow recovery of a patient undergoing ERCP should always raise suspicion of a post-ERCP complication, such as duodenal perforation. A comprehensive evaluation of the patient should be conducted, maintaining constant communication with the endoscopist to identify patients with elevated risk factors, requesting additional studies if needed, and achieving timely diagnosis of the perforation to provide appropriate treatment, tailoring it to each individual case.

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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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CASE REPORT

Case report: Buschke-Lowenstein tumor, a giant anal condyloma acuminata

Reporte de caso: tumor de Buschke-Lowenstein, un condiloma acuminado gigante anal

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Abstract

24-year-old man with positive HIV, with a giant exofitic anal condyloma, with a clinical presentation of a painfull suppurative anal condyloma with a pathology report of an in situ squamous cell carcinoma. The purpose of the investigation is a case report and the procedure was observational. The finding was a Buschke-Lowenstein tumor.

Keywords: *Buschke-Lowenstein tumor. Papillomavirus. Condyloma acuminata.*

Resumen

Varón de 24 años, con infección por el virus de la inmunodeficiencia humana, que presenta una tumoración exofítica, dolorosa y supurativa, con reporte positivo de virus de papiloma humano y reporte histopatológico de carcinoma espinocelular sin evidencia de diseminación (in situ). El propósito de la investigación es un reporte de caso y el procedimientos fue observacional. El hallazgo fue un tumor de Buschke-Lowenstein.

Palabras clave: *Tumor de Buschke-Lowenstein. Virus del papiloma humano. Condiloma acuminado.*

Introduction

Giant condyloma acuminatum, or Buschke-Lowenstein tumor, is considered a rare presentation of human papillomavirus (HPV) infection, characterized by a large, slow-growing, exophytic, cauliflower-like verrucous lesion, primarily in immunosuppressed patients[1].

Initially described by Buschke in 1896 and later by Lowenstein in 1925, cases have been reported in various anatomical locations such as the mouth, penis, scrotum, vulva, vagina, perianal area, and anorectal region. It has a higher incidence in men vs women (3:1)[2].

The tumor has been associated with HPV types 6 and 11, which are recognized as low-risk oncogenic due to their minimal malignancy potential. However, there is a possibility of co-infection with high-risk types, especially 16 and 18, which have evidence of oncogenesis and development of anorectal cancer[3].

Currently, there are several available treatment options for this tumor presentation, mainly due to its proximity to important structures and its biological behavior, which is not fully understood. Most authors recommend early disease control through radical excision and, if necessary, abdominoperineal resection in

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cases of recurrence, pelvic invasion, or malignant transformation[4].

Case report

A 24-year-old male, recently diagnosed with human immunodeficiency virus (HIV) and on antiretroviral treatment, began experiencing symptoms 13 months prior to consultation, including progressive volume increase in the perianal region, which was painless, firm, and immobile. One month before admission, he reported exacerbation with difficulty walking, defecating, and sitting, along with pain, bleeding, and discharge through the lesion, leading him to seek medical consultation. Upon initial assessment, the patient was hemodynamically stable, with an ectomorphic build, and had a cauliflower-like verrucous tumor in the perianal region, approximately 12 cm in horizontal diameter and 8 cm in vertical diameter, with purulent, fetid discharge (Fig. 1). Laboratory tests were requested and reported within normal ranges; viral load was undetectable. An outpatient surgical resection of the lesion along with anoscopy was planned. As part of the protocol due to the COVID-19 pandemic, a polymerase chain reaction (PCR) test for SARS-CoV-2 was requested, which turned out negative. The procedure was performed under epidural block, with complete resection of the lesion, leaving resection margins of 1.5 cm to the periphery and 1 cm in depth (Fig. 2). A specimen weighing approximately 600 g was obtained (Fig. 3) and sent for pathological examination. The patient was admitted to the general surgery ward for ongoing monitoring.

Analgesics and antibiotics were started, and wet dressings were applied to the wound frequently for 4 hours. The patient was discharged with follow-up by the general surgery clinic. One week later, the surgical wound was in the granulation process with no satellite verrucous lesions, and the patient reported an improvement in quality of life.

The histopathological report was superficial squamous cell carcinoma (in situ).

Discussion

Condyloma acuminatum is the most widespread viral sexually transmitted disease worldwide. It is associated with HPV types 6 and 11, which are highly contagious and transmitted predominantly through anogenital and oral sexual contact. This phenomenon is often attributed to early sexual initiation and a high

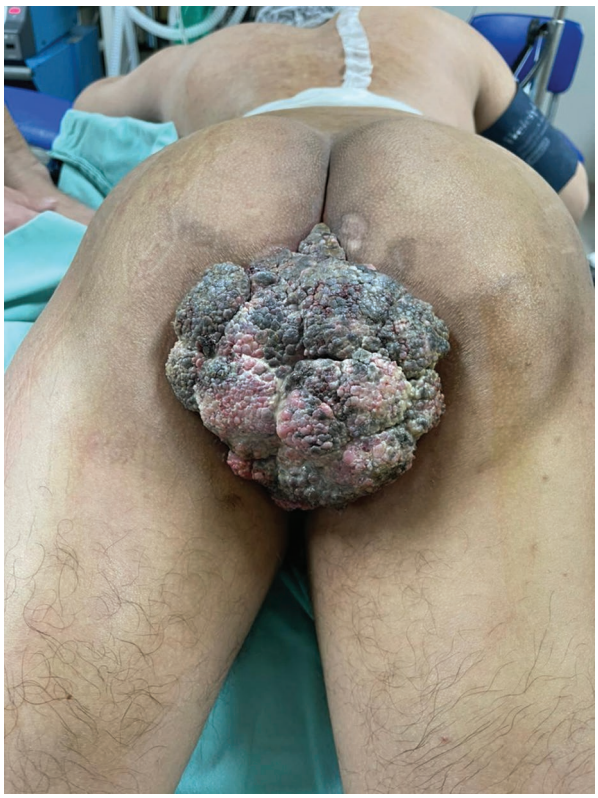

Figure 1. *Physical examination of exophytic tumor located in the perianal region.*

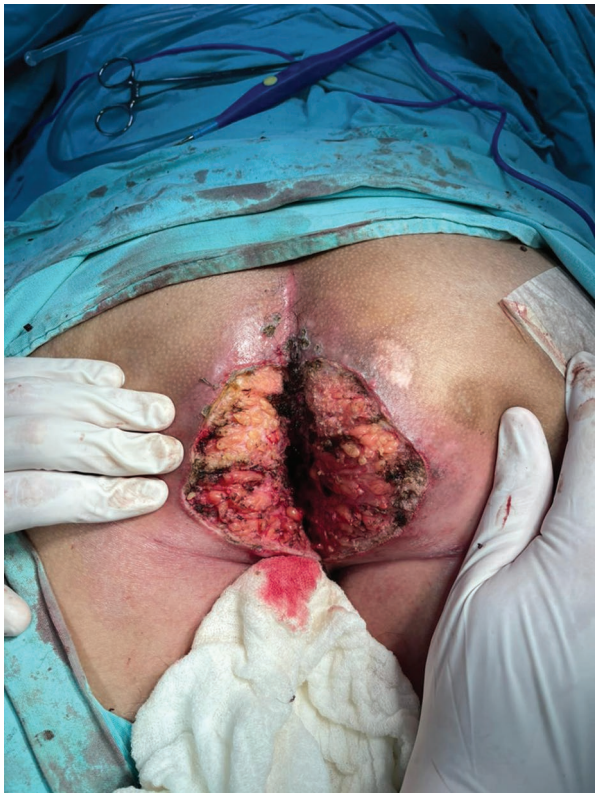

Figure 2. *Postoperative image following complete resection of the exophytic perianal tumor.*

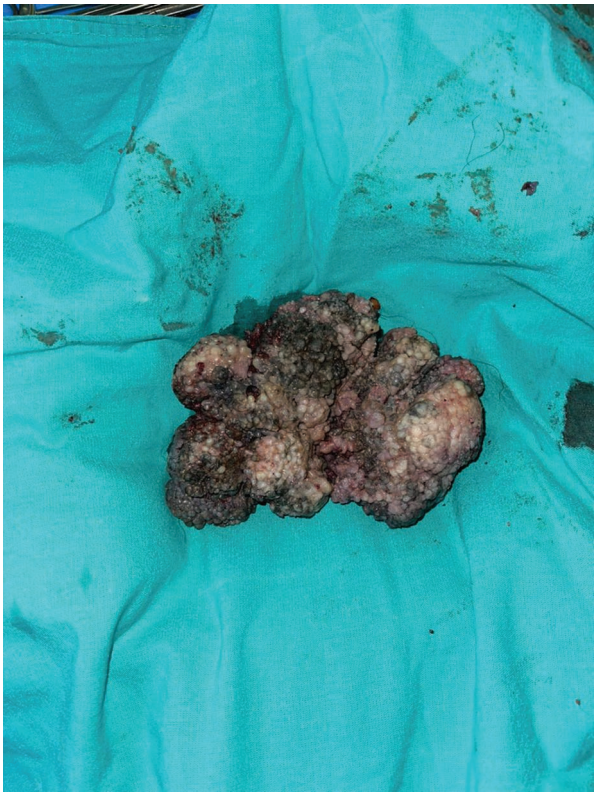

Figure 3. *Specimen from the resection of the exophytic perianal tumor.*

number of sexual partners. While most cases regress spontaneously, a small percentage of individuals experience long-term persistence of warts, influenced by risk factors such as immunosuppression, age, and co-infection with other high-risk HPV types (especially 16 and 18). This phenomenon could be considered a precursor to more aggressive lesions, such as giant condyloma acuminatum or Buschke-Lowenstein tumor[5].

