Cross-sectional Study

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C-reactive protein/lymphocyte ratio as a prognostic biomarker in acute pancreatitis: a cross-sectional study assessing disease severity

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Background: The C-reactive protein/lymphocyte ratio (CLR) is a prognostic biomarker of various diseases. However, its significance in acute pancreatitis (AP) remains unknown. The main aim of this study was to investigate the association between the CLR and disease severity in patients with AP.

Methods: This cross-sectional study included 476 AP patients [mild acute pancreatitis (MAP), $n = 176$; moderately severe acute pancreatitis (MSAP) and severe acute pancreatitis (SAP), $n = 300$]. The primary exposure of interest was the baseline CLR. The primary outcome was the incidence of moderate to severe AP. Multivariate logistic regression and restricted cubic spline analyses were performed to evaluate the association between the CLR and the incidence of moderate to severe AP. Receiver operating characteristic (ROC) analysis was conducted to assess the predictive efficacy, sensitivity, and specificity of CLR in predicting the incidence of moderate to severe AP.

Results: The mean age of the patients was 44 ± 13.2 years, and 76.5% were male. The distribution of CLR was 31.6 (interquartile range, 4.5, 101.7). Moderate to severe AP occurred in 300 cases (63.0%). After multiple adjustments, CLR was independently associated with the incidence of moderate to severe AP (odds ratio, 1.04; 95% CI: 1.03–1.05; $P < 0.001$). A nonlinear relationship was found between CLR and the incidence of moderate to severe AP, with a threshold of approximately 45. The effect size and CI below and above the threshold value were 1.061 (1.033–1.089) and 1.014 (0.997–1.031), respectively. The area under the curve (AUC) for CLR was 87.577% (95% CI: 84.443– 90.710%) with an optimal cut-off value of 30.835, resulting in a sensitivity of 73.7% and a specificity of 88.6%.

Conclusions: There was a nonlinear relationship with a saturation effect between the CLR and the incidence of moderate to severe AP. The CLR measured within 24 h of admission may serve as a promising biomarker for predicting the emergence of moderate to severe AP, thereby providing a more scientifically grounded basis for preventing such cases. Nonetheless, further research is warranted to validate and strengthen these findings.

Keywords: acute pancreatitis, C-reactive protein/lymphocyte ratio, severity

Introduction

Acute pancreatitis (AP) is a common gastrointestinal emergency characterized by rapid progression. The chief etiological factors that contribute to AP include biliary tract disease, excessive alcohol consumption, and hypertriglyceridemia[1–3]. Mild acute pancreatitis (MAP) has prompt resolution and favorable prognostic outcomes. In contrast, moderately severe acute pancreatitis (MSAP) and severe acute pancreatitis (SAP) tend to cooccur with organ failure and local or systemic complications, resulting in an increased mortality risk[4–6]. Accordingly, the timely and accurate identification of high-risk patients who are prone to developing moderate to severe AP, coupled with diligent monitoring and timely therapeutic intervention, is of paramount importance for the diagnosis and management of AP.

Numerous scoring systems have been devised for the anticipation of AP severity. Predominantly employed are scores tailored explicitly for AP, including the Ranson score[7], Bedside Index of Acute Pancreatitis Severity (BISAP)[8], and computed tomography severity index (CTSI)[9]. Additionally, there are scores not exclusive to AP, such as the Acute Physiology and

HIGHLIGHTS

- Elevated C-reactive protein/lymphocyte ratio (CLR) is an independent risk factor for moderate to severe acute pancreatitis (AP).
- The relationship between CLR and the incidence of moderate to severe AP exhibits a nonlinear pattern.
- Increased CLR on admission serves as a predictive factor for an extended length of hospital stay among patients diagnosed with AP.

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Chronic Health Examination (APACHE)-II[10]. However, scoring systems featuring a greater number of indicators pose challenges in terms of accessibility.

Recently, evidence highlighting the utility of several serum markers in predicting the occurrence of local and systemic complications as well as in assessing the severity and mortality risk of AP is increasing[11–13]. The C-reactive protein/lymphocyte ratio (CLR) has recently emerged as a novel biomarker with prognostic potential in a range of diseases, such as pancreatic cancer[14], colorectal cancer[15], and COVID-19[16]. Elevated C-reactive protein (CRP) levels are correlated with the onset of pancreatic necrosis and a more severe course of AP[17]. However, its role and significance in AP have yet to be reported. This study aimed to address this research gap by investigating the potential association between CLR and disease severity in patients with AP.

