ORIGINAL ARTICLE

Can direct bilirubin-to-lymphocyte ratio predict surgery for pediatric adhesive small bowel obstruction?

¿La relación bilirrubina directa-linfocitos puede predecir la cirugía para la obstrucción adhesiva del intestino delgado en niños?

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Abstract

Objective: *Estimating which patients might require surgical intervention is crucial. Patients with complete bowel obstructions exhibit disrupted enterohepatic cycles of bile and bacteremia due to bacterial translocation. The goal of this study was to develop a prediction index using laboratory inflammatory data to identify patients who may need surgery.* **Materials and methods:** *The patients were divided into two groups based on their management strategy: Non-operative management (Group 1) and surgical management (Group 2).* **Results:** *The indirect bilirubin, direct bilirubin, and total bilirubin were significantly higher in Group 2 than in Group 1 ($p = 0.001$, $p < 0.001$, and $p < 0.001$, respectively). The neutrophil-to-lymphocyte ratio (NLR), platelet-to-NLR (PNLR), and direct bilirubin-to-lymphocyte ratio (DBR) were significantly higher in Group 2 compared to Group 1 ($p = 0.041$, $p = 0.020$, and $p < 0.001$, respectively). In group 2, 78% have viable bowels. Resection was performed in 40% of cases, with 12% mortality and a 10-day average hospital stay. DLR performs the best overall accuracy (72%), demonstrating a well-balanced sensitivity (62%) and specificity (81%).* **Conclusions:** *This study suggested that DBR is a more accurate predictive index for surgical intervention in pediatric adhesive small bowel obstruction patients compared to NLR and PNLR, providing valuable guidance for treatment strategies.*

Keywords: *Neutrophil-to-lymphocyte ratio. Platelet-to-neutrophil-to-lymphocyte ratio. Direct bilirubin-to-lymphocyte ratio. Adhesive small bowel obstruction.*

Resumen

Objetivo: *Desarrollar un índice de predicción utilizando datos inflamatorios de laboratorio para identificar qué pacientes podrían necesitar cirugía.* **Método:** *Los pacientes se dividieron en dos grupos según su estrategia de manejo: no quirúrgico (grupo 1) o quirúrgico (grupo 2).* **Resultados:** *Las bilirrubinas indirecta, directa y total fueron significativamente más altas en el grupo 2 que en el grupo 1 ($p = 0.001$, $p < 0.001$ y $p < 0.001$, respectivamente). Las relaciones neutrófilos-linfocitos, plaquetas-neutrófilos-linfocitos y bilirrubina directa-linfocitos fueron significativamente más altas en el grupo 2 que en el grupo 1 ($p = 0.041$, $p = 0.020$ y $p < 0.001$, respectivamente). En el grupo 2, el 78% tenían intestino viable. Se realizó resección en el 40% de los casos, con un 12% de mortalidad y una estancia hospitalaria promedio de 10 días. La relación bilirrubina directa-linfocitos tuvo la mejor precisión general (72%), demostrando una sensibilidad bien equilibrada (62%) y una buena especificidad (81%).*

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Conclusiones: *Este estudio sugiere que la relación bilirrubina directa-linfocitos es un índice predictivo más preciso para la intervención quirúrgica en pacientes pediátricos con obstrucción adhesiva de intestino delgado en comparación con la de neutrófilos-linfocitos y la de plaquetas-neutrófilos-linfocitos, proporcionando una valiosa orientación para las estrategias de tratamiento.*

Palabras clave: *Relación neutrófilos-linfocitos. Relación plaquetas-neutrófilos-linfocitos. Relación bilirrubina directa-linfocitos. Obstrucción adhesiva de intestino delgado.*

Introduction

A complicated combination of cellular elements involved in inflammation and tissue repair results in post-operative adhesion development. According to the current theory, altering the serosal surfaces and being exposed to non-organic substances disrupt the mesothelium, causing a localized inflammatory reaction and an influx of fibroblasts that promote the formation of fibrin-based adhesions[1,2]. Although the actual prevalence of adhesive small bowel obstruction (ASBO) in children is unknown, reports suggest that it can range from 1.1 to 8.3%, with the majority of cases occurring during the 1st year following surgery[3-5]. Compared to adults, children have a higher lifetime risk of developing adhesion-related issues because of their age. The success rate of non-operative management has been reported to range substantially from 0 to 63%[4-6].

