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Risk factors for postoperative hypoalbuminemia in ovarian cancer: a predictive nomogram



Yinggen Chen^{1,2}, Shilin Hu^{1,2}, Shuzhi Zhou^{2*} and Zhuoxuan Yang^{2*}

Abstract

Objective Postoperative hypoalbuminemia increases the risk of delayed wound healing and infections and prolongs hospital stays, and may even increases mortality. Hypoalbuminemia is commonly observed after radical ovarian cancer surgery. The primary aim of this study is to determine risk factors for postoperative hypoalbuminemia after radical ovarian cancer surgery, and to develop a prediction nomogram for its prevention and management.

Methods This retrospective study analyzed patients who underwent radical ovarian cancer surgery at Ya'an People's Hospital, Sichuan Province, China, from January 2018 to December 2023. All surgeries were performed by the same surgical team. A total of 142 patients were included for analysis. Patients were divided into two groups based on their serum albumin(ALB) levels on postoperative day 1: the hypoalbuminemia group (ALB < 35 g/L) and the control group (ALB \geq 35 g/L). Univariate and multivariate analyses were used to identify risk factors, and a prediction nomogram was developed based on the statistical results. The prediction performance of the risk factors and the model was evaluated using receiver operating characteristic (ROC) curves.

Results Among the 142 patients, 69 developed postoperative hypoalbuminemia, with an incidence rate of 48.6%. Univariate and multivariate binary logistic regression analyses revealed that the independent risk factors for postoperative hypoalbuminemia in ovarian cancer patients included: preoperative C-reactive protein (CRP) level, preoperative ALB level, excessive intraoperative net fluid gain, weight loss > 5% in the month prior to surgery, and concomitant gastrointestinal surgery. The nomogram model, based on these five independent risk factors (Area Under the Curve [AUC] = 0.898, 95% CI: 0.846–0.949, sensitivity: 0.826, specificity: 0.836).

Conclusion Preoperative CRP level, preoperative ALB level, excessive intraoperative net fluid gain, weight loss > 5% in the month prior to surgery, and concomitant gastrointestinal surgery are independent risk factors for postoperative hypoalbuminemia in patients undergoing radical ovarian cancer surgery. The nomogram prediction model, based on these five factors, can effectively predict the risk of postoperative hypoalbuminemia, offering a guide for managing this complication.

Keywords Ovarian cancer, Radical surgery, Hypoalbuminemia, Risk factors, Nomogram

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Introduction

Ovarian cancer is one of the most common malignant tumors of the female reproductive system and ranks as the fifth leading cause of cancer-related deaths in women [1]. Due to its insidious onset, most ovarian cancer patients are diagnosed at an advanced stage with either local or distant metastases, contributing to a low 5-year survival rate of only 46%. Currently, surgery is the most effective treatment for ovarian cancer. Surgery also allows for staging, prognosis assessment, and guidance for subsequent treatments [2].

Studies have shown that the malnutrition rate among cancer patients in China is as high as 80.4%, yet only 33.7% of these patients receive nutritional therapy [3]. ALB, an essential indicator of nutritional status, is often reduced in malnourished patients, indicating a higher risk of hypoalbuminemia [4]. Furthermore, preoperative fasting, intraoperative fluid infusion, and perioperative stress can all contribute to the development of hypoalbuminemia in surgical patients [5, 6]. These findings highlight the high risk of perioperative hypoalbuminemia in cancer patients.

Clinically, ALB levels below 35 g/L are typically defined as hypoalbuminemia [7]. Perioperative hypoalbuminemia in surgical patients can result in interstitial edema, delayed wound healing, prolonged hospital stay, and increased mortality [8, 9]. A study by Curran et al. [10] found that patients with hypoalbuminemia undergoing outpatient surgery had higher rates of postoperative readmission and mortality. Another retrospective study on rectal cancer surgery [11] showed that hypoalbuminemia was associated with an increased incidence of wound dehiscence and longer hospital stay.

While studies have examined the risk factors for postoperative hypoalbuminemia in gastrointestinal surgery [12], orthopedics surgery [6], and cardiothoracic surgery [13], research on ovarian cancer patients undergoing radical surgery is limited. We aims to investigate the risk factors for postoperative hypoalbuminemia in ovarian cancer patients undergoing radical surgery and to develop a nomogram prediction model to guide clinical interventions and reduce the incidence of hypoalbuminemia in this population.