Buschke-Lowenstein tumor is considered by some authors as a benign lesion with carcinomatous features, while others view it as an intermediate condition between condyloma acuminatum and squamous cell carcinoma, presenting a high rate of recurrence (66%), a high rate of malignant transformation (56%), and a 20% mortality rate[5].

Typically, the malignant transformation of this giant condyloma results in a verrucous carcinoma, which is a well-differentiated, low-grade variant of squamous cell carcinoma. Although it appears benign histologically, with minimal atypia and few mitotic cells, it behaves aggressively and destructively on a locoregional basis. It rarely presents metastases to regional or distant lymph nodes. Most cases are not recognized as malignant due to the absence of epithelial dysplasia and stromal invasion in early stages[6]. Our patient presented with a malignant tumor diagnosed histologically as squamous cell carcinoma. The malignant transformation rate reaches 20% in condyloma acuminatum and up to 56% in Buschke-Lowenstein tumors[7].

Clinical management should be preceded by a comprehensive clinical and pathological analysis to determine the extent and degree of tumor invasion[8].

In isolated cases, various treatment modalities have been used. In a report of 42 cases, Chu et al.[9] suggest surgical excision of the tumor with wide margins, with or without adjuvant chemotherapy is the gold standard for Buschke-Lowenstein tumors.

Subsequent treatment with radiotherapy, immunotherapy, antiviral therapy, or chemotherapy should be individualized for each patient, depending on tumor extent and histopathological report.

The treatment administered in our case was initially surgical, and to date, at the last follow-up consultation, there is no clinical evidence of tumor recurrence[10].

Conclusions

Buschke-Lowenstein tumor has a high rate of recurrence and malignant transformation, leading to the development of squamous cell carcinoma. Pre-treatment clinical and pathological diagnosis is essential for selecting the appropriate therapy. Wide-margin surgery, with or without other treatment modalities, is effective for controlling the disease. Long-term follow-up is necessary for cases of recurrent condylomatosis resistant to conventional treatments or with evidence of clinical and histological recurrence.

Funding

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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

Sigmoid volvulus and descending colon adenocarcinoma, a double cause of intestinal obstruction: a case report

Vólvulo del sigmoide y adenocarcinoma de colon descendente, una doble causa de obstrucción intestinal: un reporte de caso

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Abstract

Large bowel obstruction is caused by colorectal cancer, diverticular disease or volvulus. The latter is caused by rotation of the intestinal loop on its own mesenteric axis, and occurs in the sigmoid colon (80%) and in the cecum (15-20%) Its management includes devolution by colonoscopy or surgery. Malignant bowel obstruction is the initial presentation in 7-29% of colorectal cancer, and its optimal treatment is controversial. We describe a clinical case of a double obstructive lesion and its surgical approach, an unusual presentation that poses a diagnostic and medical-surgical management challenge.

Keywords: *Sigmoid volvulus. Sigmoid cancer. Colonic obstruction.*

Resumen

La obstrucción del intestino grueso es causada por cáncer colorrectal, enfermedad diverticular o vólvulo. Este último, por la rotación del asa intestinal sobre su propio eje mesentérico, y se da en el colon sigmoide (80%) y en el ciego (15-20%). Su manejo incluye devolvulación por colonoscopia o quirúrgica. La obstrucción intestinal maligna es la presentación inicial en el 7-29% del cáncer colorrectal, y su tratamiento óptimo es controvertido. Describimos un caso clínico de una doble lesión obstructiva y su abordaje quirúrgico; una presentación inusual que conlleva un reto diagnóstico y de manejo médico quirúrgico.

Palabras clave: *Vólvulo sigmoideo. Cáncer de sigmoide. Obstrucción colónica.*

Introduction

Colon volvulus is the third leading cause of intestinal obstruction worldwide and occurs in 2 main locations: the sigmoid colon, accounting for 80% of cases, and the cecum, accounting for 15% up to 20% of cases[1]. On the other hand, malignant bowel obstruction occurs in 8% up to 29% of patients with colorectal cancer[2] and can be its presenting feature in up to 80% of cases, with distal colon neoplasms (below the splenic flexure) being the most common presentation (70%)[2]. However, a volvulus associated with an unrelated tumor lesion is an unusual presentation that poses a diagnostic and surgical management challenge for these patients.

We present the case of a patient with bowel obstruction, with an intraoperative finding of a neoplastic lesion in the descending colon, associated with a

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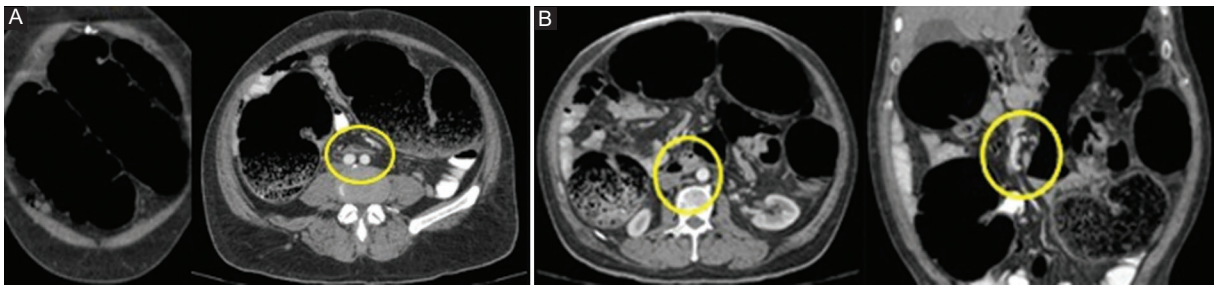

Figure 1. *Computed tomography of the abdomen.* **A:** *transition zone at the junction of the descending colon and sigmoid.* **B:** *focal, circumferential thickening of a short segment of the descending colon forming an endoluminal mass.*

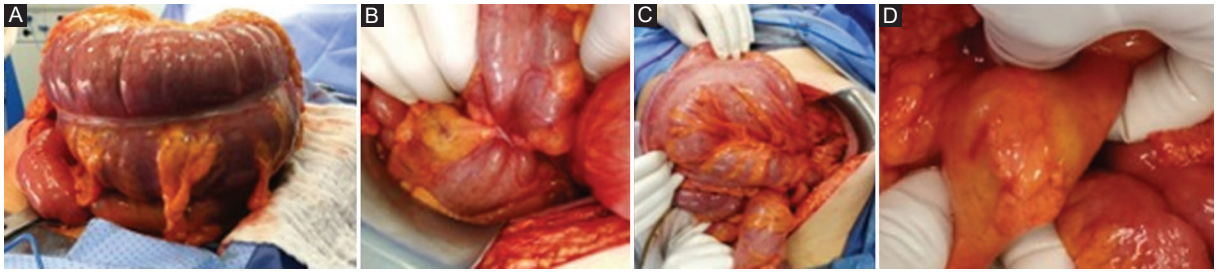

Figure 2. *Intraoperative findings.* **A:** *critical dilation of the transverse colon.* **B:** *100% stenosing napkin-ring tumor in the descending colon.* **C:** *sigmoid colon volvulus with dilation.* **D***: lymph node conglomerate at the root of mesocolon.*

sigmoid volvulus, causing a secondary obstructive process. In this case, the descending colon tumor was not the cause of volvulation.

Case report

A 63-year-old man presented with a 5-day history of abdominal distension, absence of bowel movements, and flatus. Physical examination revealed the presence of a distended abdomen with decreased bowel sounds, tympanic to percussion, and no relevant findings or evidence of bleeding on rectal examination.

Initial studies showed mild leukocytosis with neutrophilia, and abdominal x-rays revealed significant distention of large bowel loops without distal gas, prompting a contrast-enhanced abdominal CT scan, which revealed a coffee bean sign, and a transition zone at the junction of the descending colon and sigmoid colon with retractive changes suggestive of possible neoplastic involvement, causing retrograde dilatation of large bowel loops, reaching a diameter of up to 95 mm in the transverse colon and 147 mm in the cecum, with competence of the ileocecal valve (Fig. 1).

The patient was taken for exploratory laparotomy, which revealed critical dilatation of the transverse colon without evidence of ischemia of the bowel wall. A napkin-ring stenosing tumor was found in the descending colon, causing 100% obstruction and retrograde dilation of the transverse, ascending, and cecal colon. At sigmoid level, a volvulus with twisting and dilatation was observed. Carcinomatosis foci and Blummer's shelf metastatic foci were noted in the pouch of Douglas and the mesentery of the ascending colon, with a 3 cm × 4 cm lymph node mass (Fig. 2).

Sigmoid colon devolvulation with mesosigmoidoplasty, decompression of the transverse colon with a Nelaton tube, decompression of the rectum with an endorectal tube, and loop colostomy of the transverse colon were performed. The patient had a satisfactory postoperative recovery with early discharge on day 4, without readmission or complications. Histopathological study revealed the presence of fibroadipose tissue with moderately differentiated metastatic adenocarcinoma of the colon, with non-mutated KRAS and NRAS.