Estimating which patients might require surgical intervention is crucial. ASBO, a common intra-abdominal infection, is frequently associated with *Escherichia coli* and *Bacteroides fragilis*[6]. Bacteremia caused by these bacteria can lead to endotoxemia and impaired bilirubin excretion, increasing direct bilirubin (DB) levels in ASBO patients. Furthermore, patients with complete bowel obstructions exhibit disrupted enterohepatic cycles of bile and bacteremia due to bacterial translocation. These conditions contribute to both inflammation and neutrophil-to-lymphocyte ratio (NLR) and platelet-to-neutrophil-to-lymphocyte ratio (PNLR) and increased DB and direct bilirubin-to-lymphocyte ratio (DLR), levels, particularly in complete obstructions[7,8].

In this study, receiver operating characteristic (ROC) curve analysis was used to investigate the predictive value of several biomarker combinations related to the requirement for surgical treatment for ASBO.

Methods

This study comprises patients who presented with ASBO to the Pediatric Surgery Clinic at Dicle University between 2010 and 2022. The study commenced following the approval of the ethics committee (no: 211, date: April 12, 2023). Variables such as patients' age, sex, prior surgery (primary pathology), physical examination findings at the time of presentation, duration of symptoms, laboratory blood test results, radiological findings, performed surgery, viability status of the intestines, surgery duration, post-operative complications, mortality, and length of stay were retrospectively evaluated.

Some patients with ASBO were managed nonoperatively, successfully following a non-operative management approach. However, a portion of the patients required surgery. The patients were divided into two groups based on their management strategy: non-operative management (Group 1) and surgical management (Group 2). The aforementioned factors were compared between the two groups.

Inclusion criteria

Patients under the age of 18, those with a previous history of surgery, and those with consistent and accurate data in retrospective file scans were included in this study.

Exclusion criteria

Patients over the age of 18, neonates (due to highly variable laboratory parameters), and those presenting with COVID-19, upper respiratory tract diseases, or any other diseases affecting laboratory parameters beyond the diagnosis of ASBO were excluded from the study.

Clinical monitoring

All patients presenting with vomiting, absence of fecal output, and abdominal distension (Fig. 1), who had a previous history of surgery, underwent a physical examination. This was followed by laboratory blood tests. Subsequently, every patient underwent radiography (Figs. 2 and 3) and ultrasonography. Advanced imaging techniques such as computed

Figure 1. *Distended abdomen in a patient with adhesive small bowel obstruction.*

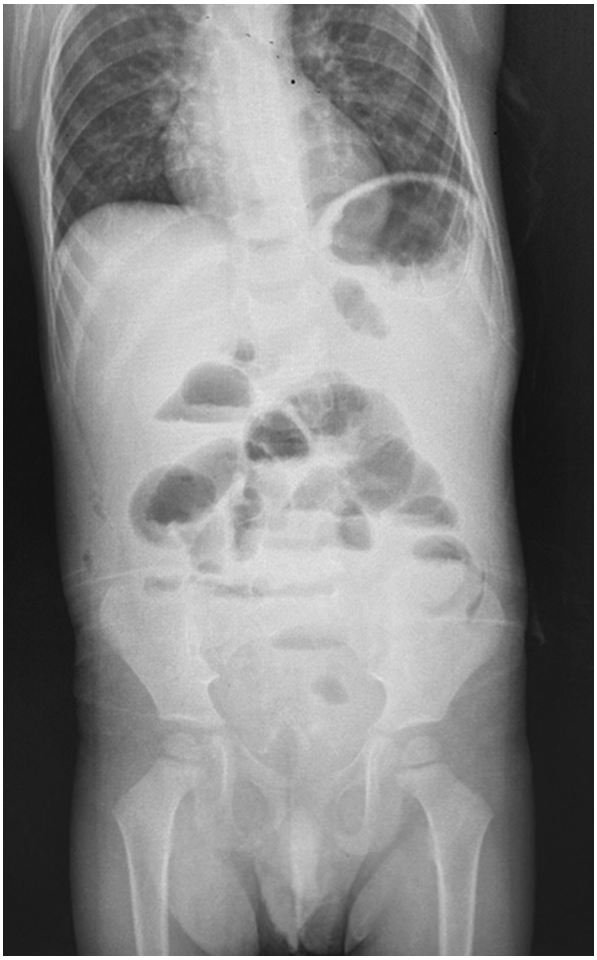

Figure 2. *Pre-opertaive radiograph from a patient who treated non-operatively (Group 1).*