Materials and methods

Data sources and study population

This retrospective cross-sectional study was conducted at our institution to evaluate hospitalized patients diagnosed with AP between January 2018 and December 2019. The study assessed various demographic and clinical factors including sex, age, etiology, smoking history, alcohol consumption, diabetes mellitus, fatty liver, duration of hospitalization, blood counts, and CRP levels within 24 h of admission. The exclusion criteria comprised patients with chronic pancreatitis, as well as various tumors such as pancreatic, esophageal, colorectal, and breast cancers. Pregnant women and individuals with missing information were also excluded (Fig. 1). Ultimately, 476 patients with AP were included in the analysis, including 176 with MAP and 300 with moderate to severe AP based on the Atlanta classification[18]. MAP is characterized by the absence of organ failure and the absence of local or systemic complications. MSAP is characterized by the presence of transient organ failure or local or systemic complications in the absence of persistent organ failure. SAP is characterized by persistent organ failure. Ethical approval for this study was obtained from the Clinical Research Ethics Committee of our institution(QYL 2021-233), and all procedures adhered to the principles outlined in the Declaration of Helsinki and its later amendments. The requirement for written informed consent was waived due to the retrospective nature of the study. The research was retrospectively registered in the Chinese Clinical Trial Registry. The work has been reported in line with the STROCSS criteria[19].

Measurement of CLR

Inflammatory markers were used to identify a correlation that offers accuracy in predicting the severity of AP. The CLR was calculated as follows: CLR = CRP level (mg/l)/lymphocyte count (10^9/l)[15].

Statistical analysis

The baseline data distribution of the patients enrolled in this study is presented according to the different halves of the CLR groups. Continuous variables are expressed as mean and SD for normally distributed data or median and interquartile range (IQR) for skewed data. Categorical variables were presented as percentages (%). To assess the differences between groups, a one-way analysis was conducted for normally distributed continuous variables, while the χ^2 test and trend test were employed for categorical variables.

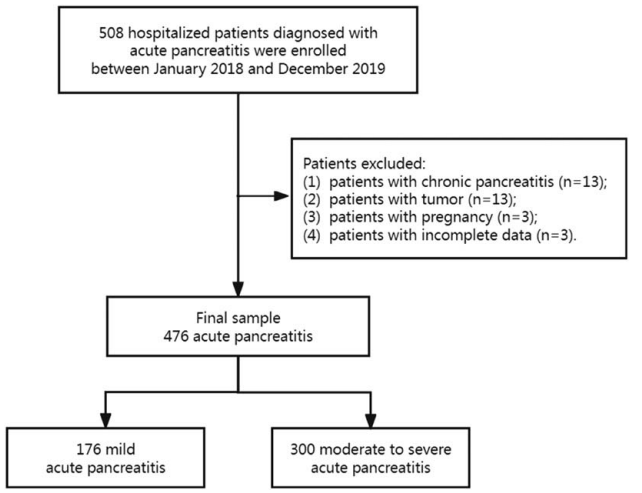

Figure 1. The flow chart of the study.

Univariate and multivariate logistic regression models were used to assess the odds ratios (OR) and 95% CI for the association between variables and moderate to severe AP incidence. Covariables for inclusion in the model were determined based on their association with the outcomes of interest, or if they led to a change in the effect estimate greater than 10%[20]. The multivariate logistic regression model incorporated the following variables: CLR, age, sex, smoking, alcohol consumption, diabetes, fatty liver disease, etiology, and hospitalization days.

Restricted cubic spline analyses were conducted to investigate the relationship between CLR and moderate to severe AP incidence. A two-piecewise linear regression model was employed to identify potential threshold effects. The likelihood ratio test and bootstrap resampling method were used to determine inflection points.

Subgroup analyses were conducted for age, sex, smoking status, alcohol consumption, diabetes, fatty liver, and etiology using logistic regression models.

The predictive efficacy, sensitivity, and specificity of CLR in predicting the incidence of moderate to severe AP were evaluated through Receiver operating characteristic (ROC) analysis. The optimal threshold for CLR was determined utilizing the Youden Index.