Method

Patients

The study included patients who underwent radical ovarian cancer surgery at Ya'an People's Hospital, Sichuan Province, China, between January 2018 and December 2023. This study was approved by the Ethics Committee of Ya'an People's Hospital (Ethics Approval NO.2023034).

Inclusion Criteria: (1) Age>18 years; (2) Surgical approach: laparoscopic ovarian cancer radical surgery or open ovarian cancer radical surgery (including patients

who underwent conversion from laparoscopic to open surgery); (3) Postoperative pathological diagnosis of ovarian cancer; (4) Anesthesia: combined intravenousinhalation general anesthesia; (5) Postoperative pain management: standardized intravenous analgesia protocol. Exclusion Criteria: (1) No ALB recheck within 1 day post-surgery; (2) Change in surgical method, without undergoing radical surgery; (3) Preoperative liver dysfunction as defined as serum total bilirubin levels > 2 times the upper limit of normal or alanine aminotransferase (ALT) levels > 3 times the upper limit of normal [14].

Data collection

All patients included in the study were operated on by the same surgeon, and there were no other comorbidities causing weight loss prior to surgery. Patient case data were retrospectively collected from the electronic medical record system of Ya'an People's Hospital, including pre- and intraoperative indicators, and clinical outcomes. Preoperative indicators include: age, weight, height, BMI, duration of disease, history of chemotherapy, weight loss in the month prior to surgery (based on Nutritional Risk Screening 2002 (NRS-2002) assessment), history of hypertension, diabetes, American Society of Anesthesiologists(ASA)classification, CRP, white blood cell count (WBC), hemoglobin (Hb), and ALB. Intraoperative indicators include: duration of surgery, net fluid gain, urine output, colloid-crystalloid ratio, blood loss/ weight, volume of ascites, laparoscopic surgery, concomitant gastrointestinal surgery, administering a nerve block, packed red blood cells (PRBC) transfusion and infusion of Human Serum Albumin (HSA). Clinical outcomes include: ICU admission rate, overall complication rate, degree of postoperative ALB decrease, time to first postoperative feeding, and length of postoperative hospital stay. Gastrointestinal surgery is defined as preoperative diagnosis or intraoperative findings of tumor metastasis to the gastrointestinal tract, leading to intestinal resection. Net fluid gain is defined as the total fluid intake during surgery minus urine output. Regional nerve block procedure: bilateral transversus abdominis plane block under ultrasound guidance, with 20 mL of 0.25% ropivacaine injected bilaterally. Postoperative complications include: (1) delayed wound healing (wound not fully healed after 2 weeks post-surgery); (2) pulmonary infection; (3) fever; and (4) abdominal infection.

Outcome

The postoperative day-1 ALB levels were categorized into two groups: the hypoalbuminemia group (ALB < 35 g/l) and the control group (ALB \ge 35 g/l).

Data analysis

Statistical analysis was performed using SPSS 26.0 (IBM, USA). Normality of continuous variables was tested using the Kolmogorov-Smirnov test. Normally distributed variables were expressed as mean ± standard deviation and compared between groups using the independentsample *t*-test. Paired-sample *t*-test was used for pre- and post-comparisons of the same data. Non-normally distributed variables were expressed as median and interquartile range (M (P25, P75)) and compared using the Mann-Whitney U test. Categorical data were presented as frequency (%), and inter-group comparisons were conducted using the chi-square test or continuity-corrected chi-square test. Multivariate analysis was performed using binary logistic regression. R software (version 4.4.1, R Foundation for Statistical Computing, Austria) was used to generate nomograms for prediction models, plot ROC curves, and calculate the Youden index and AUC, statistical critical value. p < 0.05 was regarded statistically significant.

Results

Occurrence of postoperative hypoalbuminemia

Between January 2018 and December 2023, a total of 235 patients underwent radical surgery for ovarian cancer in our hospital. Among them, 142 patients met the inclusion criteria, of which 69 developed hypoalbuminemia, an incidence rate of 48.6%.

