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Association Between the Systemic Inflammation Response Index and Severity of Acute Pancreatitis: A Retrospective Cohort Study

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Purpose: This study aimed to determine the association of the systemic inflammatory response index (SIRI) with severity in patients with acute pancreatitis (AP).

Methods: This retrospective study was conducted using clinical data of 1514 patients with AP who were admitted between January 2019 and October 2023 to the First Clinical Medical College of Three Gorges University. SIRI was calculated as peripheral blood neutrophils × monocytes/lymphocytes ratio, and patients were divided into tertiles according to the SIRI levels. The comparison of demographic characteristics, clinical manifestations, laboratory parameters, and outcomes was made among groups. We also carried out multivariate logistic regression to analyze risk factors independently and forecast AP severity. Furthermore, the relationship between SIRI and AP severity was assessed using restricted cubic spline analysis. Subgroup analysis was conducted according to age, sex, body mass index, diabetes, white blood cell count, sequential organ failure assessment score, requirement for continuous renal replacement therapy, and etiology of AP.

Results: Among the 1514 enrolled patients, 171 (11.3%) developed severe AP. Higher SIRI levels were independently related to the higher incidence of severe AP (adjusted $P < 0.05$) after adjusting the possible confounders. Nonlinear curve fitting demonstrated the reverse J-shaped relationship of SIRI with AP severity, with inflection points at 13. A consistent association was observed across various subgroup analyses.

Conclusion: SIRI independently forecasts the severity of AP. This readily available biomarker may facilitate early stratification of risk and prompt intervention in clinical practice.

Keywords: acute pancreatitis, systemic inflammatory response index, severity

Introduction

Acute pancreatitis (AP) is a complex inflammatory condition characterized by significant incidence and potential mortality. AP has a relatively low mortality rate; however, severe acute pancreatitis (SAP) can reach up to 22.7%.[1] Patients who develop SAP are defined as having persistent organ dysfunction, with mortality rates reaching up to 30%, although more than 50% of AP cases follow a mild and self-limiting course.[2] The disparity in outcomes highlights the critical need for early assessment of severity and prompt intensive care unit admission.[3] However, there are currently no reliable, feasible, and definitive biomarkers.

Systemic inflammatory response index (SIRI) is a novel inflammatory variable that exhibits a wide clinical utility across multiple medical fields. For example, SIRI has demonstrated its ability to predict multiple organ dysfunction syndrome in patients with wasp sting injuries,[4] correlate with outcomes in subarachnoid hemorrhage,[5] and function as a prognostic marker in ischemic stroke[6] and coronary artery disease.[7,8] These results underscore the potential of SIRI as a reliable biomarker for systemic inflammation and immune dysregulation, which are also critical features of acute pancreatitis.

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SIRI is a comprehensive indicator of the activation of inflammatory response and deterioration of immune function. SIRI provides a widespread assessment by incorporating monocytes (MONO), neutrophils (NEU), and lymphocytes (LYM) into a single metric compared to single-parameter measurements, such as counts of NEU, LYM, or total white blood cells (WBC). Consequently, this composite nature presents enhanced stability and superior predictive value because SIRI shows reduced susceptibility to individual pathophysiological variations.[9]

Based on these advantages, this cohort study was conducted to investigate the relationship of SIRI with disease severity among Chinese individuals with AP. To the best of our knowledge, this is the first study to systematically evaluate SIRI as a potential prognostic indicator in this clinical context.

Materials and Methods

Study Design

This study included 1514 patients with AP who were hospitalized at Central People's Hospital of Yichang between January 2019 and October 2023, in line with the eligibility criteria. The inclusion criterion was as follows: inpatients with AP who fulfilled the diagnostic criteria.[10] Patients aged <18 or >80 years; pregnant or lactating women; those with a hospital stay of less than 2 days; and those with malignant tumors, chronic pancreatitis, and incomplete data were excluded. Figure 1 illustrates the procedure of case screening. This study gained approval from the ethics committee of our institution (ethics approval number: 2023–130-01).

Clinical Definitions and Laboratory Data

AP Severity

The severity of AP could be categorized into mild (AP without local or systemic complications or organ failure), moderate (AP that is accompanied by local or systemic complications but not lasting organ failure and/or transient organ failure that resolved in 2 days), and severe (AP accompanied by persistent organ [single/multiple] failures that lasted >48 h) AP in line with the revised Atlanta classification.[11]

Data Collection

Comprehensive clinical data was collected from all enrolled patients. Demographic and anthropometric data were recorded for age, sex, and body mass index (BMI). Clinical characteristics encompassed hospital stay length, systolic blood pressure, the requirement of continuous renal replacement therapy (CRRT), mechanical ventilation support, and blood transfusion. The disease severity was assessed by adopting the Bedside Index of Severity in Acute Pancreatitis (BISAP),[12] and the sequential organ failure assessment (SOFA) scores.[13] These were determined in 24 h post-admission.