All analyses were performed using the statistical software packages R 3.3.2 (http://www.R-project.org, The R Foundation) and Free Statistics software version 1.7. Statistical significance was set at $P < 0.05$ (two-sided).

Results

Demographics and baseline information

A total of 476 patients were included in the study. The baseline characteristics of all participants stratified into halves of CLR are presented in Table 1. The mean age of the patients was 44 ± 13.2 years, and 76.5% were male. The distribution of CLR was 31.6 (IQR, 4.5, 101.7). Individuals with the higher CLR

Table 1

Baseline characteristics of selected participants.

Covariates	ALL ($n=476$)	Low ($n=238$)	High ($n=238$)	P
Age, Mean ± SD	44.0 ± 13.2	45.1 ± 13.4	42.9 ± 13.0	0.075
Sex, *n* (%)				0.031
Male	364 (76.5)	172 (72.3)	192 (80.7)	
Female	112 (23.5)	66 (27.7)	46 (19.3)	
Etiology, *n* (%)				< 0.001
Hypertriglyceridemia	277 (58.2)	117 (49.2)	160 (67.2)	
Biliary	92 (19.3)	49 (20.6)	43 (18.1)	
Alcohol	53 (11.1)	32 (13.4)	21 (8.8)	
Other	54 (11.3)	40 (16.8)	14 (5.9)	
Smoking, *n* (%)				0.208
No	315 (66.2)	164 (68.9)	151 (63.4)	
Yes	161 (33.8)	74 (31.1)	87 (36.6)	
Alcohol consumption, *n* (%)				0.094
No	280 (58.8)	149 (62.6)	131 (55)	
Yes	196 (41.2)	89 (37.4)	107 (45)	
Diabetes, *n* (%)				< 0.001
No	322 (67.6)	180 (75.6)	142 (59.7)	
Yes	154 (32.4)	58 (24.4)	96 (40.3)	
Fatty liver, *n* (%)				< 0.001
No	196 (41.2)	120 (50.4)	76 (31.9)	
Yes	280 (58.8)	118 (49.6)	162 (68.1)	
Hospitalization days, Mean ± SD	7.4 ± 4.1	6.0 ± 2.6	8.7 ± 4.9	< 0.001
Moderate to severe AP, *n* (%)	300 (63.0)	82 (34.5)	218 (91.6)	< 0.001
CLR	31.6 (4.5–101.7)	4.5 (2.0–11.9)	102.0 (60.1–162.7)	< 0.001

AP, acute pancreatitis; CLR, C-reactive protein/lymphocyte ratio.

(termed as 'high') were predominantly male, tended to have high triglyceride levels, had longer hospitalization durations, and exhibited a higher prevalence of diabetes and fatty liver. Moderate to severe AP occurred in 300 cases (63.0%). Notably, there was a significant difference in the incidence of moderate to severe AP among the CLR halves.

Univariate and multivariable regression analyses

The results of the univariateand multivariate logistic regression analysesare presented in Table 2. In multivariate logistic regression model, the CLR displayed a positive correlation with the incidence of moderate to severe AP. After multiply adjustment, each unit increase in CLR was associated with a 4% higher risk of developing moderate to severe AP [OR = 1.04; 95% CI:1.03–1.05; $P < 0.001$; Table 2].

Subgroup analyses

The findings of the subgroup analyses are shown in Figure 2. Upon stratification by age, sex, smoking status, alcohol consumption, diabetes, fatty liver, and etiology, no significant interactions were observed among the any of the subgroups (all $P > 0.05$).

Nonlinear relationship between CLR and the incidence of moderate to severe AP

After accounting for certain covariates, we identified a nonlinear dose-response relationship between CLR and the incidence of moderate to severe AP (Fig. 3). Using a two-piecewise linear regression model, the CLR threshold was determined to be 45. Below this threshold, each unit increase in CLR was associated with a 6.1% higher risk of developing moderate to severe AP (OR, 1.061; 95% CI: 1.033–1.089; $P < 0.001$; Table 3 and Fig. 3). Conversely, above this threshold, a stable association was observed between the CLR and moderate to severe AP incidence (OR, 1.014; 95% CI: 0.997–1.031; $P > 0.05$; Table 3 and Fig. 3).

