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C-reactive protein to albumin ratio (CAR) in predicting surgical site infection (SSI) following instrumented posterior lumbar interbody fusion (PLIF)

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Abstract

Identification of novel markers would contribute to the individualised risk assessment and development of a risk prediction model. This study aimed to investigate the role of the C-reactive protein to albumin ratio (CAR) in predicting surgical site infection (SSI) following instrumented posterior lumbar interbody fusion (PLIF) of lumbar degenerative diseases. This study enrolled patients who underwent PLIF and instrumentation for treatment of lumbar degenerative diseases between 2015 and 2020. Electronic medical records were inquired for data collection, with follow-up register for identifying SSI cases. The optimal cut-off for CAR was determined by constructing the receiver operator characteristic (ROC) curve. Patients with high- or low-CAR value were compared using the univariate analyses, and the association between CAR and the risk of SSI was investigated using multivariate logistics regression analysis. A total of 905 patients were enrolled, twenty-nine (3.2%) had developed an SSI with 72.4% occurring during index hospitalisation, and 11 (1.2%) had deep and 18 (2.0%) superficial SSIs. An SSI was associated with additional 10.7 days of index total hospital stay ($P = .001$). The CAR was 0–5.43 (median, 0.05), and the optimal cut-off was 0.09 and area under the curve was 0.720 ($P < .001$). 336 (37.1%) patients had a CAR ≥0.09 and 22 (6.5%) developed an SSI, with a crude risk of 5.6 relative to those with a low CAR. The multivariate analyses showed CAR ≥0.09 was associated with 8.06-fold increased risk of SSI, together with diabetes ($P = .018$), while hypertension was identified as a protective factor (OR, 0.34; 95%CI, 0.11–1.00, $P = .049$). High CAR is found to significantly predict the incident SSI following instrumented PLIF of lumbar degenerative diseases, and can be considered as a useful index in practice only after it is verified by future high-level evidences.

LIST OF ABBREVIATIONS: ASA, American Society of Anesthesiologists; AUC, area under the curve; BMI, body mass index; CAR, C-reactive protein to albumin ratio; COPD, chronic obstructive pulmonary disease; CRP, C-response protein; FBG, fasting blood glucose; H-L, Hosmer–Lemeshow; MRSA, methicillin-resistant Staphylococcus aureus; MRSE, Staphylococcus epidermidis; OR, odds ratio; PLIF, Posterior Lumbar Interbody Fusion; ROC, receiver operator characteristic; SSI, surgical site infection; WBC, white blood cell.

KEYWORDS

C-reactive protein to albumin ratio, lumbar degenerative disease, posterior lumbar interbody fusion, surgical site infection

Key Messages

- high C-response protein to albumin ratio (CAR) ≥0.09 was associated with 8.1-fold increased risk of SSI following instrumented PLIF for lumbar degenerative diseases
- CAR ≥0.09 showed a medium predicting ability for incident SSI, with an AUC of 0.720 and sensitivity of 0.759, but a relatively poor specificity of 0.642
- CAR can be considered as a useful tool for use in clinical practice, due to its readily accessible, ease to use and cheapness

1 | INTRODUCTION

Posterior lumbar interbody fusion (PLIF) and pedicle screw fixation is increasingly used for treatment of various lumbar degenerative disease, for example, spondylolisthesis and lumbar spinal stenosis, primarily due to technical ease, safety, and greater cost-effectiveness.[1,2] However, the postoperative surgical site infection (SSI) is relatively more prevalent in PLIF than in other types of procedure[3] and often results in undesirable, occasionally disastrous or even long-term consequences.[4] As was estimated, SSI occurred in 1.6% to 7.2% of patients who underwent PLIF for varying degenerative spine diseases,[5-8] and half was caused by multi-drug resistant bacteria, that is, methicillin-resistant Staphylococcus aureus (MRSA) and Staphylococcus epidermidis (MRSE).[6] Consequently, about 70% of SSIs required secondary surgery and one third necessitated revision surgery.[6] In addition, the cost from the prolonged hospital stay, readmission, and secondary surgical procedure constituted a serious concern for health-care system.[1]