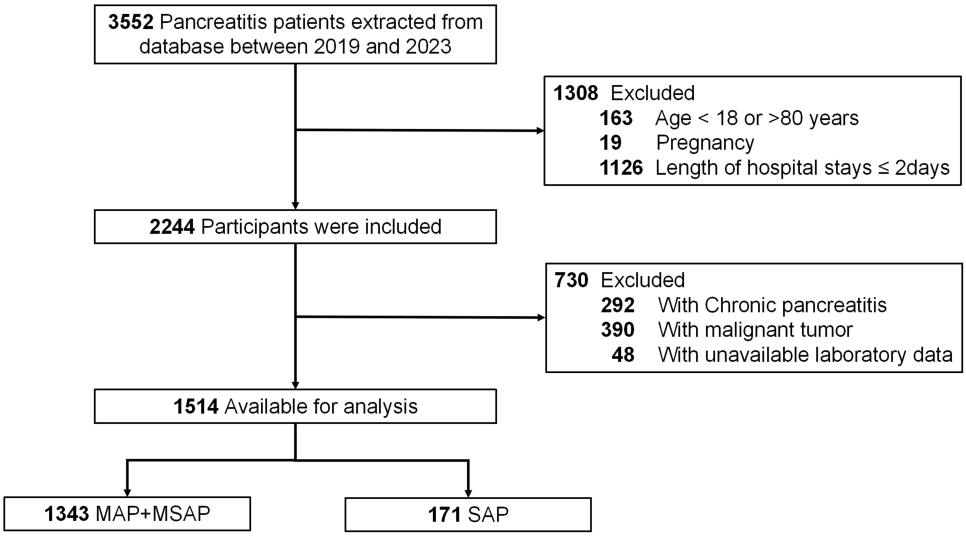

Figure 1 Flow diagram of the screening and enrollment of the participants of the study.
Abbreviations: MAP, mild acute pancreatitis; MSAP, moderate acute pancreatitis; SAP, severe acute pancreatitis.

Hematologic factors, including WBCs, platelets, LYM, NEU, MONO counts, and hemoglobin (HGB) levels, were obtained from complete blood count analyses. Biochemical parameters included fasting plasma glucose (FPG), albumin, C-reactive protein (CRP), triglyceride (TG), creatinine (CREA), calcium (Ca^{2+}), aspartate aminotransferase (AST), and procalcitonin. The formula below was adopted for calculating SIRI: (NEU × MONO)/LYM from peripheral blood measurements. The primary outcome was the severity of AP.

Statistical Analysis

Continuous data were indicated using means and standard deviations and assessed through one-way analysis of variance (for normally distributed data) or the Kruskal–Wallis *H*-test (for non-normally distributed data). Categorical data were represented using frequencies and percentages and analyzed using Chi-square and Fisher's exact tests. Thereafter, patients were classified into tertiles according to the SIRI value. Multiple logistic regression was performed to investigate the relation of SIRI with AP severity. According to the Strengthening the Reporting of Observational Studies statement,[14] this study examined unadjusted and multivariable-adjusted models. Variables of P<0.1 upon univariate analysis or those with ≥10% odds ratio change after adding or removing covariates were adjusted. A total of three models were used, namely, in model 1, age, sex, BMI, hypertension, diabetes mellitus (DM), and coronary heart disease (CHD) were adjusted; while heart rate (HR), respiratory rate (RR), pulse oxygen saturation (SpO_2), blood transfusion, SOFA score, BISAP score, and etiology were adjusted according to model 1 in model 2. In model 3, Ca^{2+}, HGB, CRP, AST, TG, CREA, and FPG were adjusted based on model 2. The confounders were basic variables with clinical association or those changing >10% of the effect estimate. The covariables incorporated into model 3 were adopted for adjustment, after conducting a restricted cubic spline (RCS) analysis. There was a nonlinear relationship between SIRI and severity through logical regression. In addition, subgroup analyses based on age (< 65 vs ≥65 years), sex, BMI (< 28 vs ≥28 kg/m^2), diabetes, SOFA (< 8 vs ≥8), CRRT requirement, WBC (< 12 vs ≥ 12 × 10^9/L), and etiology of AP [(biliary vs hyperlipidemic vs other (alcoholic and others)] were implemented. The estimated mean matching approach was used to fill in the missing values.[15] The discovered results were reported through descriptive analysis, while participants with multiple input data were incorporated into regression models.