tomography were utilized where necessary. Dehydrated patients, which constituted the majority of cases,

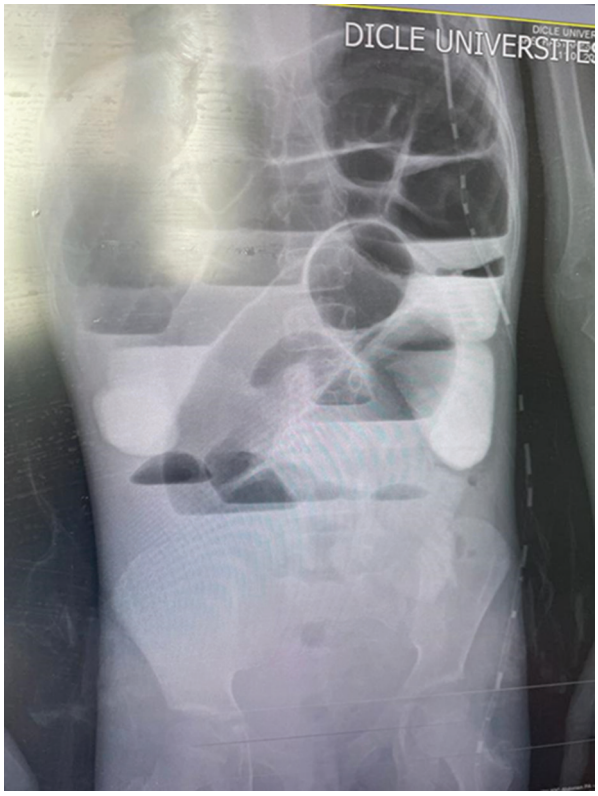

Figure 3. *Pre-operative radiograph from a patient who was treated with surgical intervention (Group 2).*

were rehydrated with 20 mL/kg of 0.09% NaCl saline. All patients were put on nil per os and a nasogastric tube was inserted. Suitable antibiotic therapy was administered, and adequate analgesia was ensured. Patients in poor general condition were monitored in intensive care. Initially, all patients were followed up with enema administration. Those patients who had gas and fecal output after the enema, and showed a reduction in distension, continued to be nonoperatively managed. However, patients who persisted in vomiting (those continuing to produce bile from the nasogastric tube) and showed no decrease in distension were subjected to surgical intervention.

Statistical analysis

The statistical analysis of patient data employed descriptive statistics, frequency, and other characteristics for all items. Mean and standard deviation were used for displaying continuous data. Shapiro–Wilk and Kolmogorov–Smirnov tests were used to determine whether continuous data were normal. When data varied from a normal distribution, non-parametric

tests were used instead of the Student's t-test for continuous and regularly distributed variables. For categorical variables, Chi-square tests were utilized, and Fisher's exact tests were applied as necessary. The diagnostic performance of the NLR, PNLR, and DLR was investigated using ROC analysis. SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA), was used to analyze the data. A $p < 0.05$ was considered statistically significant.