Discussion

In the case of a double obstructive lesion, as evidenced in our case report (neoplastic obstruction plus sigmoid volvulus), decision-making is crucial for both

Table 1. Cases of neoplastic lesions with concomitant obstructive process

Authors	Year	Patient age (years)	Sex	Volvulus location	Tumor location	Surgical management
Lee et al.[3]	2015	50	Female	Sigmoid	Rectum	Ileostomy and anterior resection of rectum
Mortensen and Hoffman[4]	1979	36	Female	Transverse	Hemartoma	Decompression, devolvulation, and colopexy
Meyers et al.[5]	1972	54	Male	Cecum	Left colon carcinoma	Cecal volvulus detorsion and transverse colostomy
Figiel and Figiel[6]	1953	80	Female	Ascending colon	Splenic flexure carcinoma	Cecectomy
Wecksell and Gordon[7]	1979	80	Male	Ascending colon	Transverse adenocarcinoma	Devolvulation, right hemicolectomy, and primary anastomosis
Aras et al.[8]	2015	80	Male	Sigmoid colon	Sigmoid colon cancer	Total colectomy and Hartmann's procedure

recovery and the patient's clinical and oncological prognosis. Currently, few cases of neoplastic lesions occurring concomitantly with an obstructive process are known, which could guide health care professionals in their management[3-8] (Table 1).

The most common site of colonic volvulus is the sigmoid, accounting for 50% up to 90% of colonic volvulus cases. Endoscopic devolvulation is the preferred management in cases of hemodynamic stability and absence of peritonitis, as it allows the evaluation of mucosal viability and resolution of the malrotation within the same procedure. However, the risk of recurrent volvulus, which occurs in up to 67% of cases, must be considered[9]. Therefore, definitive management with colectomy with or without anastomosis during the same hospitalization is advised. In 2018, Dolejs et al.[9] conducted a comparative analysis between colectomy with primary anastomosis without proximal diversion and colectomy with terminal colostomy (Hartmann's procedure), finding similar outcomes in terms of morbidity and mortality between the 2 procedures.

Despite this, Hartmann's colostomy remains one of the preferred management options regardless of the clinical scenario. Of note that in cases of hemodynamic instability or signs of peritonitis, the management must undoubtedly be surgical, with a sigmoidectomy following the acute phase of the volvulus, as recommended by the American Society of Colon and Rectal Surgeons[10], to prevent recurrence. If surgical resection is not possible, mesosigmoidoplasty or sigmoidopexy is recommended.

Nevertheless, the most effective approach for surgical treatment of sigmoid volvulus has long been a matter of controversy. With the advent of laparoscopy, minimally invasive surgery has gained ground due to its short- and mid-term benefits. This was demonstrated by Lee et al.[10], who compared postoperative outcomes between laparoscopic and open surgery in patients with sigmoid volvulus in elective or emergency surgery, showing a higher rate of postoperative complications, greater need for a stoma, and longer hospital stay in the emergency open surgery approach compared to elective laparoscopic surgery after sigmoid decompression.

Malignant bowel obstructions are often the initial presentation of colorectal cancer in 8% up to 29% of patients[2,11], representing a common cause of emergency surgery. The most common site of obstruction is the sigmoid colon and typically presents in advanced stages of the disease.

Conventional treatment for malignant bowel obstruction has been resective surgery, adhering to oncological principles and based on 3 therapeutic principles: resection of the tumor lesion with or without primary anastomosis, proximal colostomy, and subsequent stoma closure. Various surgical options are available, including primary resection and anastomosis with or without protective ileostomy, right, left, near-total, or total colectomy with ileocolic or ileorectal anastomosis, and palliative management with colostomy with or without resection of the lesion.

In cases in which colostomy is chosen, the Hartmann technique is the most widely used, allowing resection of the affected segment without primary anastomosis, with a shorter operative time in the context of emergency surgery and avoiding the morbidity associated with anastomosis. However, of note that closure requires a second surgical stage, with a morbidity rate of 5% up to 57% and mortality from 0% up

to 34%. Due to comorbidity (severe adhesion syndrome or progression of oncological disease), only 60% achieve adequate closure.

In the last 2 decades, endoscopic decompression with stenting for palliation or as a bridge therapy to surgery with curative intent has been proposed to convert emergency into elective surgery, significantly reducing the risk of adverse events and need for a temporary stoma[9,12-15].

Of note that after stenting, the initiation of chemotherapy should be evaluated to reduce the risk of tumor growth. Cases must be carefully selected due to the long-term risk of perforation and stent migration[13,14].

Transanal drainage tubes are a therapeutic option in cases of malignant bowel obstruction. They have demonstrated a success rate of up to 80%, with a serious complication rate, such as perforation, under 5%[16]. A meta-analysis conducted by Xu et al.[16] compared the effects of metal stents and endorectal tubes in relieving obstructive symptoms in patients with colorectal cancer obstruction and found no statistically significant difference in terms of technical success. However, higher clinical success and a lower complication rate were observed with the use of metal stents.

Conclusions

The choice of surgical management for malignant obstruction depends on the location of the lesion, its characteristics, the presence of synchronous neoplasms, the clinical urgency, the patient's hemodynamic status, and the proposed curative or palliative management, which can be challenging for the surgeon. In our patient, a surgical approach was considered via laparotomy, and also given the intraoperative findings of critical large bowel distension with a risk of bowel perforation, associated with a double obstructive lesion, one of which was an advanced-stage neoplastic lesion due to peritoneal involvement, a palliative approach was performed. This included decompression of the colon with a Nelaton tube and endorectal tube, mesosigmoidoplasty for volvulus management, and transverse loop colostomy without resection of the tumor lesion to reduce surgical morbidity and allow the patient to undergo complementary oncological treatment. This approach allowed the patient to recover within 48 hours, with early hospital discharge and rapid initiation of oncological management.

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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

Roux-en-Y partial volvulus in biliary-digestive reconstruction in children

Vólvulo segmentario de la Y de Roux en la reconstrucción biliodigestiva en niños

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Abstract

Various complications occur after a biliary-digestive reconstruction. Volvulus of a segment of the biliodigestive loop has not been described. Two patients who underwent biliodigestive bypass, years later, began with sudden and intense abdominal pain, associated with a volvulus with necrosis of a segment of this biliodigestive loop. This complication occurred many years after the initial correction, and manifested with sudden abdominal pain without impaired liver function, as occurred in these patients.

Keywords: *Portoenterostomy. Roux-en-Y hepaticojejunostomy. Intestinal volvulus.*

Resumen

Diversas complicaciones pueden ocurrir después de una reconstrucción biliodigestiva. El vólvulo de un segmento del asa biliodigestiva no ha sido descrito. Dos pacientes operados de derivación biliodigestiva, años después iniciaron con dolor abdominal súbito e intenso, asociado a un vólvulo con necrosis de un segmento de la asa interpuesta. Se ha descrito el vólvulo de toda el asa interpuesta, pero no el de solo una pequeña porción de esta. La complicación ocurrió muchos años después de la corrección inicial y se manifiesto con dolor abdominal súbito sin deterioro de la función hepática, como sucedió en estos pacientes.

Palabras clave: *Anastomosis porto-yeyunal. Anastomosis hepático-yeyunal. Vólvulo intestinal.*

Introduction

Various complications can occur after biliodigestive reconstruction for choledochal cyst or biliary atresia[1,2]. These complications can be either medical or surgical. Among the former, cholangitis is undoubtedly the most common, reported in up to 7% of patients[3]. Other medical complications include ascites, central venous catheter thrombosis, respiratory failure, and worsening liver failure[1,4]. Surgical complications are rare[5]. Hemorrhage, originating from portal vein injury, has been reported in up to 5% of cases[6,7]. Less frequently reported are portal vein thrombosis and bleeding at the biliodigestive anastomosis[1]. Among surgical complications, there is a higher incidence rate of inguinal

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hernias in children who have undergone Kasai procedures vs the general population[7].

Complications related to the Roux-en-Y loop reported so far include intestinal obstruction due to transmesenteric herniation of the intestine[8], leak at the distal anastomosis reported in up to 3% of case[7], and even intestinal intussusception at the bilioenteric anastomosis in patients with a choledochal cyst[2]. Volvulus of the entire Roux-en-Y loop has been described for biliodigestive bypasses and bariatric diversion procedures, yet not in a segment of the loop. Additionally, volvulus of the entire loop is an early complication of this type of bypass[9-12].

The objective of the present manuscript is to report 2 cases of patients who underwent biliodigestive bypass and later presented with an acute, segmental volvulus of the interposed loop, with circulatory compromise but without cholestasis.

Case report #1

An 18-year-old female underwent a Kasai portoenterostomy at 65 days of life for type 3 biliary atresia. She had an adequate postoperative course with normalization of bilirubin levels and liver function tests by 4 months of age and received prophylactic antibiotics and steroids for 4 months after the Kasai surgery. She experienced 2 episodes of cholangitis at 12 and 26 months of age, both of which resolved with IV antibiotics. Eighteen years later, the patient presented with sudden-onset severe abdominal pain (10/10) that had been continuous for 4 hours and worsened with movement, along with nausea and vomiting of gastric contents. On physical examination, she showed signs of pain, mild dehydration, and abdominal tenderness with decreased bowel sounds. Lab test result revealed hemoglobin 14.2 g/dL, hematocrit 42.6%, leukocytes 11.2 $10^3/\mu L$, platelets 185,000, ALT 45 U/L, AST 28 U/L, GGT 45 U/L, total bilirubin 1.2 mg/dL, indirect bilirubin 0.7 mg/dL, direct bilirubin 0.5 mg/dL, and alkaline phosphatase 224 U/L. A plain abdominal X-ray showed small air-fluid levels in the left hypochondrium without signs of intestinal obstruction (Fig. 1). A contrast-enhanced abdominal CT scan with axial views from the lung bases to the pelvic cavity showed a target sign with a cystic image inside and retrograde dilation in the biliodigestive loop (Fig. 2). Diagnostic laparoscopy revealed bloody fluid and evidence of a necrotic loop (Fig. 3). Procedure was converted, and a 5 cm segmental volvulus of the biliodigestive loop caused by an adhesion, with circulatory compromise (Fig. 4) was found 10 cm away from the jejunal anastomosis. The damaged loop was resected, and a termino-terminal anastomosis was performed. Oral intake was initiated after 72 hours, and the patient was uneventfully discharged 5 days after surgery. The patient remains asymptomatic at the 1-year follow-up.