Statistical analysis was performed using Free Statistics software version 1.9 and statistical software package R (http://www.R-project.org, The R Foundation). Statistical significance was set at P < 0.05 upon a two-sided test.

Results

Patient Basic and Clinical Information

There were 1514 cases enrolled, including 171 (11.3%) with moderate to SAP. Table 1 presents basic demographic data of patients according to the SIRI value. Compared with those with the lowest serum SIRI tertile (T1), patients with intermediate (T2) and high (T3) SIRI levels had enhanced blood transfusion requirements, increased levels of WBC, FPG, NEU/MONO quantities, and decreased LYM quantity. The incidence of moderate to severe pancreatitis increased among those with higher SIRI levels (P < 0.001).

Univariate and Multivariate Regression for SIRI with Severity

Based on the univariate regression, age; sex; hypertension; DM; CHD; HR; RR; SpO_2; etiology; blood transfusion; BISAP score; and WBC, NEU, MONO, and LYM counts were prominent confounders affecting the severity of AP (P < 0.001). According to multivariate logistic regression results, SIRI demonstrated a positive relation with the severity as the continuous variable (odds ratio [OR] 1.05, 95% confidence interval [CI] 1.03–1.06, P<0.001, Table 2). This positive correlation remained to be of statistical significance when confounders were adjusted (OR 1.02, 95% CI 1.00–1.04, P = 0.036). When dividing the SIRI value in diverse tertiles, SAP had ORs of 2.17 and 4.10 for T2 and T3 vs T1 when unadjusted (Table 2). Following multivariate regression, the SAP risk for the T2 and T3 remained significantly higher than that of the T1 in models 1 (OR 4.27, 95% CI 2.69–6.77, P < 0.001) and 3 (OR 2.96, 95% CI 1.46–6.00, P = 0.003).

Nonlinear Relation of SIRI with Severity

Figure 2 illustrates the nonlinear relationship of SIRI with the severity of AP (P for non-linearity = 0.046) through RCS analysis. Two distinct slopes for their relationship were identified through further threshold analysis using the piecewise

Table 1 Basic Characteristics of Enrolled Patients Classified According to the SIRI Tertile