ROC curve analysis

We plotted ROC curves for CLR to predict the occurrence of moderate to severe AP, and the data from Figure 4 is summarized in Table 4. The area under the curve (AUC) for CLR was 87.577% (95% CI: 84.443– 90.710%) with an optimal cut-off value of 30.835, resulting in a sensitivity of 73.7% and a specificity of 88.6%.

Discussion

In this retrospective cross-sectional study, we observed an independent correlation between the CLR and disease severity in patients with AP. Specifically, we found a positive association between CLR and moderate to severe AP risk. Importantly, this association remained consistent and robust, even after accounting for underlying covariates and confounding factors. To the best of our knowledge, this study represents the first evidence of a

Table 2

Univariate and multivariate logistic regression analysis for moderate to severe acute pancreatitis.

Covariates	Comparisons	OR (95% CI)	P	Adjusted OR (95% CI)	P
CLR		1.04 (1.03–1.05)	< 0.001	1.04 (1.03–1.05)	< 0.001
Age		0.97 (0.96–0.99)	< 0.001	0.96 (0.94–0.98)	0.001
Sex	Female vs. Male	0.45 (0.29–0.69)	< 0.001	0.42 (0.21–0.86)	0.017
Smoking	Yes vs. No	1.11 (0.75–1.64)	0.612	0.48 (0.22–1.01)	0.054
Alcohol consumption	Yes vs. No	1.43 (0.97–2.1)	0.068	1.3 (0.58–2.87)	0.523
Diabetes	Yes vs. No	1.99 (1.31–3.03)	0.001	1.08 (0.57–2.06)	0.81
Fatty liver	Yes vs. No	2.8 (1.9–4.11)	< 0.001	1.32 (0.71–2.45)	0.381
Etiology	Biliary vs. Hypertriglyceridemia	0.44 (0.27–0.71)	0.001	0.86 (0.36–2.03)	0.731
	Alcohol vs. Hypertriglyceridemia	0.39 (0.22–0.72)	0.002	0.7 (0.27–1.81)	0.461
	Other vs. Hypertriglyceridemia	0.15 (0.08–0.28)	< 0.001	0.22 (0.08–0.56)	0.002
Hospitalization days		1.34 (1.23–1.46)	< 0.001	1.34 (1.19–1.52)	< 0.001

CLR, C-reactive protein/lymphocyte ratio.