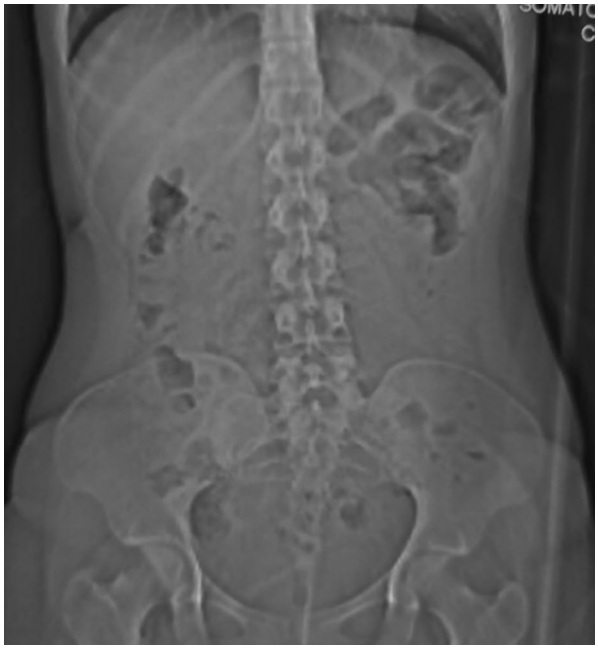

Figure 1. *Plain X-ray showing air-fluid levels in the left hypochondrium, normal air distribution, without signs of intestinal obstruction.*

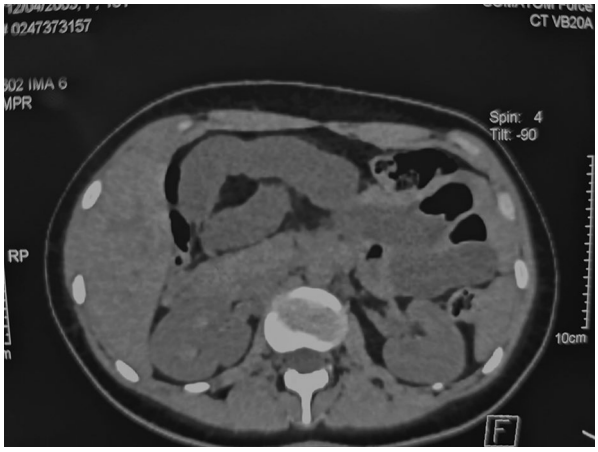

Figure 2. *Contrast-enhanced abdominal CT scan showing a target sign with a cystic interior and retrograde dilation in the biliodigestive loop.*

Case report #2

A 5-year-old boy, operated on for a type I choledochal cyst at 1 year and 7 months of age, underwent cyst resection and hepatojejunal anastomosis with an

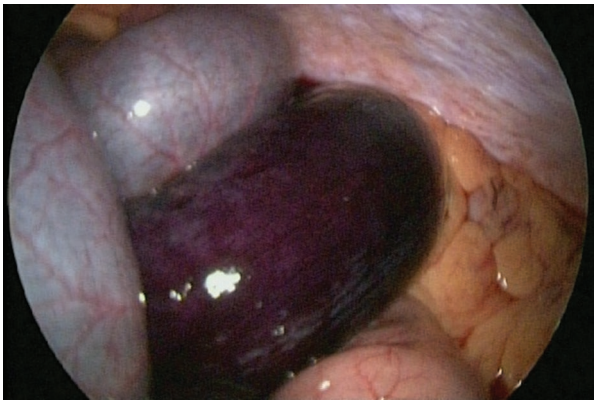

Figure 3. *Diagnostic laparoscopy showing a necrotic loop.*

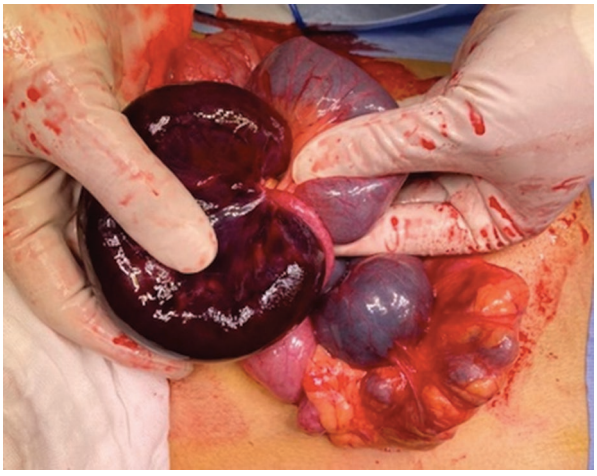

Figure 4. *Segmental volvulus of the biliodigestive loop caused by an adhesion, with circulatory compromise.*

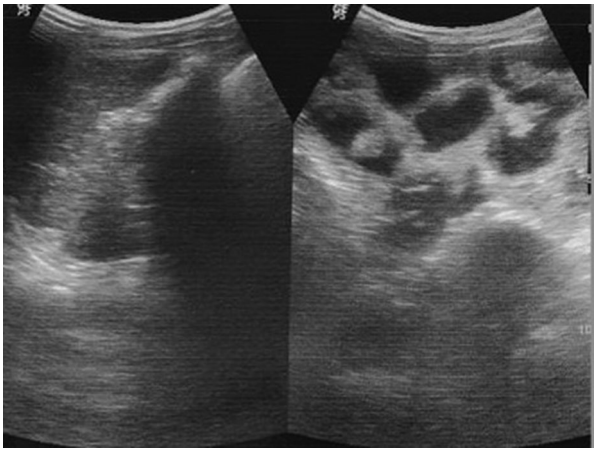

Figure 5. *Abdominal ultrasound showing intestinal dilation below the liver, in the interposed loop topography.*

adequate postoperative course. Four years later, he exhibited intense, acute colicky abdominal pain, along with nausea and vomiting of gastric contents. Lab test results revealed hemoglobin 15.3 g/dL, hematocrit 46.6%, leukocytes 9.2 $10^3/\mu L$, platelets 285,000, ALT 53 U/L, AST 26 U/L, GGT 49 U/L, total bilirubin 1.0 mg/dL, indirect bilirubin 0.5 mg/dL, direct bilirubin 0.5 mg/dL, and alkaline phosphatase 275 U/L. An abdominal ultrasound revealed intestinal dilation below the liver, corresponding to the interposed loop (Fig. 5). During laparotomy, a 5 cm segmental volvulus of the interposed loop was found (Fig. 6), which was resected, and a termino-terminal anastomosis was performed 10 cm from the jejunum. Oral intake was initiated on postoperative day 5, with good tolerance, being the patient uneventfully discharged on day 6. The patient remains asymptomatic at the 2-year follow-up.

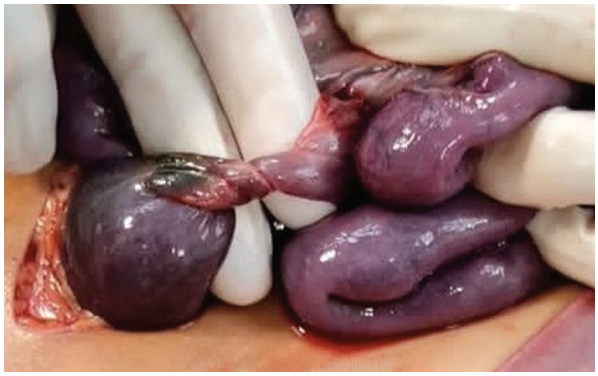

Figure 6. *Segmental volvulus of the interposed biliodigestive loop.*

Discussion

After a biliodigestive bypass, various complications can occur[1,4,6]. These can be medical or surgical, with the former being more common.[1] The most frequent is cholangitis[9,13]. Early surgical complications include hemorrhage from the portal vein, intussusception at the base of the interposed loop, portal vein thrombosis, and bleeding at the Roux-en-Y anastomosis. Late obstruction of the biliodigestive loop due to a transmesenteric hernia manifesting as cholestasis with elevated bilirubin levels has been reported in some liver transplant recipients[8]. In long-term survivors of the Kasai procedure who have obstruction of the Roux-en-Y, it shows as sudden deterioration of liver function[14,15]. The reported cases correspond to patients who had a good postoperative course—one case of biliary atresia and another choledochal cyst—with normalization of liver function tests. In both cases, the condition had a sudden onset, with the main symptom being intense abdominal pain and signs of peritoneal

irritation, but without laboratory changes. In one patient, the CT scan showed a dilated loop in the mesogastrium, which was later found to be the dilated biliodigestive loop, and in the other, the ultrasound also revealed a dilated loop below the liver. Laparoscopic exploration was chosen initially, as it was not possible to rule out other causes of acute abdomen, and a volvulus with circulatory compromise of a short segment of the Roux-en-Y loop was found. Volvulus of the entire interposed loop has been reported in both biliodigestive reconstruction and bariatric surgery[1–12], but volvulus of just one segment of the loop with circulatory compromise and late onset has not been reported, as occurred in the cases described here. This complication should be considered in patients who have undergone biliodigestive reconstruction and present with sudden and intense pain. They should be treated as soon as possible to avoid peritoneal or hepatic complications.