Characteristics	T1 (n = 505) < 2.697	T2 (n = 504) 2.697–7.344	T3 (n = 505) > 7.344	P value
Male	232 (45.9)	281 (55.7)	299 (59.2)	< 0.001
Age(years)	54.0(43.0, 65.0)	52.0(39.0, 62.0)	54.0(43.0, 68.0)	0.002
Death	9 (1.8)	6 (1.2)	8 (1.6)	0.736
LOS (days)	15.9 ± 12.8	15.5 ± 11.3	18.5 ± 13.8	< 0.001
ICU	53 (10.5)	70 (13.9)	124 (24.6)	< 0.001
BMI (kg/m^2)	23.4 (21.2, 26.2)	24.5 (22.0, 27.1)	24.4 (22.0, 27.1)	< 0.001
Hypertension	127(25.1)	120(23.8)	145(28.7)	0.185
DM	67(13.3)	83(16.5)	75(14.9)	0.36
CHD	36(7.1)	29(5.8)	38(7.5)	0.503
SBP (mmHg)	124.0 (114.0, 138.0)	130.0 (119.0, 143.0)	131.0 (117.0, 149.0)	< 0.001
DBP (mmHg)	80.0 (70.0, 88.0)	80.0 (74.0, 91.0)	81.0 (73.0, 90.0)	0.001
HR (bpm)	78.0(72.0, 87.0)	80.0(72.0, 92.0)	84.0(74.0, 103.0)	< 0.001
RR (bpm)	20.0(18.0, 20.0)	20.0(19.0, 20.0)	20.0(19.0, 20.0)	< 0.001
SpO_2(%)	99.0(98.0, 100.0)	99.0(97.0, 100.0)	98.0(97.0, 100.0)	< 0.001
Ventilation	35 (6.9)	36 (7.1)	87 (17.2)	< 0.001
Transfusion	44(8.7)	45(8.9)	79(15.6)	< 0.001
CRRT	21 (4.2)	24 (4.8)	47 (9.3)	< 0.001
WBC ($\times 10^9$/L)	5.7(4.7, 7.5)	10.0(8.0, 12.2)	14.5(11.9, 18.0)	< 0.001
HGB(g/L)	124.0 (110.0, 137.0)	131.0 (116.0, 148.0)	134.0 (118.0, 150.0)	< 0.001
NEU($\times 10^9$/L)	3.9 (3.0, 5.6)	8.2 (6.5, 10.2)	12.7 (10.5, 15.8)	982.347
LYM ($\times 10^9$/L)	1.3 (0.9, 1.7)	1.0 (0.7, 1.4)	0.7 (0.5, 1.0)	240.136
MONO ($\times 10^9$/L)	0.4 (0.3, 0.5)	0.6 (0.4, 0.7)	0.8 (0.6, 1.1)	571.415
HGB (g/L)	124.0 (110.0, 137.0)	131.0 (116.0, 148.0)	134.0 (118.0, 150.0)	< 0.001
PLT($\times 10^9$/L)	182.0 (140.0, 227.0)	174.5 (133.8, 233.2)	178.0 (139.0, 238.0)	0.515
AMY (U/L)	123.0 (63.0, 408.0)	162.5 (65.0, 568.0)	299.0 (84.0, 1034.0)	< 0.001
FPG (mmol/L)	5.7(4.7, 7.6)	6.9(5.6, 10.4)	7.3(6.0, 9.5)	< 0.001
PCT (ng/m/L)	0.1 (0.0, 0.4)	0.2 (0.1, 0.6)	0.5 (0.1, 1.8)	< 0.001
CRP (mg/L)	9.1 (3.0, 41.2)	59.7 (11.5, 134.2)	102.3 (18.3, 196.6)	< 0.001
ALB (g/L)	38.6 (35.2, 42.3)	38.8 (34.1, 42.6)	37.6 (31.8, 42.1)	0.003
AST(U/L)	43.0 (22.0, 155.0)	36.0 (22.0, 115.0)	48.0 (26.0, 147.0)	0.002
TG (mmol/L)	1.4 (0.9, 2.4)	1.9 (1.0, 6.0)	1.4 (1.0, 3.1)	< 0.001
Ca^{2+} (mmol/L)	2.2 (2.1, 2.3)	2.2 (2.0, 2.4)	2.2 (2.0, 2.3)	0.005
CREA (μmol/L)	72.7 (59.6, 85.0)	74.0 (61.0, 86.0)	79.0 (64.0, 92.0)	< 0.001
Etiology of AP				
Biliary	378(74.9)	299(59.3)	342(67.7)	
Hyperlipidemic	83(16.4)	161(31.9)	110(21.8)	
Alcoholic	12(2.4)	21(4.2)	18(3.6)	
Others	32(6.3)	23(4.6)	35(6.9)	
Severity of AP				< 0.001
Mild and moderate	479(94.9)	451(89.5)	413(81.8)	
Severe	26(5.1)	53(10.5)	92(18.2)	
BISAP (score)	1.0(0.0, 1.0)	1.0(0.0, 2.0)	2.0(2.0, 3.0)	< 0.001
SOFA (score)	2.3 ± 2.3	2.5 ± 2.3	3.4 ± 2.8	< 0.001
SIRI	1.3(0.8, 2.0)	4.5(3.5, 5.7)	12.5(9.6, 19.9)	< 0.001

Notes: Values are expressed as mean ± SD or median (IQR) for continuous variables and percentage for categorical variables. P < 0.05 was considered statistically significant.

Abbreviations: LOS, Length of hospital stay; DM, diabetes mellitus; CHD, coronary heart disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; SpO_2, pulse oxygen saturation; Ventilation, noninvasive or invasive mechanical ventilation; Transfusion, blood transfusion; CRRT, continuous renal replacement treatment; WBC, white blood cell count; NEU, neutrophil count in peripheral blood; LYM, lymphocyte count in peripheral blood; MONO, monocyte count in peripheral blood; HGB, hemoglobin; PLT, platelet count; FPG, fasting plasma glucose; PCT, procalcitonin; CRP, C-reactive protein; ALB, albumin; AMY, amylase; AST, aspartate aminotransferase; BISAP, Bedside Index of Severity in Acute Pancreatitis score; SOFA, sequential organ failure assessment score; SIRI, systemic inflammation response index.

Table 2 Multivariate Logistic Regression Analyses of SIRI on the Risk of Severe Acute Pancreatitis (SAP)

Variable	Non-adjusted Model		Adjusted Model 1		Adjusted Model 2		Adjusted Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
SIRI	1.05 (1.03~1.06)	<0.001	1.04(1.03~1.06)	<0.001	1.02 (1~1.03)	0.032	1.02 (1~1.04)	0.036
SIRI, tertile								
T1	Reference		Reference		Reference		Reference	
T2	2.17(1.33~3.52)	0.002	2.26 (1.38~3.69)	0.001	3.16(1.62~6.16)	0.001	2.85(1.41~5.75)	0.004
T3	4.10(2.6~6.47)	<0.001	4.27 (2.69~6.77)	<0.001	3.31 (1.7~6.45)	<0.001	2.96 (1.46~6)	0.003
***p* for trend**	<0.001		<0.001		0.001		0.006	

Notes: Results for each model are presented as OR (95% CI), P value. Non-adjusted model: no other covariates were adjusted. Model 1: adjusted for age, sex, BMI, hypertension, DM, and CHD; Model 2: adjusted as for the Model 1, additionally adjusted for HR, RR, SpO_2, blood transfusion, SOFA score, BISAP score, and etiology; Model 3: adjusted as for the Model 2, additionally adjusted for Ca^{2+}, HGB, CRP, AST, TG, CREA, and FPG.