Results

The mean age of patients in Group 1 was 4.40 ± 3.85 years, while in Group 2, it was 4.64 ± 3.43 years ($p = 0.745$). Regarding gender, 50% of patients in Group 1 and 58% in Group 2 were men ($p = 0.418$). White blood cell count was significantly higher in Group 2 (15.47 SD2.54) compared to Group 1 (13.16 ± 3.32) ($p < 0.001$). Similarly, the neutrophil count (NEU) was also significantly higher in Group 2 (12.34 ± 3.19) compared to Group 1 (10.01 ± 3.48) ($p < 0.001$). Lymphocyte (LYM) counts and platelet counts were slightly higher in Group 2 than Group 1, but the difference was not statistically significant ($p = 0.307$ and $p = 0.082$, respectively). The indirect bilirubin, DB, and total bilirubin were significantly higher in Group 2 than in Group 1 ($p = 0.001$, $p < 0.001$, and $p < 0.001$, respectively). Although the C-reactive protein (CRP) level was higher in Group 2 (68.39 ± 57.59) than in Group 1 (63.1 ± 25.52), the difference was not statistically significant ($p = 0.065$). The NLR and PNLR were significantly higher in Group 2 compared to Group 1 ($p = 0.041$ and $p = 0.020$, respectively). However, the PLR was not significantly different between the groups ($p = 0.195$). DLR was significantly higher in Group 2 (0.224 ± 0.124) than in Group 1 (0.147 ± 0.113) ($p < 0.001$) (Table 1).

The surgical management group consisted of 50 patients. Evaluation of bowel status revealed that in the majority of the cases (n = 39, 78%), the bowel was viable, whereas in a smaller proportion of cases (n = 11, 22%), the bowel was gangrenous. Of the surgical procedures performed, intestinal resections were carried out in 20 patients (40%), while non-resection procedures were conducted in the remaining 30 patients (60%). In cases where a resection was performed, further procedures involved anastomosis in 8 patients (16%) and stoma creation in 12 patients (24%). At post-operative period, 16 patients (32%) need to be observed in intensive care unit. Post-operative complications were observed in 12 patients (24%). The mortality rate was 12% (n = 6). The mean length of hospital stay was reported as 10 SD7 days (Table 2).

Table 1. Comparison of non-operative management and surgical group

	Group 1 (n = 52)		Group 2 (n = 50)		p-value
	Mean	SD	Mean	SD	
Age	4.40	3.85	4.64	3.43	0.745
Gender (M)*	26	50%	29	58%	0.418
WBC	13.16	3.32	15.47	2.54	<0.001
NEU	10.01	3.48	12.34	3.19	<0.001
LYM	2.08	0.96	1.89	0.90	0.307
PLT	266	55	287	64	0.082
IB	0.33	0.23	0.49	0.25	0.001
DB	0.23	0.11	0.33	0.12	<0.001
TB	0.57	0.32	0.83	0.83	<0.001
CRP	63.12	25.52	68.39	57.59	0.065
NLR	6.47	5.23	8.76	5.89	0.041
PLR	159	86	181	81	0.195
PNLR	1692	1354	2360	1487	0.020
DLR	0.147	0.113	0.224	0.124	< 0.001

*n(%), Chi-square test; other items, Independent T-test. SD: standard deviation; WBC: white blood cell count; NEU: neutrophil; LYM: lymphocyte; PLT: platelet; IB: indirect bilirubin; DB: direct bilirubin; TB: total bilirubin; CRP: c-reactive protein; NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio; PNLR: platelet neutrophil–lymhocyte ratio; DLR: direct bilirubin lymphocyte ratio.

Table 2. Characteristics of the patients underwent surgery

Surgical group	n = 50 (%)
Bowel status	
Viable	39 (78)
Gangrenous	11 (22)
Procedure performed	
Resection	20 (40)
Non-resection	30 (60)
Procedure after resection	
Anastomosis	8 (16)
Stoma	12 (24)
Post-operative ICU	16 (32)
Post-operative complication	12 (24)
Mortality	
Dead	6 (12)
Survived	44 (88)
Lenght of stay (days)*	10 (7)

*mean (SD); other items: n(%). ICU: intensive care unit.