Funding

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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

Importance and use of corneal biomechanics and its diagnostic utility

Importancia y uso de la biomecánica corneal y su utilidad diagnóstica

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Abstract

The study of corneal biomechanics has become relevant in recent years due to its possible applications in the diagnosis, management, and treatment of various diseases such as glaucoma, keratorefractive surgery and different corneal diseases. The clinical biomechanical investigation has become of great importance in the setting of refractive surgery to identify patients at higher risk of developing iatrogenic ectasia. This review focuses on two of the technologies available for clinical use, the Ocular Response Analyzer (Reichert Ophthalmic Instruments, Buffalo, NY, USA) and the Corvis ST (Oculus Optikgergäte GmbH, Wetzlar, Germany). Both are non-contact tonometers that provided a clinical evaluation of corneal biomechanics. The fundamentals and main parameters of each device are described, as well as their use in eye surgery and the corneal biomechanical behavior in eye diseases. Finally, we will discuss the more recent Brillouin microscopy biomechanical analysis, and the integration Scheimpflug-based corneal tomography and biomechanical data with artificial intelligence to increase accuracy to detect risk of ectasia.

Keywords: *Dynamic bidirectional applanation tonometry. Contactless Scheimpflug tonometry. Corneal biomechanics.*

Resumen

El estudio de la biomecánica corneal ha cobrado relevancia en los últimos años debido a sus posibles aplicaciones en el diagnóstico, el manejo y el tratamiento de diversas enfermedades, como glaucoma, cirugía queratorrefractiva y diferentes enfermedades corneales. La investigación de la biomecánica corneal es de mucha importancia en el contexto de cirugía refractiva, pues podría identificar pacientes en riesgo de desarrollar una ectasia corneal iatrogénica. Esta revisión se centra en dos de las tecnologías disponibles para uso clínico: el Ocular Response Analyzer (Reichert Ophthalmic Instruments, Buffalo, NY, EE. UU.) y el Corvis ST (Oculus Optikgergäte GmbH, Wetzlar, Alemania). Ambos son tonómetros de no contacto que proporcionan una evaluación clínica de la biomecánica corneal. Se describen los fundamentos y los principales parámetros de cada dispositivo, así como su uso en cirugía ocular y el comportamiento biomecánico corneal en las enfermedades oculares. Finalmente, se mencionan los dispositivos más recientes de análisis biomecánico, como la microscopía de Brillouin, así como la integración de los datos biomecánicos y topográficos basados en Scheimpflug con la inteligencia artificial para aumentar la precisión en la detección del riesgo de ectasias.

***Palabras clave*:** *Tonometría de aplanación bidireccional. Tonometría Scheimpflug sin contacto. Biomecánica corneal.*

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Introduction

Corneal overview

The cornea is a transparent, avascular connective tissue that acts as a structural barrier, protecting the eye from trauma and infection. Together with the tear film, it forms the first refractive surface of the eye. The cornea measures, on average, approximately 540 μm in central thickness and gradually increases in thickness towards the periphery[1]. It also maintains a delicate and complex balance between stiffness, strength, extensibility, and overall hardness to withstand internal and external forces that stress its surfaces, distort its shape, or threaten its integrity.

The stiffness of the anterior stroma (40%) seems important in maintaining corneal curvature[2,3]. The cornea is tensile, meaning it resists stretching because collagen is an extension-resistant material that has a great ability to absorb energy through viscous friction provided by its gelatinous proteoglycan matrix.

Corneal diseases, such as keratoconus, as well as refractive surgical procedures, can alter the mechanical and optical properties of the cornea. Therefore, it is essential to understand and determine the biomechanical consequences of these alterations in corneal shape, thus gaining a better understanding of its behavior and improving the safety and efficacy profile of various ocular procedures or refractive surgical techniques.

Biomechanics

Biomechanics is defined as "mechanics applied to biology"[4]. Given the variety and complexity of the behavior of biological structures, it is better defined as the development, extension, and application of mechanics to better understand physiology and pathophysiology, as well as to improve the diagnosis and treatment of diseases[5].

The goal of biomechanical models is to describe the response of biological material to an applied load, correlating different input parameters with the output (mechanical behavior). This model depends on the internal constitution of the material studied. Its main goal in human tissues is to predict the outcomes or effects of various surgical treatments or therapies. Currently, there are different tests available that allow us to characterize corneal biomechanics both in vivo and ex vivo. Among the described in vivo methods, we have bidirectional applanation tonometry[6,7], non-contact Scheimpflug tonometry[8,9], Brillouin microscopy[10], high-frequency ultrasonographic analysis[11], and ultrasound elastography. Ex vivo methods include speckle pattern electronic interferometry[12] and radial speckle pattern interferometry.

Biomechanically, the cornea can be compared to a composite material or fiber-reinforced tissue, consisting of 2 components. The first is mainly composed of collagen fibers, making it a rigid tissue that is the primary source of load resistance, while the second is the viscous extracellular matrix surrounding the collagen fibers and formed by glycosaminoglycans and proteoglycans[13,14]. Although the primary function of the extracellular matrix is not necessarily mechanical, it significantly contributes to the mechanical properties of the tissue[15,16]. Besides absorbing mechanical stress, the extracellular matrix also determines a tissue damping capacity and is considered a thixotropic substance that changes its viscosity through shear stress[17]. For these reasons, the cornea is considered a viscoelastic tissue, with viscoelasticity being a material property that implies that the way the material behaves depends on both the deformation rate (time) and the loading and unloading phases. Unlike purely elastic materials, viscoelastic materials do not return to their original state by the same stress-strain path during unloading as during loading. This leads to behavioral differences during the loading and unloading phases in corneal biomechanics, which is not a linearly elastic structure; instead, it is described as a complex, anisotropic composite with nonlinear elastic and viscoelastic properties, as its properties are not uniform in all directions but are determined by the interaction of various materials such as collagen and a hydrophilic base substance[18].

For the purposes of this review, we will study the only 2 devices with potential for clinical use that provide corneal biomechanical data: the Ocular Response Analyzer (Reichert Technologies, Depew, NY, United States), a dynamic bidirectional applanation device, and Corvis ST (Oculus Optikerate GmbH, Germany), a dynamic Scheimpflug analyzer. Newer biomechanical analysis devices, such as Brillouin microscopy, as well as the integration of biomechanical data with artificial intelligence (AI) to enhance precision in detecting ectasia risk, will also be mentioned.

Bidirectional applanation tonometry

The Ocular Response Analyzer (ORA) uses a rapid air pulse to indent the cornea and an advanced electro-optical system to record 2 applanation pressure measurements: one while the cornea is indented and

another as the cornea returns to its normal position[7]. The difference between the 2 pressure values is called corneal hysteresis (CH: P1 - P2), which reflects the cornea viscous properties. It is important to note that the maximum applied air pressure is not constant and depends on P1, which is determined by the actual intraocular pressure (IOP) value and the structural resistance inherent to each individual[7]. Moreover, the corneal resistance factor (CRF) is an empirical measure representing the cornea elastic properties, derived from the formula P1 - Pk[2], with k being a constant determined by the relationship between applanation pressures and central corneal thickness, strongly associated with a positive correlation with CH and CRF[19] (Fig. 1).

The measurements of both corneal hysteresis and CRF appear to have adequate accuracy, according to various studies[20,21].

The primary measurements reported by the ORA have been used to measure and even predict the progression of various corneal diseases. In patients with varying degrees of keratoconus severity, CH and CRF values are lower than in healthy subjects[6]. However, other studies have found that these differences are not statistically significant[22]. Within the spectrum of glaucoma diseases, numerous studies have found that CH values are reduced in this group of patients[23]. The 2 main measurements performed by the ORA (CH and CRF) can change after refractive surgery. A systematic review and meta-analysis demonstrated that the type of refractive surgery performed alters CH and CRF to a greater or lesser extent, with less corneal strength changes in patients treated with SMILE vs those who underwent FS-LASIK or LASIK[24].

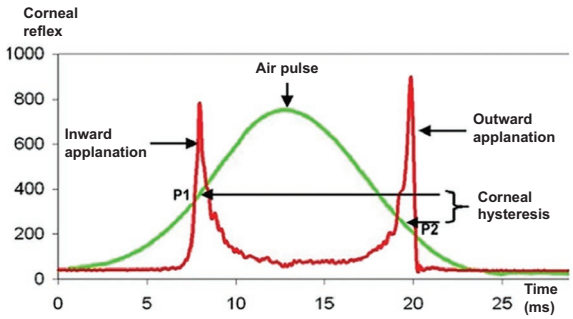

Figure 1. *Measurements of the Ocular Response Analyzer. The effect of the air pulse on the deformation of the cornea (first applanation) is recorded as the corneal signal along the Y-axis over time in milliseconds on the X-axis, where P1 represents the first moment of applanation. When the air pulse signal ceases, the cornea adopts a concave shape as the magnitude of the air pulse continues to increase. In the release phase (when the air pressure decreases), the cornea experiences a second applanation, at which point the air pulse pressure is recorded again (P2). The parameters derived from the pressure are corneal hysteresis and the corneal resistance factor.*

Non-contact Scheimpflug tonometry

Although Corneal Visualization Scheimpflug Technology (Corvis ST), like the ORA, is also a dynamic applanation device, it uses an ultra-high-speed Scheimpflug camera to record the corneal deformation process across an 8.5 mm horizontal span at 4330 frames per second (Fig. 2).