All patients who underwent radical surgery for ovarian cancer showed a decrease in ALB levels postoperatively, with levels dropping from a preoperative mean of 43.72 ± 4.12 g/L to a postoperative mean of 33.51 ± 6.53 g/L, a decrease of 10.21 ± 5.51 g/L (p < 0.001). Specifically, ALB concentrations in the study group decreased from a preoperative mean of 41.96 ± 4.61 g/L to 27.91 ± 4.51 g/L postoperatively, while in the control group, levels dropped from 45.38 ± 2.73 g/L to 38.80 ± 2.29 g/L, both showing significant differences (p < 0.001) (Table 1).

Clinical outcomes

The postoperative ICU admission rate, postoperative overall complication rate (delayed wound healing, pulmonary infection, fever, abdominal infection), degree of postoperative ALB decrease, time to first postoperative feeding, and length of postoperative hospital stay all showed significant differences (p < 0.05) (Table 2).

Table 1 Comparison of ALB between the two groups (g/L)

Patients	Pre-op	Post-op	t	p value
Totality(n = 142)	43.72 ± 4.12	33.51 ± 6.53	22.082	< 0.001
Control ($n = 73$)	45.38 ± 2.73	38.80 ± 2.29	23.732	< 0.001
Hypoalbuminemia (<i>n</i> = 69)	41.96 ± 4.61	27.91 ± 4.57	22.105	< 0.001

Univariate analysis

We conducted a univariate analysis of the risk factors for postoperative hypoalbuminemia. There were significant differences (p < 0.05) in preoperative CRP, ALB, weight loss > 5% in the month prior to surgery, the number of patients with ASA ≥ III, surgical time, intraoperative net fluid gain, blood loss, ascites volume, laparoscopic surgery, concomitant gastrointestinal surgery, and administering a nerve block (Table 2).

Logistic regression analysis

A multivariate binary logistic regression analysis was performed with hypoalbuminemia as the dependent variable and factors identified as significant in the univariate analysis as independent variables. The variable assignments are shown in Table 3. The results of the analysis indicated that weight loss > 5% in the month prior to surgery (OR = 3.705; 95% CI: 1.149–11.948; *p* = 0.028), elevated preoperative CRP (OR = 1.022; 95% CI: 1.006-1.038; *p* = 0.006), low preoperative ALB (OR = 0.816; 95% CI: 0.701-0.950; p = 0.009), high intraoperative net fluid gain(OR = 1.063; 95% CI: 1.024-1.134; p = 0.020), and concomitant gastrointestinal surgery during the operation (OR = 4.717; 95% CI: 1.578–14.099; p = 0.005) were independent risk factors for the development of hypoalbuminemia following radical surgery for ovarian cancer (*p* < 0.05) (Table 4).

Prediction model nomogram and ROC curve

The five independent risk factors derived from the multivariate binary logistic regression analysis were set as predictive indicators to form a combined diagnostic prediction model, and a nomogram was drawn, as shown in Figure 1. The scores corresponding to the five predictive indicators were summed to calculate the total score, which gives the corresponding predicted probability. A higher total score indicates a greater likelihood of postoperative hypoalbuminemia in ovarian cancer radical surgery patients.

The ROC curve for the prediction model, along with the five independent risk factors, was plotted. The results are as follows: The AUC value of the prediction model was 0.898 (95% CI: 0.846–0.949, sensitivity: 0.826, specificity: 0.836). Calculate the Youden's index (sensitivity + specificity-1) for CRP, ALB, and net fluid gain, and determine the optimal cut-off values based on the maximum Youden's index: Preoperative CRP 6.69 mg/L, ALB 43.35 g/L, and net fluid gain of 40.71 mL/kg(Table 5 and Figure 2).

Discussion

Our study showed the incidence of postoperative hypoalbuminemia in patients undergoing radical ovarian cancer surgery is 48.6%. Such a high incidence warrants