Abbreviations: BMI, body mass index; DM, diabetes mellitus; CHD, coronary heart disease; HR, heart rate; RR, respiratory rate; SpO_2, pulse oxygen saturation; Ca^{2+}, calcium; HGB, hemoglobin; CRP, C-reactive protein; AST, aspartate aminotransferase; TG, triglyceride; CREA, creatinine; FPG, fasting plasma glucose; SIRI, systemic inflammation response index; T, tertile; OR, odds ratio; 95% CI, 95% confidence interval.

multiple logistic regression model (Table 3). The elevating SIRI value demonstrated a significant dose-response relationship with the risk of SAP among those having SIRI < 13 (OR: 1.125; 95% CI 1.024–1.236; P = 0.014). However, the relationship plateaued at SIRI values ≥ 13 (OR: 1.029; 95% CI 0.973–1.089; P = 0.316), indicating the threshold saturation effect (Table 3).

Receiver Operating Characteristic (ROC) Curves Used to Compare Biomarkers for Predicting SAP

Different inflammatory indices were analyzed for their prognostic significance of the severity of AP, based on Figure 3. Of these, the area under the ROC curve (AUC) increased relative to those for neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), and systemic inflammation index (SII), was 67.26% (95% CI: 63.00–71.51%) for SIRI, whereas decreased relative to those for SOFA and BISAP scores. More detailed information is illustrated in Table S1.

Subgroup Analyses

This study conducted subgroup analyses to investigate possible relations of SIRI (deemed to be the continuous variable) with severity (Figure 4).

The relationship of SIRI with severity was found in the following subgroups: age (<65 vs ≥65 years; P-interaction = 0.459), sex (male vs female; P-interaction = 0.32), BMI (28 vs ≥28 kg/m^2; P-interaction = 0.068), DM (yes vs no; P-interaction = 0.088), SOFA (<8 vs ≥8; P-interaction = 0.654), the requirement of CRRT (no vs yes; P-interaction = 0.596), WBC (<12 vs.≥12 × 10^9/L; P-interaction = 0.092), and etiology of AP and etiology of AP {[biliary vs hyperlipidemic vs other (alcoholic and others)]; P-interaction = 0.642}.

Discussion

The present study provides the initial complete analysis of the relationship of SIRI with the severity of AP. Our findings demonstrate a positive, dose-dependent relationship of SIRI with the incidence of SAP, which persisted when possible confounders were adjusted. Moreover, the robustness of such a relationship could be further confirmed through stratified analyses across various subgroups.

SIRI, which was first proposed by Qi et al[16] in 2016, integrates the following three key cellular components of the immune response: NEUs, MONOs, and LYMs. This composite index effectively provides a more comprehensive assessment of the inflammatory state than traditional single-parameter measures by recording distinct immune-inflammatory pathways. Previous studies[17,18] have established the utility of SIRI as a prognostic biomarker in oncology,