The Corvis ST is similar to the ORA in that both are non-contact instruments that use an air puff with similar dimensions and profiles. However, there are several differences, the first one being that the maximum air puff pressure is constant in the Corvis ST, while in the ORA it is variable (depending on P1); the second is that the amount of information collected on corneal deformation is greater in the Corvis ST, and finally, while the ORA main parameters are based on applanation pressures P1 and P2, the Corvis ST relies on the change in dynamic corneal response parameters (Fig. 3). The parameters that the device allows for evaluation are described in Table 1. The Corvis ST calculates corneal deformation parameters based on the dynamic inspection of the corneal response. Once the cornea starts to move backward due to the air pressure, the entire eye instantly begins a slow linear movement in the same direction, which increases once the cornea has reached its maximum displacement.

Therefore, dynamic corneal response parameters must compensate for this eye movement. The parameters described as “deformation” do not include this compensation, while those of “deflection” do account for and compensate for eye displacement.

Corneal deformation amplitude (DA) refers to the displacement of the corneal apex in the anterior-posterior direction at the moment of highest corneal concavity. The DA ratio at 1 mm or 2 mm is the central deformation divided by an average deformation at 1 mm or 2 mm on either side of the center just before the first applanation. Applanation lengths (AL) and corneal velocities (CVel) are also recorded during the indentation and return phases. Additionally, the radius of curvature at highest corneal concavity is documented, and the integrated inverse radius is the reciprocal of the radius obtained during the corneal concave state. Of note that a larger concave radius is associated with greater resistance to deformation or a stiffer cornea. Therefore, the greater the integrated inverse radius and maximum inverse radius, the lower the resistance to

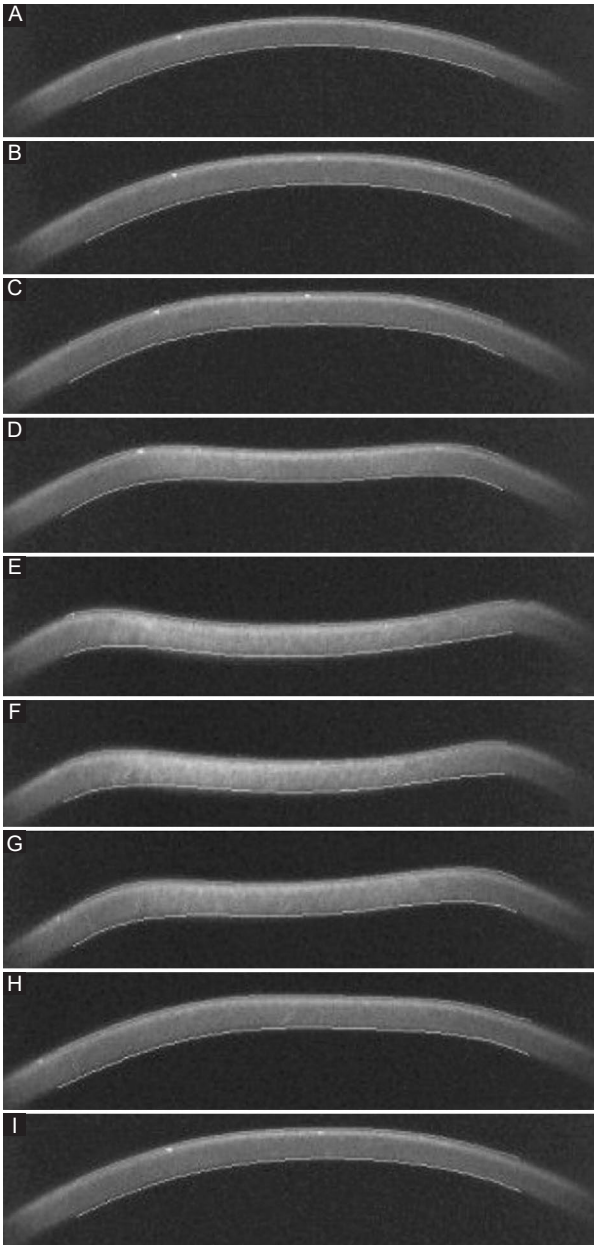

Figure 2. *Scheimpflug image from the Corvis ST during the moments of applanation: baseline* **(A)**, *deformation begins* **(B)**, *first moment of applanation* **(C)**, *onset of concavity phase* **(D)**, *moment of highest concavity* **(E)**, *oscillation period* **(F)**, *exit from concavity* **(G)**, *second moment of applanation* **(H)**, *and after the second applanation* **(I)**.

deformation and the less rigid the cornea[25]. Corneal thickness, standard Goldman-correlated IOP, and biomechanically compensated IOP (bIOP) are also recorded. Similarly, the corrected IOP is determined using compensatory formulas based on central corneal thickness (ccIOP).

Vinciguerra's report (Fig. 4) provides correlations of normal values, and the bIOP accounts for central corneal thickness and age along with deformation response parameters to reduce the effect of corneal stiffness when estimating IOP[26].

In addition to the above-mentioned parameters, the Corvis ST can measure central corneal thickness (CCT) thanks to the horizontal Scheimpflug imaging. The horizontal Scheimpflug image of the basal cornea allows for the calculation of the Ambrosio Relational Thickness over the horizontal meridian (ARTh), which consists of dividing the corneal thickness at the thinnest point by the pachymetric progression index[27]. Researchers used linear regression analysis and combined ARTh with corneal deformation parameters to generate the Corvis Biomechanical Index (CBI), which, with a cutoff value of 0.5, allows for the identification of 98.2% of keratoconus cases in normal eyes with 100% specificity[28]. Moreover, the Tomographic Biomechanical Index (TBI) combines tomographic and biomechanical information to improve the detection of ectasia.

The Corvis AT also presents parameters that function as biomarkers of corneal stiffness, such as SP-A1, which has been reported to be lower in thinner corneas[28]. The most recent development has been the introduction of the Stress Strain Index (SSI) algorithm, which allows for the detection of patients at higher risk of developing ectasia or progression after refractive surgery and provides clinical documentation of post-CXL corneal biomechanical changes[29]. Parameters that differentiate healthy corneas from keratoconus and CXL-treated ectatic corneas from non-treated ones include applanation velocity 2 (A2V), second applanation length (A2L), and the difference between first applanation length (A1L) and A2L, demonstrating their utility in monitoring post-CXL corneal changes[30].

Precision and reproducibility with the Corvis ST

Several publications in this field have reached different conclusions. Hon and Lam[8] concluded that highest concavity deformation amplitude (HCDA) and first applanation time (AT1) were the only 2 corneal distortion parameters with good reproducibility and no session differences, along with CCT. Hong et al.[31] vs the IOP of the Corvis ST with that of other devices, concluding that the Corvis ST had the best reproducibility and repeatability. Bak-Nielsen et al.[32] concluded that the following parameters had a coefficient of variation < 10%: IOP, CCT, AT1, AL1, highest concavity time (HCT), highest concavity radius (HCR), HCDA,

Table 1. Parameters obtained with the Corvis ST

Parameter	Description
Length A1 (mm)	Length of the flattened cornea during the first applanation
Speed A1 (mm/ms)	Speed of corneal deformation during the first applanation
Time A1 (ms)	Time from the start of measurement until the first applanation
IOP	Intraocular pressure measurement in mmHg
Radius DA (2 mm)	Deformation amplitude radius at 2 mm
SP-A1	Stiffness parameter at A1
SP-HC	Stiffness parameter at the highest concavity
Maximum deformation amplitude (mm)	Maximum deformation amplitude measured at the point of maximum corneal concavity. It is the sum of corneal deflection amplitude and total eye movement
Time HC (ms)	Time from the start of measurement until highest corneal concavity is reached
HCDeflAmp (mm)	Corneal deflection amplitude at the point of highest corneal concavity
Peak distance (mm)	Distance between corneal peaks at the point of highest corneal concavity
Radius HC (mm)	Corneal curvature radius during highest corneal concavity
InvRadMax (1/mm)	Maximum inverse radius
ARTh	Ambrosio Relational Thickness across the horizontal meridian, based on the thickness profile from the temporal-nasal direction
Length A2 (mm)	Length of the flattened cornea during the second applanation
Speed A2 (mm/ms)	Speed of corneal deformation during the second applanation
Time A2 (ms)	Time from the start of measurement until the second applanation
bIOP	Biomechanically corrected IOP. A measurement of IOP that is less dependent on corneal biomechanics and thickness
Maximum total eye movement (mm)	Length of the total anteroposterior linear movement of the entire eye following maximum corneal displacement
Maximum total eye movement (ms)	Time taken for the total anteroposterior linear movement of the entire eye following maximum corneal displacement
SSI	Stress-Strain Index
CBI	Corvis Biomechanical Index: general biomechanical index for detecting keratoconus
TBI	Tomographic Biomechanical Index: combines tomographic and biomechanical data to improve ectasia detection
Integrated radius	Area under the inverse concave radius vs time curve
Inverse concave radius	Inverse curvature radius during the concave deformation phase
Corneal thickness	Measurement of corneal thickness in mm
Normal curvature radius	Corneal curvature radius in its natural state (in mm)
HC curvature radius	Corneal curvature radius at the point of highest concavity during the air pulse (in mm)

highest concavity deflection length, highest concavity deflection amplitude (in millimeters and milliseconds), and AT2. Chen et al.[33] compared 40 healthy eyes with 42 post-PRK eyes, finding similar results, with healthy eyes showing an intraclass correlation coefficient (ICC) ≥ 92% for IOP, CCT, and AT1, followed by HCDA (ICC, 0.88), curvature radius (ICC, 0.70), A2V (ICC, 0.65), and maximum concavity time (ICC, 0.64). The rest