Table 2 Comparison of preoperative data between the two groups of patients

Variables	Control	Hypoalbuminemia (<i>n</i> =69)	Z/t/χ ²	<i>p</i> value	
	(n = 73)		1 5 4 7	0.124	
Age (years)	52.11 ± 12.42	55.17±11.10	1.547	0.124	
vveignt (kg)	60.0(53.8,64.5)	58.0(51.3,63.5)	1.168	0.243	
Height (cm)	158(153,160)	155(152,160)	1.088	0.276	
BMI(kg/m ²)	24.53 ± 3.64	24.22 ± 3.31	0.523	0.602	
Duration of disease (months)	30.0(10.0,105.0)	30.0(8.5,75.0)	0.897	0.370	
Chemotherapy	4(5.48%)	5(7.25%)	0.008	0.930	
Weight loss > 5%	10(13.70%)	24(34.78%)	8.659	0.003	
Diabetes	5(6.85%)	4(5.80%)	0.000	1.000	
Hypertension	15(20.55%)	12(17.39%)	0.230	0.632	
$ASA \ge III$	9(12.33%)	23(33.33%)	13.766	< 0.001	
CRP (mg/L)	3.30(2.17,9.66)	20.77(7.65,81.04)	-5.647	< 0.001	
WBC(109/L)	6.3(5.4,7.7)	6.9(5.5,9.0)	1.609	0.108	
Hb(10 ⁹ /L)	128.0(119.0,135.0)	125.0(111.0,132.5)	1.421	0.155	
ALB (g/L)	43.38±2.73	41.96±4.61	-5.346	< 0.001	
Duration of surgery (min)	230.89±97.17	290.46±95.54	3.718	< 0.001	
Net fluid gain (ml/kg)	31.25(22.94,39.18)	43.48(34.24,56.52)	5.041	< 0.001	
Urine output(ml)	300(200,600)	400(200,700)	1.005	0.315	
Colloid-crystalloid ratio (%)	0.25(0.00,0.37)	0.30(0.19,0.40)	-0.684	0.494	
Blood loss/weight (ml/kg)	3.13(1.56,5.77)	6.36(3.28,10.84)	-4.372	< 0.001	
Ascites volume (ml)	200(50,450)	400(50,2000)	1.565	< 0.001	
Laparoscopic surgery	55(75.34%)	29(42.03%)	16.293	< 0.001	
GI surgery	15(20.55%)	41(59.42%)	22.442	< 0.001	
Nerve block	44(60.27%)	30(43.48%)	4.010	0.045	
HSA	11(15.07%)	15(21.74%)	1.055	0.304	
PRBC	4(5.48%)	10(14.49%)	3.195	0.074	
ICU admission	2(4.11%)	16(20.29%)	13.4	< 0.001	
Complication	3(4.11%)	17(24.64%)	8.812	< 0.001	
Delayed wound healing	2	5	-	-	
Pulmonary infection	0	5	-	-	
Fever	0	4	-	-	
Abdominal infection	1	3	-	-	
ALB decrease(g/L)	6.2(4.4,8.05)	13.8(10.0,17.35)	-8.335	< 0.001	
First feeding (days)	3(1,4)	4(2,5)	3.376	0.001	
Hospital stay (days)	8(7,9)	10(8,13.5)	3.853	< 0.001	

Table 3 Variable assignment

Variables	Assignment
Postoperative hypoalbuminemia	Yes = 1, No = 0
Weight loss > 5%	Yes = 1, No = 0
ASA≥III	Yes = 1, No = 0
Laparoscopic surgery	Yes = 1, No = 0
Gl surgery	Yes = 1, No = 0
Nerve block	Yes = 1, No = 0

significant attention from care providers. Risk factors for postoperative hypprotenemia includes low ALB, high CRP, excessive net intraoperative fluid gain, weight loss > 5% in the month prior to surgery, and concomitant gastrointestinal surgery are risk factors for the development of hypoalbuminemia after radical ovarian cancer surgery.

Table 4 Binary logistic regression analysis of risk factors

Risk Factor	β	OR	95% CI	p value
Weight loss > 5%	1.310	3.705	1.149–11.948	0.028
ASA≥III	0.387	1.472	0.431-5.029	0.538
CRP	0.022	1.022	1.006-1.038	0.006
ALB	-0.203	0.816	0.701-0.950	0.009
Duration of surgery	-0.002	0.998	0.984-1.011	0.742
Net fluid gain	0.061	1.063	1.024-1.134	0.020
Blood loss/weight	-0.047	0.954	0.865-1.052	0.346
Ascites volume	0.001	1.001	1.000-1.002	0.109
Laparoscopic surgery	0.055	1.057	0.328-3.411	0.926
GI surgery	1.551	4.717	1.578-14.099	0.005
Nerve block	-0.349	0.705	0.245-2.029	0.517