The most cost-effective method to prevent or reduce such adverse events is identification of the related factors, thereby stratifying the individual risk and implementing targeted preventive measures. Inflammation-based prognostic factors have attracted increasing attention in multiple settings, largely because they combine the systemic inflammatory status and pathological burden. C-reactive protein to albumin ratio (CAR) has demonstrated its effectiveness in predicting clinical outcomes or adverse events in a range of conditions, for example, cancers of liver,[9] lung,[10] pancreas[11] and intestines/stomach,[12,13] severe burn injury,[14] or musculoskeletal disorders.[15-17] Specified at postoperative infection, Goulart et al[18] identified CAR on postoperative day 3 as an independent predictor after colorectal cancer surgery. Currently, worldwide the ongoing interest in developing more accurate risk prediction tools with larger studies underlines not solely relying on clinical judgement because of the its somewhat subjectivity and lagging manifestations or signs.[19]

To our best knowledge, there is no study investigating the role of CAR in predicting the SSI after spinal surgeries. In the present study, we aim to investigate the incidence of SSI following instrumented PLIF of lumbar degenerative diseases and assess the utility of CAR in predicting SSI, using the multivariate logistic regression analysis adjusting for various confounders.

2 | METHODS

This retrospective study was approved by the ethics committee of the Yantai Yuhuangding Hospital (NO 2022-004), which waived the requirement for informed consent due to the retrospective nature and identification anonymity. The protocol was performed in accordance with the Helsinki Declaration.

Two researchers (S.Q. and M.S.) retrieved and reviewed the medical records of hospitalised adult patients who had a discharge diagnosis of a lumbar degenerative disease (ie lumbar disc herniation, lumbar spondylolisthesis, lumbar spinal stenosis and adjacent lesions or combined) and undergone PLIF and instrumentation in our institution between January 2015 and December 2020. Inclusion criteria were age of 18 years or older, complete medical records and a minimum of 1-year follow-up. Patients who underwent procedures other than PLIF and instrumentation, had medical conditions that directly related to preoperative abnormal C-response protein (CRP) or serum albumin

level (eg, liver cirrhosis, renal insufficiency, infectious events), history of any lumbar surgeries, history of radiotherapy in the lumbar region, primary or metastatic lumbar tumour, loss to follow up or missing data on variables of interest, were excluded.

The classic open posterior approach was used for excision of spinous process, decompression and instrumented fusion. As per practice policy, prophylactic intravenous antibiotics (eg, cefuroxime, ceftriaxone, or ceftazidime) in single dose was routinely administered 30 minutes before skin incision, and for procedures lasting over 3 hours, an additional dose will be given. After operation, antibiotic prophylaxis was not standardised, primarily depending on the patients' individualised risk of infection assessed by their treating surgeons, as with drainage tube placement and the timing for removal.

2.1 | Definition and confirmation of SSIs

SSI status was captured by reviewing the hospitalisation medical records and follow-up register at each outpatient visit. SSI was diagnosed in accordance with the guideline proposed by US Centers for Disease Control and Prevention (2017 edition).[20] A superficial SSI was an infection of skin and subcutaneous tissues within 30 days of surgery, regardless of implant of hardware or material; and symptoms and signs of redness, tenderness, heat and pain over the wound site were referred as diagnostic base. Deep SSI was defined as an infection that involved the fascia, muscle tissues or vertebra space, occurs within 1 year if implant was left in place, which often led to marked symptoms/signs, for example, fever, pain, tenderness, persistent wound discharge or dehiscence, abscess or gangrenosis. The bacterial culture and antimicrobial susceptibility tests were performed in most suspected cases, but were not dependent on for diagnosis of SSI.

2.2 | C-reactive protein to albumin ratio (CAR)

CAR was calculated by dividing the serum albumin concentration in g/L by the CRP in mg/L. Preoperative blood sample was taken for obtaining the measurements. If patients have multiple measurements for one biomarker of interest (eg, CRP, albumin and others) before operation, the one closest to the operation was selected for analysis, to minimise the potential time-dependent confounding effect. The reference range for CRP and albumin is <8 mg/L and ≥35 g/L, in accordance with the manufactures' recommended cut-off.