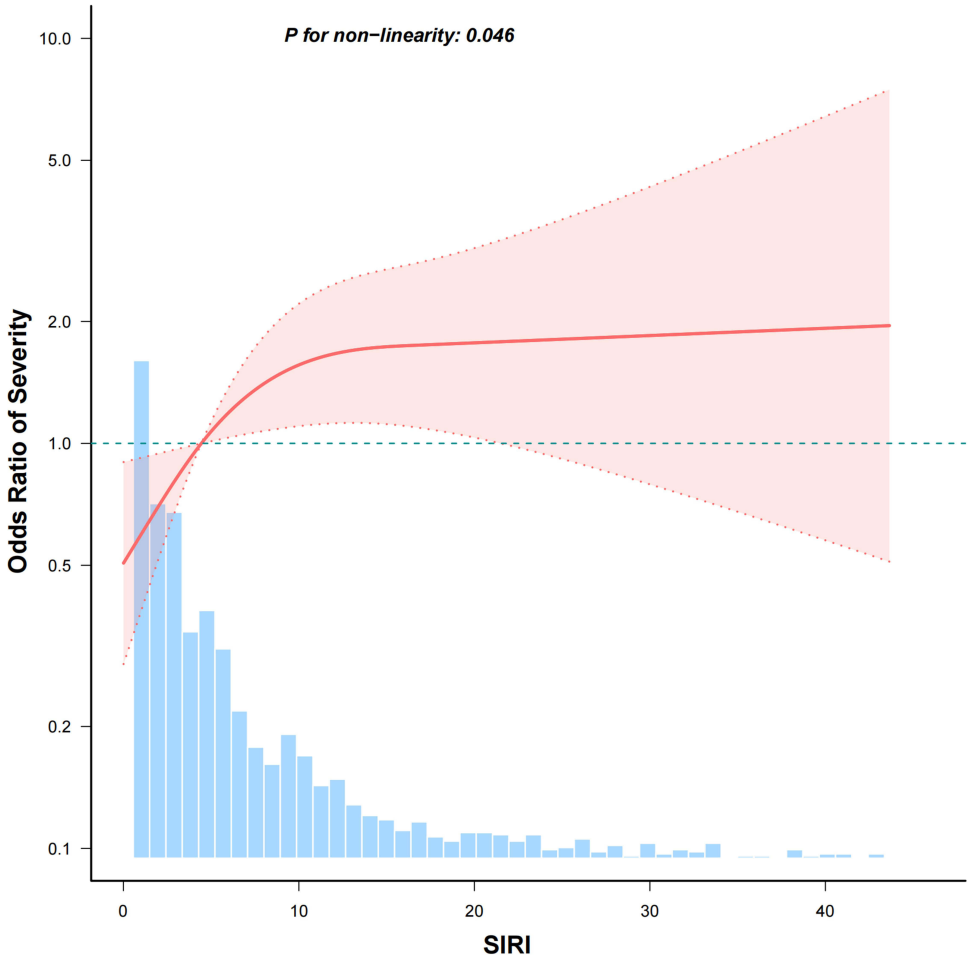

Figure 2 Multivariate adjusted restricted cubic spline for the association between SIRI and severity. The odds ratio is adjusted for variates with model 3. The red line represents the best-fit line, and the red dot lines are 95% confidence intervals.
Abbreviation: SIRI, systemic inflammation response index.

whereas recent studies[4,19,20] have expanded its application to cardiovascular diseases, chronic obstructive pulmonary disease, coronavirus disease, wasp sting injuries, and other inflammatory conditions, exhibiting superior predictive capability than conventional ratios like NLR and PLR.

Considering the complicated interactions among immune-inflammatory processes during AP, indices that integrate several cell types can more reliably reflect the innate-adaptive immunity balance,[21] and comprehensively assess the

Table 3 Threshold Effect Analyses of SIRI on the Risk of Severe Acute Pancreatitis (SAP) Using Two-Piecewise Regression Models

SIRI	Adjusted Model 3	P value
Inflection Point	OR (95% CI)	
< 13	1.125 (1.024~1.236)	0.014
≥ 13	1.029 (0.973~1.089)	0.316
Log-likelihood ratio test		0.025

Notes: The data was adjusted for all the covariates of model 3.
Abbreviations: OR, Odds ratio; 95% CI, 95% confidence interval; SIRI, systemic inflammation response index.