In this study, the NLR, PLNR, and DLR indices tested using ROC analysis to identify patients who require surgery. Accordingly, the NLR was observed to have a cut-off value of 4.1. The area under the ROC curve (AUC) for this index was 0.630, which signifies moderate predictive accuracy. The sensitivity was quite high at 86%, indicating a substantial ability to correctly identify positive cases. However, the specificity was observed to be relatively low at 40%, suggesting a moderate rate of accurately identifying negative cases. Positive Predictive Value (PPV) and Negative Predictive Value (NPV) were 58% and 75%, respectively, while the overall accuracy of the NLR was found to be 63%. The PNLR was evaluated at a cut-off value of 2137. This index had a higher AUC value of 0.662 compared to NLR, implying a somewhat improved predictive accuracy. The sensitivity was lower at 48%, but the specificity was considerably high at 83%. This suggests that the PNLR has a strong ability to accurately classify negative cases, despite a lower ability to detect positive cases. The PPV and NPV for PNLR were 73% and 62%, respectively, and the overall accuracy came out to be 65%. The DLR demonstrated the highest AUC value of 0.711 among the indices, indicating superior predictive accuracy. The cut-off value was set at 0.2. The sensitivity and specificity for DLR were recorded at 62% and 81%, respectively, showing a well-balanced ability to correctly identify both positive and negative cases. The PPV and NPV were 75% and 69%, respectively. Notably, DLR outperformed both NLR and PNLR in terms of overall accuracy, with a rate of 72% (Table 3 and Fig. 4).

Table 3. Indeces diagnostic test analysis

Index	Cut-off	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy
NLR	4.1	0.630	86%	40%	58%	75%	63%
PNLR	2137	0.662	48%	83%	73%	62%	65%
DLR	0.2	0.711	62%	81%	75%	69%	72%

NLR: neutrophil–lymphocyte ratio; PNLR: platelet neutrophil–lymhocyte ratio; DLR: direct bilirubin–lymphocyte ratio.

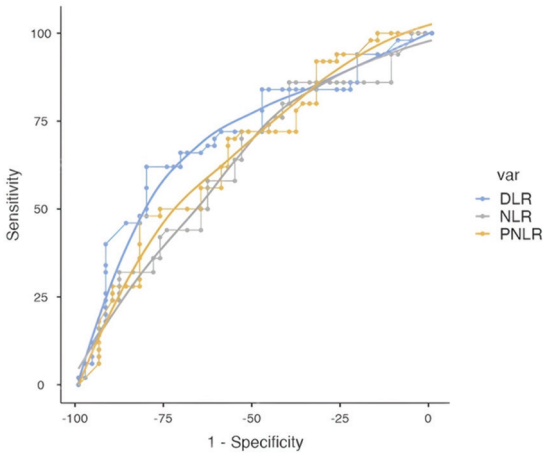

Figure 4. *ROC graph of the indexes.*

Discussion

ASBO can result in strangulation, triggering bowel ischemia and necrosis due to obstructed blood flow[9]. A recent single-center review demonstrated that 54% of pediatric cases were successfully managed nonoperatively, while 12% required immediate surgical intervention, and another 34% needed abdominal surgery later during their hospital stay[10]. These findings contrast with a multi-center study using the Kids' Inpatient Database, which reported that 85% of pediatric ASBO patients required surgical intervention, with 16.5% undergoing bowel resection[11]. However, in this study, 50% of patients were needed surgical intervention. In 22% of the cases, the patients' bowels were gangrenous. In 40% of these cases, an intestinal resection was performed. Meanwhile, stoma formation was carried out in 12 (24%) patients.

In the current study, investigated the discriminating ability of various factor combinations, particularly the up and down combinations, identified with pre-operative regular laboratory work and defined many discoveries. The main finding of this study was that patients who had surgical management had considerably greater DLR levels than patients who were managed nonoperatively, where DLR is defined as the sum of LYM counts and DB levels. The DLR was a more accurate indicator for ASBO who received surgical management when compared to other metrics, such as the NLR and PNLR levels.

Studies are collected that show a number of elements play a role in systemic inflammatory states, which can be used to assess the presence of ischemia. Measurable inflammatory factors, which were responses from and released by the local ischemic intestinal wall, were found in the peripheral blood as a result of strangulation[7,8]. Various inflammatory indicators have been reported to be helpful in the diagnosis and treatment monitoring in different disease types[7,8].

ASBO patients can use peripheral blood systemic inflammatory factor analysis to predict intestinal ischemia and necrosis, although the most accurate parameters for this analysis are still unknown.