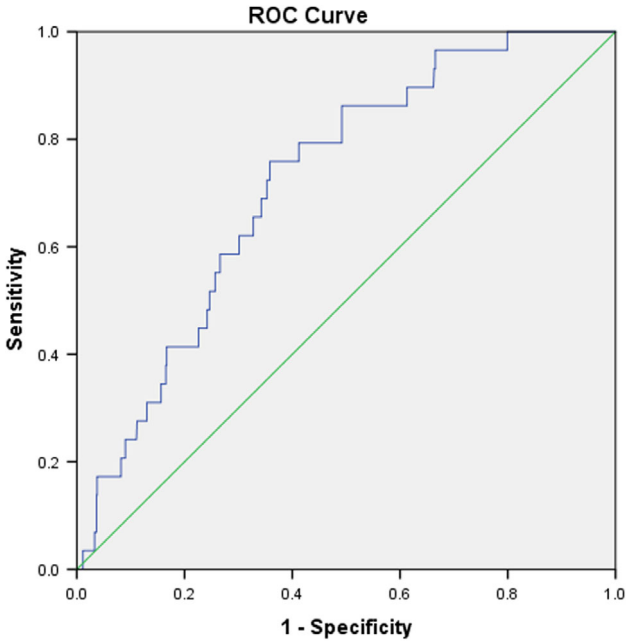

FIGURE 1 The ROC curve constructed to determine the optimal cut-off for CAR. The optimal cut-off was 0.09, corresponding to a sensitivity of 0.759 and a specificity of 0.642, and the area under the curve was 0.720 (95%CI, 0.641–0.799; $P < .001$)

2.3 | Data collection on variables of interest

Variables of interest were extracted from the hospitalisation records, including gender, age, body mass index (BMI, calculated by dividing weight in kilogram by the square of height in meter), smoking, alcohol, hypertension, diabetes, heart disease, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), American Society of Anesthesiologists (ASA) score, number of levels operated, operative duration, intraoperative blood loss, allogeneic blood transfusion, use of allograft bone, postoperative prophylactic antibiotics use, and preoperative laboratory biomarkers (white blood cell (WBC), neutrophil, lymphocyte and red blood cell count, haematocrit, haemoglobin, fasting blood glucose (FBG)).

According to the criteria recommended specifically for Chinese adults, obesity was defined as the BMI ≥28 kg/m^2.[21] Patients were regarded as current smoking or alcohol drinking if they consumed cigarette or alcohol at least 1 time per month during the past 6 months before index operation.[22]

2.4 | Statistical analysis

Data were presented with mean ± SD and frequency (percentage), respectively. χ^2 or Fisher's exact test was

TABLE 1 Univariate analysis of factors associated with CAR

Variables	Number (%) of patients with CAR ≥0.086 (n = 336)	Number (%) of patients with CAR<0.086 (n = 569)	*P*
Gender (males)	157 (46.7)	251 (44.1)	.445
Age	53.6 ± 13.2	51.1 ± 12.4	.005
18–44	75 (22.3)	157 (27.6)	.022
45–64	190 (56.5)	329 (57.8)	
≥65	71 (21.1)	83 (14.6)	
Body mass index (BMI)	26.2 ± 4.1	25.4 ± 3.4	.002
<28.0	234 (69.6)	462 (81.2)	<.001
≥28.0	102 (30.4)	107 (18.8)	
Hypertension	107 (31.8)	148 (26.0)	.059
Diabetes mellitus	58 (17.3)	56 (9.8)	.001
Heart disease	21 (6.3)	34 (6.0)	.867
COPD	13 (3.9)	17 (3.0)	.423
Cerebrovascular disease	26 (7.7)	40 (7.0)	.692
Peripheral vascular disease	45 (13.4)	27 (4.7)	<.001
Alcohol consumption	94 (28.0)	160 (28.1)	.963
Current smoking	69 (20.5)	95 (16.7)	.147
Previous operation in any site	70 (20.8)	143 (25.1)	.141
Total hospital stays (days)	16.0 ± 5.9	12.7 ± 3.9	<.001
Time from injury to definite operation (days)	4.3 ± 2.9	2.8 ± 1.7	<.001
Postoperative antibiotic use	313 (93.2)	492 (90.0)	.104
Bone grafting			<.001
Yes	247 (73.5)	535 (94.0)	
No	89 (26.5)	34 (6.0)	
ASA score			.104
I	23 (6.8)	57 (10.0)	
II-IV	313 (93.2)	512 (90.0)	
Intraoperative bleeding (ml)	753.4 ± 475.2	575.8 ± 365.8	<.001
Allogenic transfusion	146 (43.5)	144(25.3)	<.001
Surgical duration (minutes)	182.7 ± 53.9	173.3 ± 49.1	.009
WBC (>10*10^9/L)	166 (49.4)	46 (8.1)	<.001
Neutrophil (>6.3*10^9/L)	208 (61.9)	58 (10.2)	<.001
Lymphocyte (<1.1 * 10^9/L)	118 (35.1)	37 (6.5)	<.001
Platelet (>220 * 10^9/L)	36 (10.7)	47 (8.3)	.216
RBC (<Lower limit)	98 (29.2)	22 (3.9)	<.001
Haemoglobin (<Lower limit)	90 (26.8)	34 (6.0)	<.001
Haematocrit (<Lower limit)	158 (47.0)	68 (12.0)	<.001
FBG > 6.1momol/L	147 (43.8)	94 (16.5)	<.001