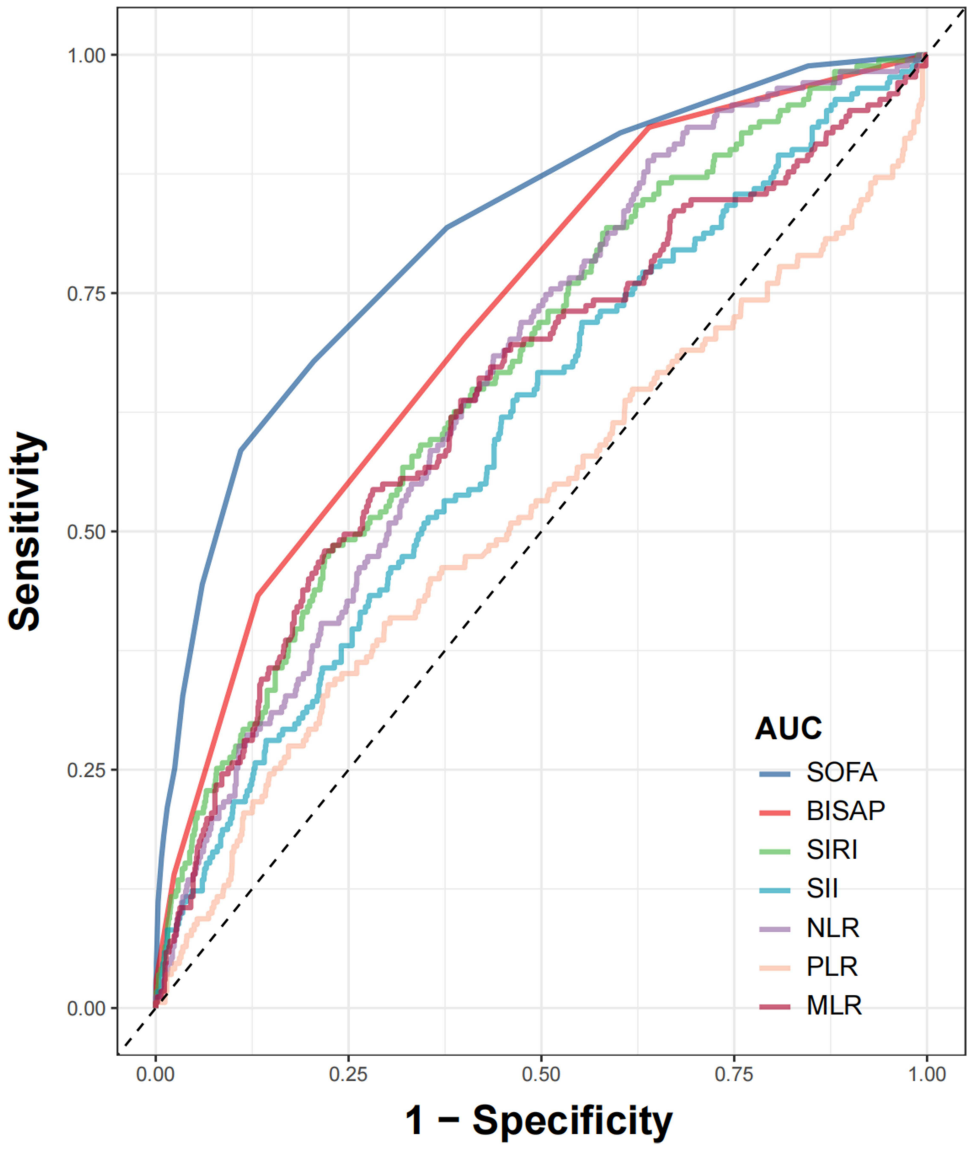

Figure 3 The receiver operating characteristic (ROC) curves for comparison of biomarkers to predict severe acute pancreatitis (SAP).
Abbreviations: SOFA, sequential organ failure assessment score; BISAP, Bedside Index of Severity in Acute Pancreatitis score; SIRI, systemic inflammation response index; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic inflammation index; PLR, platelet-to-lymphocyte ratio.

immunity, inflammation, thrombosis, and hemostasis. In this study, SIRI effectively predicted SAP. The AUC was 0.67 (0.63–0.72), with the best SIRI threshold in forecasting SAP being 9.5. Moreover, the sensitivity and specificity were 47.95% and 77.59%, respectively, outperforming other inflammatory indices such as MLR, NLR, PLR, and SII. Researchers have studied the relevant biomarkers for AP and formulated models to predict its severity. Nonetheless, the aforementioned studies had a small sample size and limited prediction model accuracy. Various scoring systems are used currently for assessing AP, such as APACHE II,[22] Ranson,[23] modified CT severity index,[24] SOFA, and BISAP scores.[25] Nevertheless, these scoring systems have limited clinical applicability due to the need for numerous parameters and complex algorithms. In contrast, SIRI is based on routine blood parameters and may not capture the full complexity and nuances of the clinical condition as effectively as the SOFA and BISAP scores, which incorporate more comprehensive clinical variables and patient assessments. Consequently, SIRI is established as a simple, efficient, and cost-effective biomarker for predicting the severity of acute pancreatitis.

To summarize, SIRI can comprehensively assess immune and inflammatory states, significantly correlating with the risk of SAP risk among the Chinese population. This positive correlation indicates that SIRI has the potential as