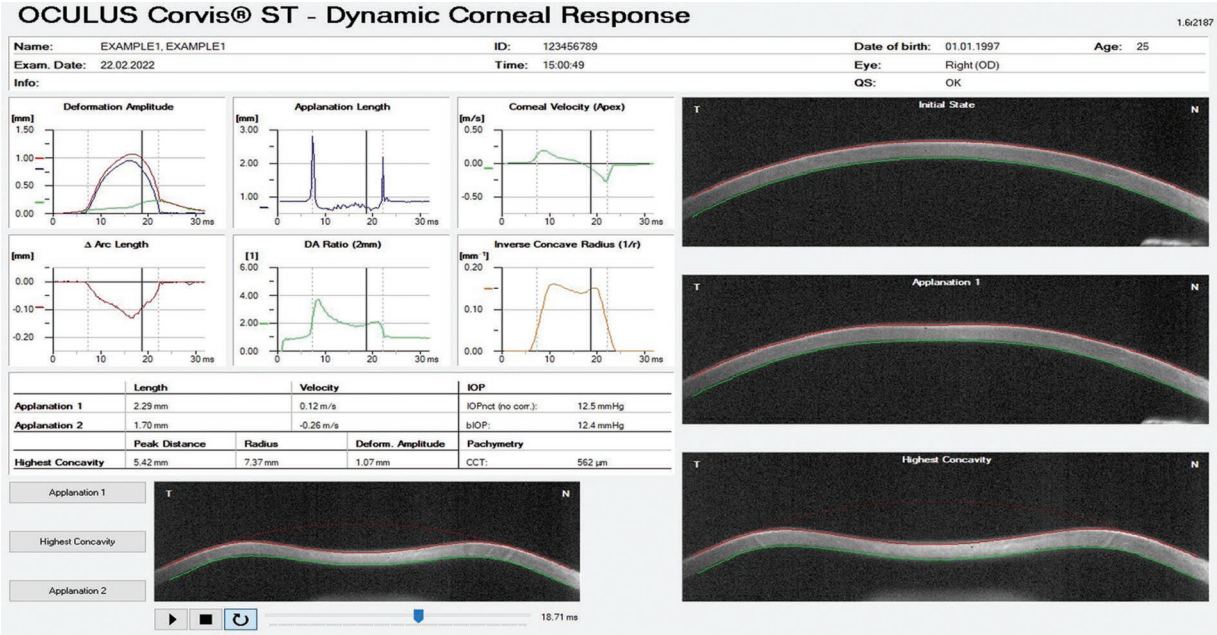

Figure 3. *Standard parameters of the Corvis ST. The image shows deformation amplitude, applanation lengths, corneal velocities, radius of curvature at highest corneal concavity, corneal thickness, and intraocular pressure during the phases of indentation and recovery.*

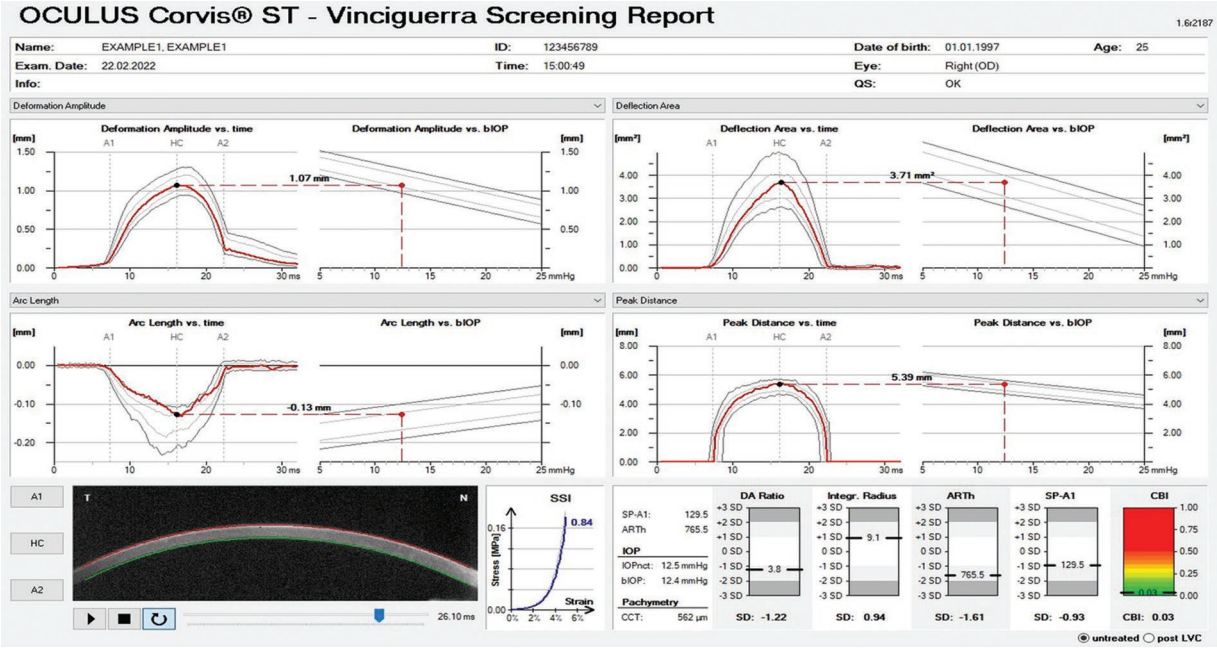

Figure 4. *Vinciguerra report. This screen shows the correlation between normal values and biomechanically adjusted intraocular pressure (IOP). A calibration factor is used to calculate the IOP based on the pressure at the first applanation. It allows for the calculation of the Ambrosio Relational Thickness over the horizontal meridian (ARTh) and the Corvis Biomechanical Index (CBI).*

of the parameters showed wide variation coefficients and low ICCs. In post-PRK patients, the highest repeatability was observed in IOP, CCT, AT1, and HCDA (ICC ≥ 90), followed by AT2 (ICC, 0.89), A2V (ICC, 0.79), HCT (ICC, 0.66), and curvature radius (ICC, 0.63). Similarly, Yang et al.[34] concluded that the repeatability of parameters is acceptable in both normal and keratoconus eyes.

Corvis ST in corneal diseases

Yang et al.[34] studied 77 eyes with keratoconus from 47 patients and 77 right eyes of 77 normal individuals. They concluded that the new parameters of the Corvis ST (inverse maximum radius, DA ratio max [2 mm], Pachy slope, DA ratio max [1 mm], ARTh, Integrated radius, SP-A1, and CBI) can diagnose keratoconus. Similar findings were made by Ren et al.[35], who stated that the results of the new parameters obtained in subclinical keratoconus were significantly different from those of normal controls and keratoconus eyes; thus, they could be used to distinguish keratoconus and subclinical keratoconus from normal eyes. Additionally, Liu et al.[36] and Vinciguerra et al.[37] claimed that combining this technology with corneal tomography improves the accuracy for detecting subclinical keratoconus, with TBI and CBI being the most valuable indices due to their high sensitivity and specificity. Conversely, Tian et al.[38] and Ali et al.[39] found that HCDA may be useful in combination with other parameters for the diagnosis and management of keratoconus patients.

A meta-analysis published by Wang et al.[40] determined that corneal biomechanics are altered in patients with diabetes mellitus, associated with increased values of CH, CRF, ccIOP, and Goldman-correlated IOP.

When studying the effects of glaucoma on corneal biomechanics, diverse results have been found. In a study published by Jung et al.[41], patients with glaucoma showed significantly less deformable corneas than controls, with differences depending on the severity of glaucoma. This contrasts with information published by Pradhan et al.[42], who stated that the biomechanical parameters obtained by the Corvis ST do not differ between individuals with pseudoexfoliation glaucoma, primary open-angle glaucoma, and controls after IOP adjustment.

Corvis ST in ocular surgery

Zarei-Ghanavati et al.[43] studied 74 patients, 37 undergoing SMILE and 37 PRK, and concluded that both procedures significantly alter the biomechanical properties of the cornea; however, the changes were more prominent after SMILE.

Bak-Nielsen et al.[44] stated that there are no significant differences in deformation resistance between keratoconic eyes and keratoconic eyes that underwent CXL. Lanza et al.[45] reported that deformation resistance was still lower in post-CXL keratoconic corneas compared to those that had not undergone CXL, and it also took longer to return to the flattened position and recover their original shape. Similar results were presented by Tomita et al.[46], who compared corneal deformation before and 1 year after conventional and accelerated CXL treatment, finding no significant differences between the 2 groups before and after treatment.

Lanza et al.[45] found that PRK-treated corneas exhibited similar resistance to deformation as the normal eyes studied, suggesting that PRK-induced corneal thinning does not change the corneal biomechanical properties. In contrast, Pedersen et al.[47] reported that flap-based keratorefractive procedures, such as LASIK and ReLEx FLEX, and flap-free procedures, such as ReLEx SMILE, change the CH and CRF vs the control group, resulting in a similar reduction in corneal biomechanics, except for CH time, which was shorter in LASIK-treated patients.