In the research conducted by Chen et al.,[12] it was discovered that the inflammatory response's intensity was discernibly higher in patients who underwent intestinal resection. This was demonstrated by increased values of CRP and leukocyte count and decreased levels of albumin and LYMs, suggesting an inflammatory reaction to intestinal ischemia and necrosis. Prior studies on inguinal hernias noted that the lymphocyte-to-CRP ratio (LCR) was generally higher in patients experiencing strangulation, indicating its potential as a predictor for the necessity of bowel resection[13]. Another multivariate study also confirmed the NLR as being significantly linked with hernia strangulation and clear bowel ischemia[14]. The findings concluded that specific surrogate markers could be utilized to anticipate intestinal necrosis and have clinical relevance. In addition, it has been observed that the LCR is related to the prognosis of certain types of cancer patients, like those with stomach cancer and colorectal cancer[14,15]. A retrospective study revealed an elevation in the levels of CRP and NLR in patients suffering from acute pancreatitis[16]. Another piece of research indicated a significant correlation between NLR levels and patients with acute mesenteric ischemia who had undergone intestinal resection[17,18]. The study led by Chen et al. found a noticeable rise in NLR, CRP levels, and NEU in patients who had an intestinal resection[12]. However, this study found that NLR, PNLR, and DLR were significantly higher in surgical group. This suggests that in the surgical group, the bowel ischemia risk is more closely, indicating that these patients need surgery. Indeed, this study observed that patients with lower NLR, PLNR, and DLR values, whose bowels have not ischemia and necrosis, are in better general condition and these inflammatory indexes are lower.

Recently, there have been numerous retrospective and a few prospective studies that have investigated hyperbilirubinemia as an indicator of acute appendicitis and perforation[8]. It is common to observe elevated serum bilirubin levels and jaundice in patients with a septic condition. ASBO is one of the most frequent intra-abdominal infections. *E. coli* and *B. fragilis* are the most commonly isolated bacteria in these situations. Bacteremia, which these bacteria cause, can lead to endotoxemia, thus impairing bilirubin excretion from the bile canaliculi. Consequently, direct bilirubin levels increase in ASBO patients[7,8]. In another perspective, patients with complete bowel obstruction (surgical group) have impaired enterohepatic cycles of bile due to the lack of intestinal transit and experience bacteremia due to bacterial translocation[7,8]. All these mechanisms result in an increase in both direct bilirubin and DLR, especially in complete obstructions (surgical group). This study is the first and only research that investigates the diagnostic value of DLR in ASBO patients. Among the tested indices, DLR demonstrated the highest AUC value of 0.711, indicating superior predictive accuracy. The cut-off value was established at 0.2. The sensitivity and specificity for DLR were documented at 62% and 81%, respectively, displaying a balanced capability to correctly identify both positive and negative cases. The PPV and NPV were calculated at 75% and 69%, respectively. Remarkably, in terms of overall accuracy, DLR outperformed both NLR and PNLR, with a success rate of 72%.

The study's limitations include its retrospective design and single-center data, which may limit generalizability. In addition, selection bias may exist in choosing management strategies. The exclusion of neonates and individuals with other diseases impacting laboratory parameters could influence results. Unaccounted confounding factors such as surgeon's experience and patients' underlying health conditions might affect outcomes. Finally, the study relies heavily on the accuracy of past medical records.

In conclusion, DLR is a more accurate predictive index for surgical intervention in pediatric ASBO patients compared to NLR, PNLR, providing valuable guidance for treatment strategies. To date, no other study has addressed this issue specifically in pediatric patients with ASBO.

Author's contributions

Research concept and design: MA, SA, EB, MHO, BA, MK, TOK, Data analysis and interpretation: MA, SA, TOK, Collection and/or assembly of data: MHO, EB, BA, MK, Writing the article: MA, TOK, BA, MHO, Critical revision of the article: EB, MA, SA, MK, Final approval of the article: MA, MHO, SA, BA, TOK, MK, EB, All authors read and approved the final version of the manuscript.

Conflicts of interest

The authors report no conflicts of interest.

Funding source

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Informed consent

Written informed consent was obtained from all individual participants and/or their gaurdians.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical disclosures

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

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

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

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

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