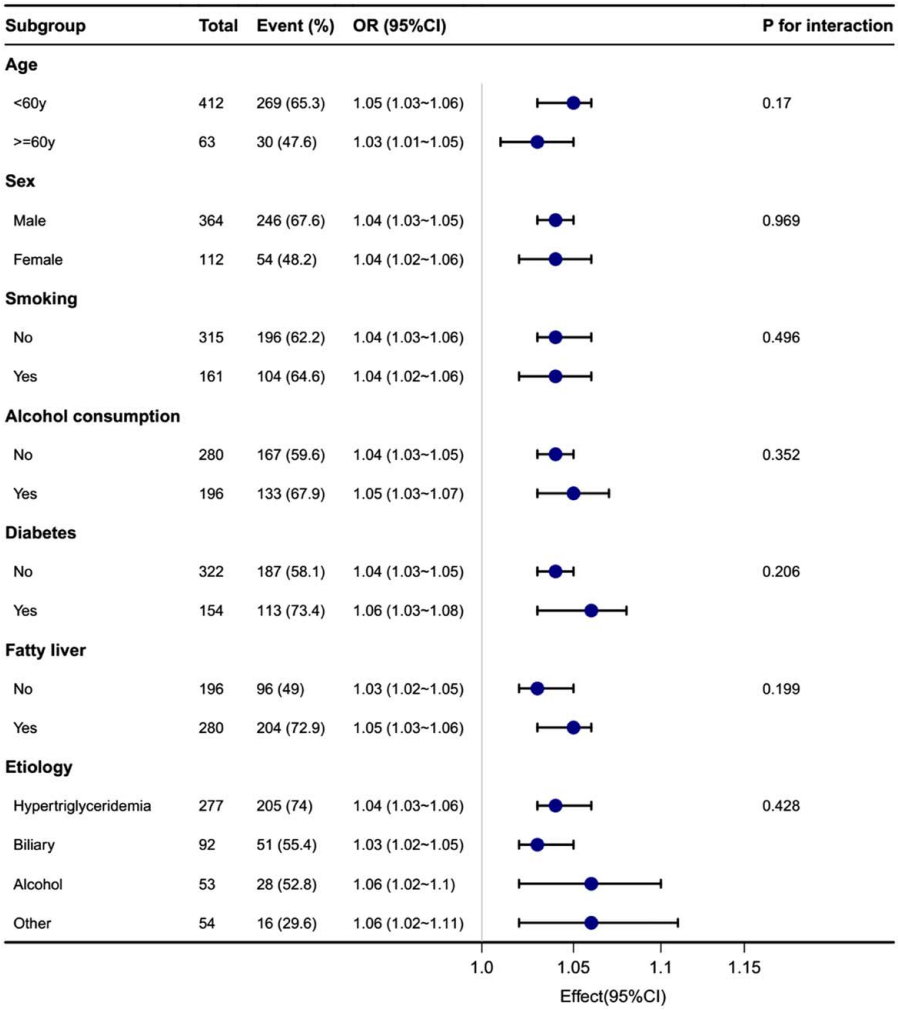

Figure 2. Subgroup analysis between C-reactive protein/lymphocyte ratio and the incidence of moderate to severe acute pancreatitis.

significant correlation between the CLR and disease severity in patients with AP.

Furthermore, we observed a nonlinear and nonisometric trend in the changing pattern of the effect size across different CLR groups, indicating a dose-response relationship between CLR and AP severity. Notably, a significant difference in the correlation between CLR and AP severity was observed when stratified using a threshold of 45. Specifically, when the CLR was less than 45, the incidence of moderate to severe AP increased with as CLR values rose. However, when the CLR was ≥ 45, the association was not statistically significant. It is suggested that there was a nonlinear relationship, characterized by a saturation effect, between CLR and disease severity in patients with AP. Therefore, beyond a CLR value of 45, there was no notable escalation in the incidence of moderate to severe AP as the CLR increased further. These results suggest that CLR exhibits potential as a promising biomarker for predicting the emergence of moderate to severe AP. AP is an inflammatory disease with considerable variability in severity. Hyperinflammation plays a pivotal role in poor prognosis of patients with AP. Consequently, employing a combination of biomarkers that reflect the inflammatory process is a promising strategy. Previous investigations have demonstrated the association between various inflammatory biomarkers, including single indicators such as CRP[17]and procalcitonin[21], as well as composite indicators like neutrophil-to-lymphocyte ratio (NLR)[11,22], platelet-to-lymphocyte ratio (PLR)[22], and systemic immune-inflammation index (SII)[23], and the outcome of AP. However, to date, no studies have explored the correlation between CLR and AP severity. Thus, our study is the first to investigate the clinical utility of CLR in the context of AP. Notably, CRP level reflects the systemic inflammatory response[24], making it a reliable predictor of AP severity[17]. Additionally, reduced lymphocyte count and increased lymphocyte apoptosis have been linked to lymphocyte dysfunction[25]. A persistently low lymphocyte count has been associated with adverse prognoses and serves as an independent marker of progressive inflammation[26]. Consequently, CLR levels could potentially signify an equilibrium state between systemic inflammatory and immune responses within the body.

Multiple studies have demonstrated that an elevated CLR serves as an independent risk factor for unfavorable prognosis in various diseases, including certain types of cancer and