Note: RBC, red blood cell, reference range: Female, 3.5–5.0 * 10^{12}/L; males, 4.0–5.5 * 10^{12}/L; Haemoglobin, reference range: Females, 110 to 150 g/L; males, 120 to 160 g/L; Haematocrit, reference range: Females, 35% to 45%; males, 40% to 50%.

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CAR, C-response protein to albumin ratio; COPD, chronic obstructive pulmonary disease; CRP, C-response protein; FBG, fasting blood glucose; WBC, white blood cell.

used for comparison of categorical data; Student-*t* test or Mann Whitney-*U* test was used for comparison of continuous data, based on their normality status which was explored by the Kolmogorov–Smirnov test.

The receiver operating characteristic (ROC) curve was constructed to determine the optimal cut-off value of CAR for the possibility of SSI, when the specificity plus sensitivity was maximised. Area under the curve (AUC) was calculated for evaluating the discrimination ability. Based on the optimal cut-off value, two groups with high- or low- CAR formed, and their differences in terms of variables were detected by univariate analyses. Variables with $P < .10$ in the univariate analyses were entered into the multivariate logistic regression model for further adjustment, namely the "total adjusted model". The effect size was reported as odds ratios (ORs) and 95% confidence intervals (95% CIs). The goodness-of-fit of the multivariate model was evaluated by Hosmer–Lemeshow (H-L) test, with a $P > .05$ indicating an acceptable result; and Nagelkerke R^2 was used to further quantify that, with greater value representing the better result. $P < .05$ was regarded as statistical significance for all analyses. SPSS 25.0 software package (IBM, Armonk, New York, USA) was used to perform all analyses.

3 | RESULTS

A total of 905 patients were enrolled, including 408 males and 497 females, with a mean age at surgery of 52.0 ± 12.7 years. The mean preoperative stay was 3.3 ± 2.4 days, and the operated levels were 1.8 ± 2.1. Twenty-nine patients developed an SSI, indicating an incidence rate of 3.2%, including 11 (incidence, 1.2%) deep and 18 (2.0%) superficial SSIs. 72.4% (21/29) of SSIs occurred at index hospitalisation, and the remaining 27.6% after discharge. Bacteria culture positive result was in 17 (70.8%) of 24 patients whose excretion or tissue sample was taken for culture, 7 were caused by mixed bacterial and 10 by single bacteria. Patients with an SSI had a significantly additional 10.7 days of index hospital stay (24.6 ± 16.1 vs 13.9 ± 1.9 days, $P = .001$, Mann Whitney-*U* test), compared to those without.

The CAR was ranging from 0 to 5.43 (median, 0.05; interquartile ranges, 0.02-0.24) and the mean was 0.35 ± 0.73, with 0.88 ± 0.98 and 0.03 ± 0.02 in the SSI and non-SSI group, respectively. As shown in Figure 1, the optimal cut-off value of CAR was 0.09, corresponding to a sensitivity of 0.759 and a specificity of 0.642, and the AUC was 0.720 (95%CI, 0.641 to 0.799; $P < .001$). 336 (37.1%) patients had a CAR ≥0.09 and 22 (6.5%) developed an SSI, while among 569 (62.9%) who had a CAR <0.09 the incidence of SSI was 1.2% (7/569). The crude relative risk ratio was 5.63 (95%CI, 2.41 to 13.34; $P < .001$).