Fig. 1 Nomogram predictive model

 Table 5
 ROC prediction model

Risk factor	AUC	Youden	Cut-off	Sensi	Spec	p value	95%Cl
CRP	0.775	0.523	6.69 mg/L	0.797	0.726	< 0.001	0.695–0.854
ALB	0.724	0.460	43.35 g/L	0.638	0.822	< 0.001	0.637-0.811
Net fluid gain	0.745	0.402	40.71 ml/kg	0.594	0.808	< 0.001	0.664-0.826
Weight loss > 5%	0.605	0.211	0.500	0.348	0.863	0.030	0.512-0.699
GI surgery	0.694	0.389	0.500	0.594	0.795	< 0.001	0.606-0.782
Model	0.898	0.662	0.531	0.826	0.836	< 0.001	0.846-0.949

A non-specific inflammatory marker, CRP is primarily synthesized in the liver in response to inflammatory mediators such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF). CRP levels are significantly elevated not only in infectious diseases but also in noninfectious conditions, tumors, trauma, surgery, and other events [15]. Zhu et al. [16] found that elevated CRP levels in cancer patients were likely to be associated with tumor cell proliferation, inflammatory responses, and the production of inflammatory mediators. The present study found that preoperative elevated CRP levels were an independent risk factor for postoperative hypoalbuminemia in ovarian cancer patients undergoing radical surgery. This finding is consistent with the research by Moghadamyeghaneh et al. [12], which identified CRP as an independent risk factor for hypoalbuminemia after hip revision surgery. Additionally, studies have confirmed that the decrease in ALB levels may be related to the damage of the endothelial glycocalyx layer (EGL), a polysaccharide-protein complex barrier mediated by inflammatory factors [17, 18]. When the EGL is damaged, ALB is more likely to leak into the extravascular space, leading to reduced ALB concentrations. In cancer patients, elevated CRP levels in the late stages of the disease may be due to the systemic inflammatory response, multiorgan dysfunction, concurrent infections, surgery, and other factors [19]. This elevation can result in EGL barrier disruption, ultimately causing the leakage of plasma ALB. Therefore, for ovarian cancer patients with elevated preoperative CRP levels, special attention should be paid to potential infectious causes, and anti-infection treatments should be considered when necessary to reduce the risk of postoperative hypoalbuminemia.

Our study also identified two indicators reflecting the nutritional status of patients: preoperative ALB levels, and weight loss > 5% in the month prior to surgery. It is well-known that ALB is a key nutritional component in the human body, and its level can directly reflect the patient's nutritional status [4]. For patients with significant preoperative hypoalbuminemia, it often suggests the presence of malnutrition. According to a survey by the Cancer Nutrition Professional Committee of the Chinese Anti-Cancer Association, by 2021, the incidence of malnutrition in cancer patients hospitalized in top-tier hospitals was as high as 80.4%, but only 33.7% of these patients received formal nutritional support therapy [3].



Fig. 2 ROC risk factors and predictive models

Furthermore, a study on the nutritional status of gynecological cancer patients indicated that the incidence of malnutrition in ovarian cancer patients was 78%, with a severe malnutrition rate of 35.6% [20]. The results of this study showed that patients with hypoalbuminemia had significantly lower preoperative ALB levels compared to the control group, and that excessively low preoperative ALB concentrations were an independent risk factor for postoperative hypoalbuminemia. Another analysis of nutritional status indicators found that weight loss greater than 5% in the past month was also an independent risk factor for postoperative hypoalbuminemia in patients undergoing radical ovarian cancer surgery. According to the NRS-2002 scale, when a patient's weight loss exceeds 5% in the past month, their NRS-2002 score can reach 3 or higher, indicating a higher risk of malnutrition [4]. Preoperative nutritional risk screening is essential for patients undergoing radical ovarian cancer surgery. For those already at risk of malnutrition, nutritional support therapy should be administered, and elective surgery should be scheduled only after the nutritional status improves. This strategy not only helps reduce the risk of postoperative hypoalbuminemia but may also improve postoperative recovery and long-term prognosis.