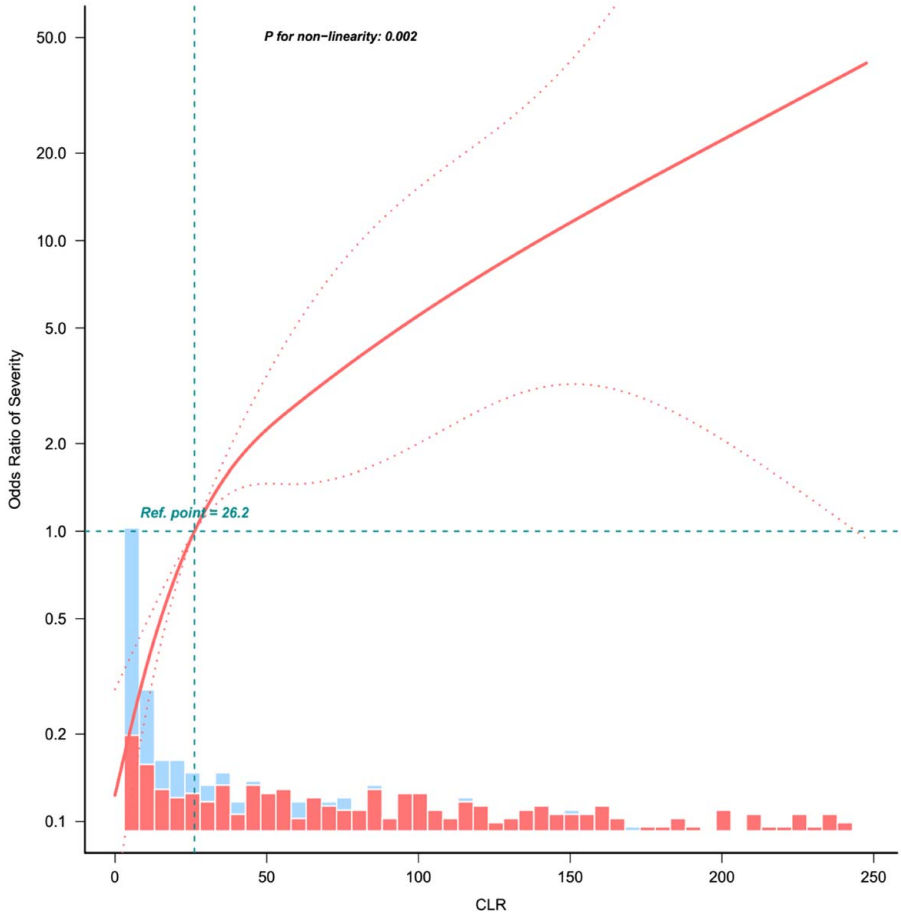

Figure 3. Nonlinear relationship between C-reactive protein/lymphocyte ratio and the incidence of moderate to severe acute pancreatitis. Adjustment factors included age, sex, smoking, alcohol, diabetes, fatty liver, etiology, and hospitalization days. The red line and the area between the red dashed lines represents the estimated values and their corresponding 95% CI, respectively.

inflammatory diseases such as COVID-19[14–16]. In our study, we observed a threshold effect using a restricted cubic spline analysis. Specifically, below the threshold value of 45, there was a notable increase in the incidence of moderate to severe AP as the CLR levels increased. Therefore, we propose that CLR measurements taken within 24 h of admission have a significant predictive value for assessing the severity of AP. The existing scoring systems utilized for the assessment of AP, including the Ranson score, BISAP, CTSI, and APACHE-II, integrate multiple indicators, making them complex to calculate and not easily accessible. However, CLR can be conveniently and swiftly calculated using the complete blood count and C-reactive protein values obtained within the first 24 h of admission. The AUC value of 87.577% for CLR in the context of predicting the occurrence of moderate to severe AP indicates a relatively good discriminatory performance. Early identification of patients at risk of developing moderate to severe AP is crucial, and the clinical utility of CLR measurement in guiding treatment decisions cannot be understated. The CLR may prove to be a more practical alternative to the complex multifactorial scoring system in clinical practice, considering its low cost and easy accessibility. This makes it a more convenient option for rapid evaluation of AP severity.

Our study has several limitations. First, it is important to note that this investigation employed a cross-sectional design; as such, caution should be exercised when inferring causality from the observed associations. Second, inherent to all observational studies, the presence of uncontrolled potential confounding factors remains possible. Finally, the prevalence of hypertriglyceridemic AP is on the rise, constituting over 50% of the AP cases admitted to our gastroenterology department. It is noteworthy that hypertriglyceridemic AP has a greater propensity to progress towards moderate to severe AP. As a result, our study revealed a higher prevalence of moderate to severe AP. Therefore, caution

Table 3

Threshold effect analysis of the relationship between C-reactive protein/lymphocyte ratio and the incidence of moderate to severe acute pancreatitis.

CLR	OR (95% CI)	*P*
< 45	1.061 (1.033–1.089)	< 0.001
≥ 45	1.014 (0.997–1.031)	0.1035
Likelihood ratio test	—	0.002

CLR, C-reactive protein/lymphocyte ratio.