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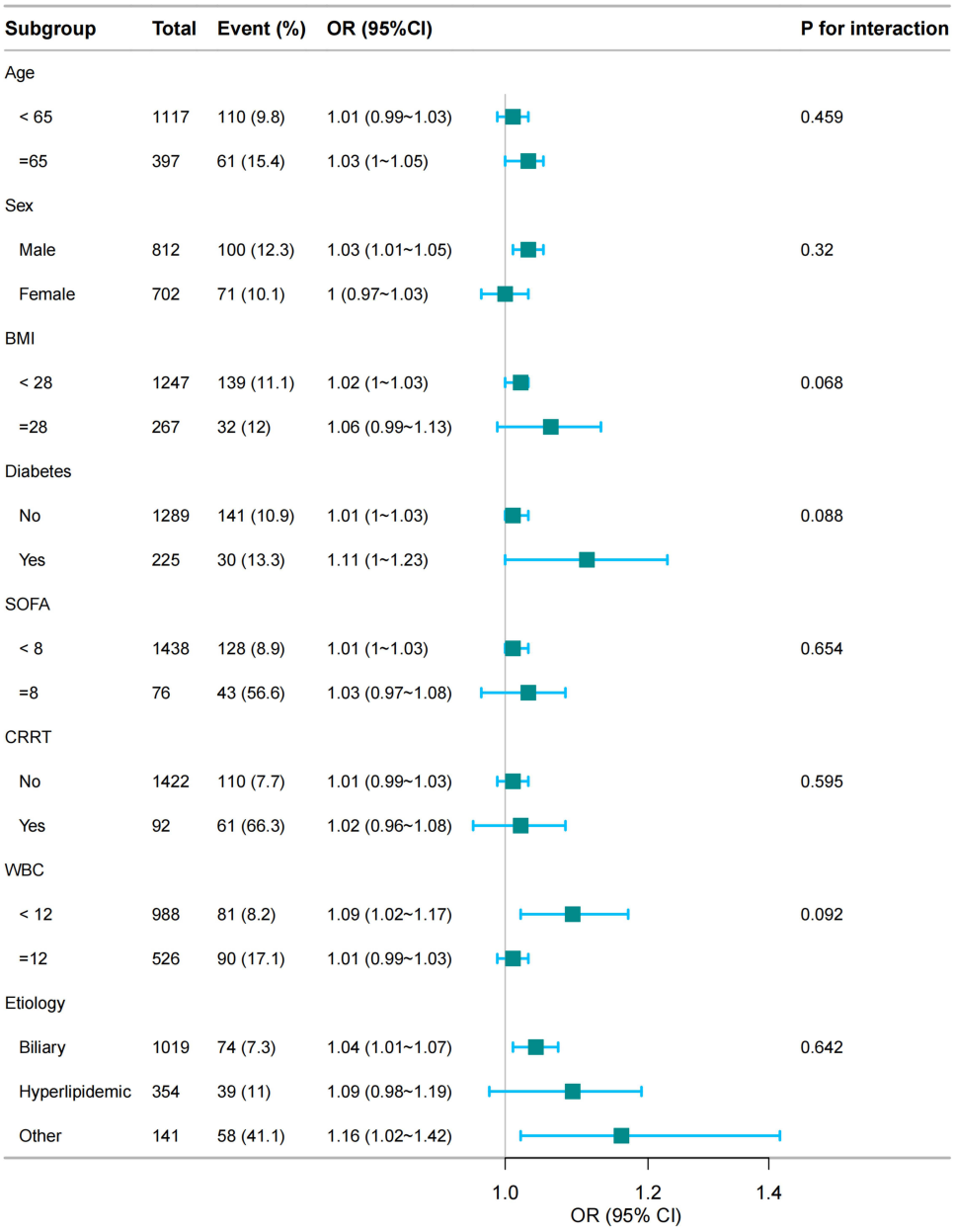

Figure 4 Stratified logistic regression analysis to identify variables modifying the correlation between SIRI values and severity. Adjusted factors include age, sex, BMI, diabetes, SOFA, CRRT, and WBC.

Abbreviations: SIRI, systemic inflammation response index; BMI, body mass index; SOFA, sequential organ failure assessment score; CRRT, continuous renal replacement treatment; WBC, white blood cell count; OR, odds ratio; 95% CI, 95% confidence interval.

a prognostic biomarker for SAP. Moreover, incorporating SIRI in standard clinical applications could assist in stratifying risk and predicting patient prognosis.

This study had the largest sample size for assessing the severity of AP among the Chinese population, with extensive adjustments for confounding factors. However, this study had some limitations. The study demonstrated selection bias because of its single-center retrospective nature. Additionally, the observational design of the study precludes the establishment of causality. More prospective research is necessary to validate these results and further explore the association between SIRI and the severity of pancreatitis.

Conclusion

Based on the study results, the accessible and cost-effective marker, SIRI, independently predicts the increased incidence of SAP among Chinese individuals. However, complex mechanisms associated with inflammation during AP are not completely comprehensible and require more explorations into intricate interactions of inflammatory indices with prognosis.

Data Sharing Statement

Data is available from the corresponding author on reasonable request.

Ethical Statement

The current retrospective study was approved by the Ethics Committee of the First College of Clinical Medical Science of China Three Gorges University (ethical approval number: 2023-130-01), which waived consent from study participants as it was not required due to the retrospective nature of the study. All patient data was anonymized during processing. This study was performed following the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests in this work.

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