TABLE 2 Association of CAR with the postoperative SSI after adjustment for numerous variables

Variables	OR and 95%CI	*P*
CAR ≥ 0.09	8.06 (2.88–22.57)	<.001[a]
Hypertension	0.34 (0.11–1.00)	.049[a]
Diabetes	3.63 (1.25–10.56)	.018[a]
Age (each 1-year increment)	0.98 (0.92–1.06)	.655
BMI (kg/m^2)	0.98 (0.82–1.16)	.790
Obesity (BMI ≥ 28 kg/m^2)	1.07 (0.25–4.53)	.925
Peripheral vascular disease	0.54 (0.10–2.86)	.467
Preoperative stay (each 1-day increment)	1.12 (0.97–1.29)	.121
Surgical duration (minute)	1.01 (1.00–1.02)	.096
Bone grafting	3.47 (0.89–13.49)	.072
FBG > 6.1 mmol/L	1.54 (0.50–4.67)	.451
WBC > 10 * 10^9/L	0.74 (0.16–3.49)	.699
Neutrophil > 6.3 * 10^9/L	0.27 (0.05–1.45)	.126
Lymphocyte < 1.1 * 10^9/L	1.47 (0.50–4.34)	.490
RBC < Lower limit	0.93 (0.21–4.14)	.928
Haemoglobin < Lower limit	2.43 (0.46–12.83)	.295
Haematocrit < Lower limit	0.38 (0.08–1.75)	.212

[a]Significant variable.
Abbreviations: BMI, body mass index; CAR, C-response protein to albumin ration; FBG, fasting blood glucose; RBC, red blood cell; WBC, white blood cell.

The relationship between CAR and the clinical characteristics was shown in Table 1. Patients with CAR ≥ 0.09 are older (53.6 ± 13.2 vs 51.1 ± 12.4, $P = .005$), more likely to be obese ($P = .002$ for continuous and $P < .001$ for categorical data form), had a higher prevalence of diabetes (17.3% vs 9.8%, $P = .001$), peripheral vascular disease (13.4% vs 4.7%, $P < .001$), longer wait to operation (4.3 ± 2.9 vs 2.8 ± 1.7, $P < .001$), more intraoperative blood loss (753.4 ± 475.2 vs 575.8 ± 365.8, $P < .001$), longer surgical duration (182.7 ± 53.9 vs 173.3 ± 49.1, $P = .009$), higher proportion of allogenic transfusion ($P < .001$), lower proportion of bone grafting (73.5% vs 94.0%, $P < .001$), and greater prevalence of WBC >10 * 109/L ($P < .001$), neutrophil >6.3 * 109/L ($P < .001$), lymphocyte <1.1 * 109/L ($P < .001$), RBC ($P < .001$), haemoglobin ($P < .001$), haematocrit ($P < .001$) and FBG ($P < .001$).

The multivariate analyses showed that CAR ≥0.09 was associated with 8.06-fold increased risk of SSI, together with diabetes (OR, 3.63; 95%CI, 1.25–10.56; $P = .018$); the hypertension was identified as a protective

factor for SSI (OR, 0.34; 95%CI, 0.11–1.00; $P = .049$). Other variables were not statistically significant (all $P > .05$). The detailed results were presented in Table 2.

The goodness-of-fit of the multivariate model was acceptable ($P = .218$, $\chi^2 = 10.722$; Nagelkerke $R^2 = 0.249$).

4 | DISCUSSION

The principal finding of the present study was the preoperative CAR could predict the SSI following PLIF and instrumentation following lumbar degenerative diseases, with a large magnitude of association (crude OR, 5.6; adjusted OR, 8.06). The optimal cut-off value of CAR was 0.09, corresponding to a sensitivity of 0.759. a specificity of 0.642 and the AUC of 0.720. We also found the overall incidence of SSI was 3.2%, 1.2% for deep and 2.0% for superficial SSI. An SSI was associated with additional 10.7 days for index hospital stay.

Currently, PLIF is increasingly used for surgical treatment of lumbar degenerative diseases. However, the relatively higher rate of complications constitutes a major concern, primarily due to the more surgical trauma from bilateral instead of unilateral approach used for discectomy, bone graft, and fusion cage implantation. In our study, this incidence rate of SSI was 3.2%, in range of the reported figures, i.e., a pooled 3.0% in a meta-analysis[23] and 3.4% in a most recent original paper,[5] which applied a very similar inclusion and exclusion criteria as ours. However, in most studies, due to the study design (e.g., focus on comparison of outcomes of PLIF versus other surgical approaches, not on SSI in a separate cohort of PLIF group), heterogenous population, and especially the relatively small sample size of the participants (range, 30-125), the incidence rates of SSI varied greatly, from 0% to 7.2%.[24-26]