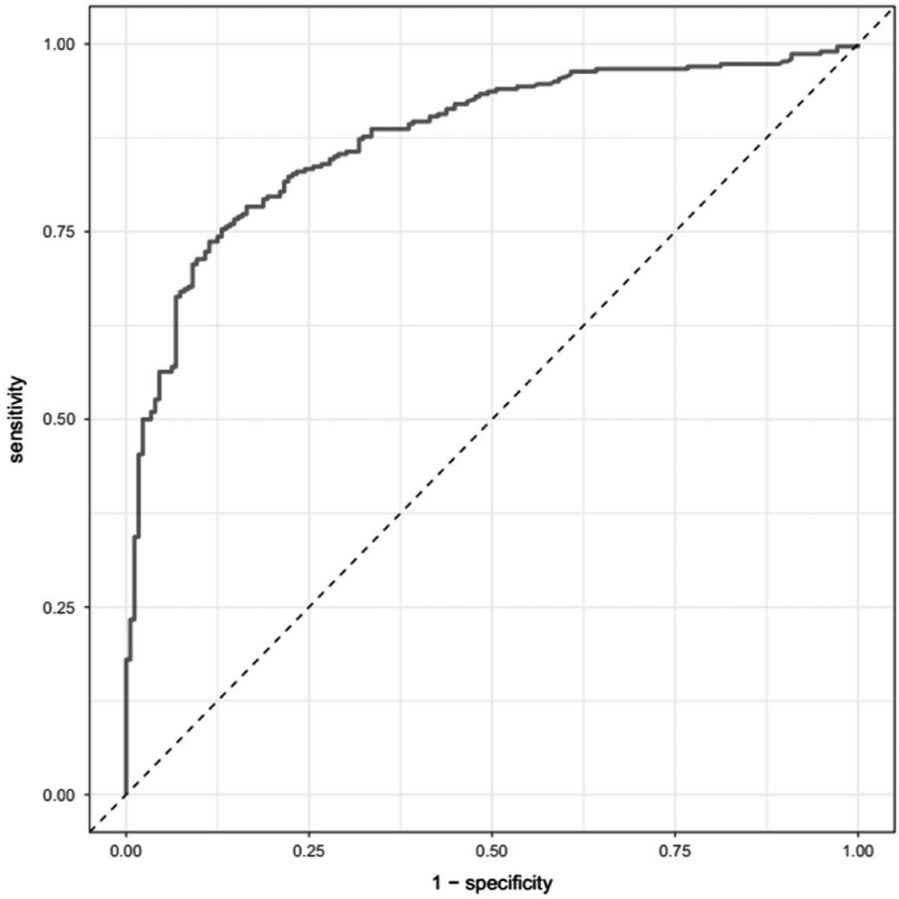

Figure 4. Receiver operating characteristic analysis of C-reactive protein/lymphocyte ratio in predicting the onset of moderate to severe acute pancreatitis.

Table 4

Information of receiver operating characteristic curve in Figure 4.

Variables	AUC	95% CI	Threshold	Sensitivity	Specificity
CLR	87.577%	84.443– 90.710%	30.835	0.737	0.886

AUC, area under the curve; CLR, C-reactive protein/lymphocyte ratio.

should be exercised when generalizing our findings to other populations.

Conclusion

There was a nonlinear relationship with a saturation effect between the CLR and the incidence of moderate to severe AP. The CLR measured within 24 h of admission may serve as a promising biomarker for predicting the emergence of moderate to severe AP, thereby providing a more scientifically grounded basis for preventing such cases. Nonetheless, further research is warranted to validate and strengthen these findings.

Ethical approval

Ethical approval for this study was obtained from the Clinical Research Ethics Committee of First Hospital of Quanzhou (QYL 2021-233).

Consent

The requirement for written informed consent was waived due to the retrospective nature of the study.

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This study did not receive any grants or funding from the public, commercial, or non-profit sectors.

Author contribution

X.C. and Z.L.: study conception and design; X.C., Y.C., and C.L.: data collection; X.C.: data analysis and interpretation; X.C.: drafting of the manuscript; Z.L. and C.L.: critical revision. All authors contributed in final approval.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: Chinese Clinical Trial Registry.

2. Unique identifying number or registration ID: ChiCTR23-00075089.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.chictr.org.cn/showproj.html?proj=203612.

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Data availability statement

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

Provenance and peer review

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Presentation

None.

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