This study found that the excessive intraoperative net fluid gain is a risk factor for postoperative hypoalbuminemia in ovarian cancer radical surgery patients. A study by Motamed et al. [21] found that the amount of intraoperative fluid administered in gastrointestinal surgery patients was negatively correlated with postoperative ALB concentrations, suggesting that the higher the amount of intraoperative fluid, the greater the likelihood of postoperative hypoalbuminemia. The results of this study are consistent with their findings. The mechanism behind this may involve multiple factors: (1) intraoperative blood loss can lead to the loss of ALB along with the blood [21]; (2) during surgery, damage to the EGL barrier can cause ALB leakage; (3) the stress response can also enhance the catabolism of ALB [22]. Excessive fluid administration also dilutes the ALB, exacerbating

hypoalbuminemia. It may be prudent to control of fluid administration during radical ovarian cancer surgery.

Al-Hishma et al. [23] showed that the incidence of preoperative hypoalbuminemia in colorectal cancer patients was 44%. We also found that the presence of concomitant gastrointestinal surgery is an independent risk factor for postoperative hypoalbuminemia in ovarian cancer radical surgery patients. It seems possible that ovarian cancer patients undergoing radical surgery who needed additional bowel surgery may have preoperative intestinal dysfunction and are more likely to have decreased preoperative ALB levels. However, we did not conduct statistical analysis, so this association requires further investigation. Additionally, surgical stress can lead to increased ALB consumption and reduced synthesis [22]. For ovarian cancer patients with concomitant bowel surgery, the surgical procedure is typically longer, and these patients may experience a prolonged stress state. We showed that the average surgical time for the hypoalbuminemia group (290.46±95.54 min) was significantly longer than that of the control group (230.89±97.17 min). Although surgical time was not included as an independent risk factor in the multivariate analysis, longer surgery may involve more fluid infusion and prolonged stress, both can lead to hypoalbuminemia.

A study by Li et al. [24] showed that a prediction model based on risk factors can effectively predict the probability of postoperative hypoalbuminemia. Similar models have also been reported in the field of orthopedic surgery [25]. We believe our postoperative hypoalbuminemia prediction model can be applied in future clinical practice for radial ovarian cancer surgery. The model showed that the model's AUC value reached 0.898, with high sensitivity (0.826) and specificity (0.836), indicating a significant predictive value and high accuracy. Future studies can further validate the reliability and applicability of this model based on larger sample sizes and multi-center data.

The study found that ovarian cancer patients who developed postoperative hypoalbuminemia had a significantly higher postoperative ICU admission rate and overall complication rate. The first postoperative feeding and hospital discharge were also delayed. A study by Seretis et al. [26] pointed that ALB concentration was negatively correlated with the likelihood of ICU admission. Huang et al. [25] also found hypoalbuminemia is an independent risk factor for pulmonary infections after hip fracture surgery. Further research is needed to determine mechanisms of these complications.

There are several limitations in this study. First, as this is a single-center retrospective analysis with a relatively small sample size, there may be selection bias, which limits the generalizability of the conclusions. Future studies should involve multi-center, larger sample sizes to further validate the conclusions of this study and enhance the reliability and applicability of the results. Second, this study focused on serum ALB levels, but since serum ALB has a long half-life, there is a lag in observation, and hypoalbuminemia from to metabolic dysfunction may not be immediately reflected in the serum ALB levels within a short postoperative period. In contrast, prealbumin, with a shorter half-life and less prone to interference, can more quickly reflect the patient's conditions [27].

Conclusion

Postoperative hypoalbuminemia occurs at a higher rate in patients undergoing ovarian cancer radical surgery. Preoperative CRP level, preoperative ALB level, excessive intraoperative net fluid gain, weight loss >5% in the month prior to surgery, and concomitant gastrointestinal surgery are independent risk factors for postoperative hypoalbuminemia in patients undergoing radical ovarian cancer surgery. The nomogram prediction model is helpful in predicting the incidence of postoperative hypoalbuminemia in these patients and has clinical application value.

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Author contributions

YG Chen, SL Hu, SZ Zhou, ZX Yang: Conceived and designed the study; YG Chen, SL Hu: Performed the experiment and wrote the paper together.; YG Chen, SL Hu, SZ Zhou, ZX Yang: Revised the paper; SZ Zhou, ZX Yang: Final approval of the version to be published.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Ya'an People's Hospital (No. 2023034), and all patients provided written informed consent. All procedures involving human participants were conducted in accordance with ethical standards set by institutional and/or national research committees, as well as the 1964 Helsinki Declaration and its later amendments, or comparable ethical standards.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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