Many risk prediction tools have been established in fields of SSI following surgically treated lumbar degenerative diseases,[5,27-29] but no single one provides robust prognostication, especially in the setting of heterogenous study population. Ideally, a prediction tool should be accessible and easy-to-use, relying upon readily available parameters that are routinely measured preoperatively. Inflammation-based biomarkers fit well these characteristics and more importantly, they are often presenting remarked change before clinical signs or symptoms are manifested.[18]

CAR, as a novel index, has proved to provide useful prognostic information for sepsis, abdominal surgeries, cancer, or emergency laparotomy.[10-13,30] However, the cut-off selected for use are often inconsistent, even quite different. For example, Hu et al[31] used 0.24 as cut-off value to predict the overall survival in patients with osteosarcoma and Shi et al used 0.27 to predict periprosthetic joint infection, both of which were 3-fold as ours (0.09); while in a study of gastric cancer, Aoyama et al[12] found the optimal cut-off point of CAR was 0.05 to optimally evaluate the overall survival and recurrence-free survival. Specific at SSI following a range of surgeries, but not including spinal surgeries, the findings were not conclusive,[18,32,33] and some researchers suggested the postoperative early-period (day 1 or 2) rather than preoperative CAR should be more applicable.[32]

CAR was derived by dividing C-response protein concentration by serum albumin level, but exhibited better performance than either single one.[32-34] The possible reasons may be related to the nature of time-dependent response of them to inflammatory, nutritional or immune status. A previous study suggested no apparent correlation between albumin level and before-infection body status or acute inflammatory reaction, which was partly explained by its long half-life.[34] The CRP concentration in serum was low, and it was very possible to have a false-negative result based on serum CRP.[35] In contrast, CAR can reduce the error caused by a single CRP or albumin, and improves the prediction ability.

In the present study, we determined the optimal cut-off of CAR to be 0.09, equal to or higher than which was associated with 8.06-fold increased risk of SSI. This is a high-magnitude association, suggesting its promising role for predicting SSI. Thus, during preoperative preparation, such a value or higher should alert the surgeons to the substantially increased risk of SSI; and more importantly, the preventive interventions should be promptly implemented to lower the value thus to control the risk of SSI to a relatively low level, for example, delaying the operation or correcting the unfavourable conditions (albumin or substitute supplement, suppressing inflammation response or optimising blood circulation function et al).

The merits of this study are the relatively large sample of a real-world group of patients, and inclusion of numerous covariables for adjustment. However, several limitations to this study should be noted. First, the retrospective nature had its inherent limitation in data collection, which might have compromised the precise of the findings. In particular, patients' self-reported comorbidities made it almost impossible to capture the true underlying pathophysiological conditions. Second, the single-centre design had compromised the generalizability of the findings to other settings despite a real-world population setting herein, because more complex conditions preferred to be centralised for management in this tertiary referral hospital. Third, as every logistics regression analysis, the residual confounding effects attributable from some unmeasured or unknown factors remain.

Since CAR is a simple, convenient and readily available index, with a high magnitude of association with SSI, future studies are warranted to verify this finding.

In summary, the incidence rate of SSI following PLIF and instrumentation for lumbar degenerative disease was 3.2%. The CAR was identified to be independently associated with 8.06-fold increased risk of SSI. CAR should be considered as a useful routine prediction tool in practice for predicting the SSI after future high-level evidences verified its effectiveness.

AUTHORS' CONTRIBUTIONS

Baiqiang Hu conceived the idea for the study; Shaozheng Qu, and Mingchuan Sun designed the study. All the authors collected the relevant data. Hongliang Sun prepared the figures and tables and performed the statistical analyses. All the authors interpreted the data and contributed to preparation of the manuscript. Shaozheng Qu and Mingchuan Sun contributed equally to this manuscript.

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CONFLICT OF INTEREST

All the authors declare that they have no competing interests.

ETHICS STATEMENT

Ethics committee of the Yantai Yuhuangding Hospital (NO 2022-004), which waived the requirement for informed consent due to the retrospective nature and identification anonymity.

DATA AVAILABILITY STATEMENT

As per the institutional policy, the data used in this study is not available publicly, but can be obtained from the corresponding author upon the justied requirement for only research purpose.

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