Brillouin optical microscopy

Brillouin optical microscopy is a recent technique used to measure corneal biomechanics in vivo through light scattering analysis and mapping corneal biomechanical properties in 3 dimensions. This method allows for the determination of intrinsic viscoelastic properties independently of structural information and applied pressure.

The cornea exhibits non-linear stress-strain behavior, indicating that its modulus is not constant. The tangent modulus, which represents the change in stiffness with tension or applied pressure, gradually increases.[48] Seiler et al.[49] conducted a study using Brillouin spectroscopy to investigate the impact of age on corneal stiffness, finding statistically significant differences between normal corneas and keratoconus. However, the accuracy of initial findings reported using this technique is relatively limited and requires additional validation and refinement, as advanced keratoconus corneas are clearly visible on Brillouin maps as regions with significantly reduced Brillouin shift. However, the correspondence between Brillouin maps and pachymetry and topography is less clear in early-stage keratoconus corneas, and Brillouin shifts correlate weakly with morphological parameters such as thickness and curvature. The large variations may originate from physiological factors and possibly additional factors associated with keratoconus pathogenesis[50].

Conclusions

Corneal biomechanics is a topic of great interest in modern ophthalmology research. Novel tools, such as Brillouin optical microscopy, provide information on the biomechanical properties of the cornea. However, most clinical data are related to the biomechanical response to non-contact tonometry. Despite substantial advances over the past 2 decades, in vivo characterization of corneal biomechanical response is influenced by intraocular pressure and central corneal thickness, which, as measured by Corvis ST, was also validated as not significantly different compared to ultrasonic pachymetry, the reference method. However, as with ORA, it was shown that central corneal pressure and thickness were correlated with the measured parameters and could, therefore, be potentially confounding. Even in light-scattering measurements, such as Brillouin optical microscopy, corneal hydration could be a confounding factor[51].

However, new developments, such as the strain-deformation index provided by the Corvis ST, have managed to estimate stiffening after CXL treatment.

Understanding corneal biomechanics would be useful in various clinical applications, including glaucoma management, assessing the risk of ectasia, and determining the degree and depth of CXL. The integration of tomographic and biomechanical data has shown potential for improving accuracy in detecting ectatic diseases and identifying susceptibility to developing this complication after corneal laser vision correction. Additionally, integration with other data, such as ocular wavefront, axial length, and segmented layer tomography (epithelial) and microlaminar (Bowman), is also promising. We foresee continued and accelerated research and development in this field, which will further integrate corneal multimodal imaging, biomechanics, molecular biology, and genetics. In this environment, with an overwhelming amount of clinical data, AI will play a fundamental role in improving patient care efficiency. Since its introduction in 1956, AI has become increasingly relevant in ophthalmology, offering numerous potential applications. AI algorithms leverage computer processing power to simulate and enhance human interpretation, streamlining data analysis and clinical decision-making. A pioneering study used a neural network based on 11 indices from Placido disc topography to perform an automated interpretation of corneal maps. Although this model achieved correct classification for all maps in the training set, AI has had an even greater impact on detecting and treating keratoconus and other corneal ectatic diseases. This advancement has led to a paradigm shift in the management of these diseases, especially with the introduction of techniques like cross-linking and intracorneal ring segments. Early or subclinical detection of corneal ectatic diseases is of paramount importance, particularly for identifying patients at risk of developing ectasia after undergoing laser corneal refractive surgery. TBI has been developed using AI, demonstrating high sensitivity and specificity for detecting these diseases in external validation studies.

Despite these advances, some research has found relatively low sensitivity in detecting abnormalities in subclinical keratoconus cases. This indicates the need to improve sensitivity to more effectively identify mild or subclinical cases. AI is playing an increasingly important role in ophthalmology, particularly in the early detection and treatment of corneal ectatic diseases, and there is a focus on improving detection accuracy through the optimization of AI algorithms in biomechanics[52].

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LETTER TO THE EDITOR

Determining surgical course limitations for students during COVID-19 pandemic

Determinación de las limitaciones del curso de cirugía para los estudiantes durante la pandemia de COVID-19

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To the Editor,

We congratulate Sánchez-Balderas et al.[1] on their article about the limitations faced by students in the undergraduate general surgery course during the isolation period caused by the COVID-19 pandemic. The lag in knowledge of surgical branches has been significant. Some authors argue that surgical knowledge cannot be acquired virtually due to the lack of exposure to procedures within the operating room, while others advocate for greater use of simulation models[2,3].

Medical education has evolved during the pandemic, and there is ample evidence of the barriers and challenges faced by students[1,4,5]. Authors should reinforce the use of literature that enriches the information demonstrated in the theoretical framework. Analyzing previous evidence is essential to understanding the problem statement and recognizing advances in the development of distance surgical education.

In a proper methodological design, it should be clear whether the study will be qualitative, quantitative, or mixed. The type of variables used in the survey should preferably be of the same category. The validity of a survey that seeks to measure a student's perception is just as important as the study methodology; there are numerous tools and scales already validated in Spanish that measure aspects of learning and could have been conveniently used. Therefore, we question the decision to use a self-designed, quantitative tool that was not validated for this study, which creates a significant risk of bias. This study could have used a mixed-methods approach (qualitative and quantitative) or been entirely qualitative.

Research on medical education in Mexico is essential for developing medical education models, taking into account the needs of students and the limitations they perceive. Dr. Sánchez-Balderas' team makes a valuable contribution to our literature.

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LETTER TO THE EDITOR

Norovirus in stool of patients with SARS-CoV-2, clinical and social importance

Norovirus en heces de pacientes con SARS-CoV-2, importancia clínica y social

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To the Editor,

Diarrhea is one of the initial symptoms that can occur in SARS-CoV-2 infection (particularly with Omicron subtypes), with a mild clinical course and a duration of 1 to 3 days[1]. However, other viruses can also cause diarrhea in pediatric patients, such as norovirus, which is characterized by self-limiting diarrhea accompanied by nausea, vomiting, and abdominal pain, similar to COVID-19[2]. Considering that SARS-CoV-2 infection causes dysregulation of the immune system, this allows opportunistic infections to join the process, and noroviruses could be one of them, especially in pediatric patients. In this regard, stool samples from 123 pediatric patients aged between 2 months and 5 years with Omicron lineages BA.1, BA.2, BA.4, and BA.5, of mestizo ancestry from western Mexico, were studied. RNA was extracted from the stools to perform a real-time reverse transcriptase polymerase chain reaction (RT-PCR) test to detect noroviruses using the primers JV12Y-ATACCACTATGATGCAGAYTA and JV13I-TCATCATCACCATAGAAIGAG to amplify the norovirus RNA polymerase gene, followed by automated sequencing. Positive results were found for genotypes of the GI.1-8 group (Norwalk/68/US, Toronto 24/91/CA, VABeach/01/US) and GII.[1-17] (M7/03/US, Fayetteville/02/US) in 70.73% of cases (Table 1). The genotypic distribution was compared with that obtained from controls, which correspond to stool samples from the family members of the pediatric patients (n = 123), with RT-PCR negative for COVID-19. In controls, different genotypes of noroviruses tested positive in 16.26% (n = 20). In both cases and controls that tested positive for norovirus, no different genotypes were detected in the samples from the same person. This distribution indicates a positive association, with chi-square test = 30.3, $p < 0.0000001$, odds ratio of 1.6, confidence interval of 1.3-1.8, etiological fraction in the population of 15.9%, and etiological fraction in the exposed of 38.5%. There was intrafamilial transmission in 16.26% of cases (Table 1), with concordance in Omicron BA.2 cases of 33.3% for the Norwalk/68/US agent and 100% for the Toronto 24/91/CA genotype. In BA.4 cases, concordance with family members was 100%. In BA.5 cases, familial concordance was 100% for the Fayetteville/02/US genotype, 50% for M7/03/US, 75% for Toronto 24/91/CA, and 60% for VABeach/01/US.

The above data suggest that SARS-CoV-2 infection increases the risk of diarrhea caused by norovirus in pediatric patients. Regardless of the genotype, this is very important from both clinical and social perspectives, as diarrhea associated with gastroenteritis is one of the primary causes of medical consultation in pediatric patients. Transmission is fecal-oral, through contaminated water or food, and should be considered in the management of pediatric patients with COVID-19, as they are immunosuppressed, as well as in cases of persistent infection and also in oncological patients and immunosuppressed adults[2].

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Table 1. Distribution of norovirus in pediatric patients with mestizo ancestry and SARS-CoV-2 omicron infection

SARS-CoV-2 Omicron Subtype	Norovirus genotype	No. of positive subjects	Genotype concordance with family members
BA.1	Norwalk/68/US	0	0
	Toronto 24/91/CA	3	0
	VABeach/01/US	8	0
	M7/03/US	9	0
	Fayetteville/02/US	11	0
BA.2	Norwalk/68/US	6	2
	Toronto 24/91/CA	1	1
	VABeach/01/US	1	0
	M7/03/US	1	0
	Fayetteville/02/US	6	0
BA.4	Norwalk/68/US	1	0
	Toronto 24/91/CA	2	0
	VABeach/01/US	1	0
	M7/03/US	1	0
	Fayetteville/02/US	5	5
BA.5	Norwalk/68/US	13	0
	Toronto 24/91/CA	4	3
	VABeach/01/US	10	6
	M7/03/US	2	1
	Fayetteville/02/US	2	2
Family members of patients with SARS-CoV-2 Omicron	Norwalk/68/US	25	-
	Toronto 24/91/CA	6	-
	VABeach/01/US	16	-
	M7/03/US	0	-
	Fayetteville/02/US	0	-

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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 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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