

# Development and Validation of a Novel Prognostic Score Based on Thrombotic and Inflammatory Biomarkers for Predicting 28-Day Adverse Outcomes in Patients with Acute Pancreatitis

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**Background:** Acute pancreatitis (AP) is a multifactorial disease that is associated with substantial morbidity and mortality. Thrombosis and inflammation are involved in the development and progression of AP.

**Aim:** To develop and validate a novel and simple scoring system for predicting 28-day adverse outcomes in AP patients based on a thrombotic and an inflammatory biomarker.

**Methods:** A single-center, retrospective cohort study was used to establish the new scoring system (thrombo-inflammatory prognostic score; TIPS), and another study was used to verify it. The study end points were 28-day mortality, requirement for mechanical ventilation (MV), persistent organ failure (POF), and admission to the intensive care unit (AICU). Receiver operating characteristic (ROC) curves was drawn to validate the predictive value of the TIPS. The performance of the TIPS was compared with that of conventional predictive scoring systems. Logistic regression models were used to investigate the relationship between the TIPS and the different end points.

**Results:** Among 440 patients with AP in the derivation group, 27 patients died within the 28-day follow-up period. Prothrombin time (PT) and interleukin-6 (IL-6) were used to calculate the TIPS. The TIPS (AUC=0.843) showed a performance comparable to that of the more established APACHE II (AUC=0.841), SOFA (AUC=0.797), BISAP (AUC=0.762), and Balthazar CT (AUC=0.655) in predicting 28-day mortality in AP. The 28-day mortality and the incidence of MV, POF, and AICU were significantly higher among patients with a higher TIPS ( $P<0.001$ ). The results of logistic regression analyses indicated that the TIPS was independently associated with the risks of 28-day mortality, AICU, MV and POF.

**Conclusion:** The TIPS can enable prediction of 28-day adverse clinical outcomes with AP patients in the ED.

**Keywords:** acute pancreatitis, prognosis, clinical outcomes, thrombosis, inflammation

## Introduction

Acute pancreatitis (AP) is an inflammatory disorder of the pancreas and is associated with substantial morbidity and mortality.<sup>1</sup> The Revised Atlanta Classification of 2012 proposed new classification criteria for AP. According to these criteria, AP can be divided into three types: mild AP (MAP) with no organ failure (OF), moderately severe AP (MSAP) with OF lasting  $\leq 48$  h, and severe AP (SAP) with persistent OF (POF) lasting  $> 48$  h.<sup>2</sup> Extensive research over the last few decades has demonstrated that the first 24 h after symptom onset in AP are critical for identifying patients who are at risk of developing complications or death.<sup>3</sup> Therefore, it is crucial to identify high-risk patients quickly and effectively and initiate evidence-based intensive care in order to prevent severe complications and reduce morbidity and mortality.<sup>4</sup>

Scoring systems and biochemical markers that predict disease severity are commonly used for AP management.<sup>5</sup> Several scoring systems, including the Acute Physiology and Chronic Health Evaluation II (APACHE II) score; the Sequential Organ Failure Assessment (SOFA) score; Bedside Index for the Severity in Acute Pancreatitis (BISAP) score; and Balthazar CT score, have been developed for predicting disease severity and clinical outcomes in AP patients in the emergency department (ED). Further, biochemical markers such as blood urea nitrogen (BUN), creatinine (Cr), glucose, procalcitonin (PCT), and hematocrit (HCT) have also been used for this purpose. Pancreatitis-specific scoring systems depending on large numbers of whole body physiologic indicators or required the image findings obtained by computed tomography (CT) are useful for predicting the severity and progression of AP, but they are relatively complex and time-consuming.<sup>6</sup> In addition, the biomarkers used may be influenced by time-dose expression curves or time-dependent changes and may not accurately reflect the severity of different AP-linked pathological processes. There are few single biomarkers that are easily available upon admission and show good sensitivity in predicting disease severity and clinical outcomes in AP patients. Therefore, the development of simple, accurate, cheap, and reproducible methods for predicting the severity and clinical outcomes of AP is currently a focus in research.

The early identification of AP patients with serious illness is very important for providing appropriate care and optimizing the use of limited resources. The severity of pancreatitis is closely related to thrombosis and inflammation. Previous studies have shown that inflammatory biomarkers such as PCT, C-reactive protein (CRP), and interleukin 6 (IL-6) are useful indicators of severity and prognosis in AP and can be used for the early selection of appropriate treatment methods for preventing AP progression.<sup>7–11</sup> In addition, coagulation-related systemic changes contribute to the complications caused by AP and are an important cause of high mortality in AP. Thrombotic biomarkers including D-dimer, fibrinogen (FIB), and platelet count (PLT) are indicators of disease severity and adverse outcomes in AP patients.<sup>12–15</sup> However, no combination of thrombotic and inflammatory biomarkers is currently used to assess disease severity and adverse outcomes in patients with AP, even though a multi-biomarker strategy combining thrombotic and inflammatory biomarkers could allow graded prognostication. Therefore, the main purpose of this study was to establish a novel thrombo-inflammatory prognostic score (TIPS) that combines thrombotic and inflammatory biomarkers in order to predict the short-term prognosis of AP patients.

## Materials and Methods

### Study Design

This was a single-center, retrospective cohort study that evaluated the association between the TIPS and the risk of adverse outcomes in patients with AP. The study complied with the Declaration of Helsinki, and the study protocol was approved by the Human Ethical Committee of West China Hospital of Sichuan University (No.2019–334). Written or oral informed consent was obtained from all participants. Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

### Study Population

AP patients admitted to the Emergency Department of West China Hospital of Sichuan University from January 1, 2017, to September 30, 2017 (derivation group), and from January 1, 2016, to June 30, 2016 (validation group), were retrospectively enrolled. Information from the derivation group was used to establish the new scoring system, and this system was tested in the validation group. Based on the 2012 Atlanta classification, MAP was defined as AP with the absence of OF and local or systemic complications; MSAP was defined as AP with the presence of local or systemic complications and/or OF resolved within 48 h, with no evidence of POF failure; and SAP was defined as AP with POF (>48 h).<sup>2</sup>

### Inclusion and Exclusion Criteria

Patients were included in the study if they: 1. Had been diagnosed with AP for the first time; 2. Were  $\geq 18$  years old; and 3. Met the diagnostic criteria for AP according to the revised Atlanta Classification (2012) guidelines.<sup>2</sup> According to these guidelines, two of the following three features are required for the diagnosis of AP: persistent abdominal pain, a three-fold increase in the serum levels of amylase and/or lipase, and characteristic findings on abdominal imaging.<sup>6</sup>

The exclusion criteria for the study were as follows: 1. Chronic pancreatitis; 2. History of malignancy; 3. AP caused by poisoning, surgical operation, or trauma; 4. Postoperative pancreatic lesions; 5. Pregnancy or perinatal period; 6. Systemic hematological diseases; 7. AP complicated with chronic diseases of liver and kidney insufficiency; 8. Administration of anticoagulants before admission; 9. Patients with vein thrombosis events on admission; 10. Incomplete clinical data; and 11. Missing follow-up information.

## Data Collection

The study used data from the retrospective AP database of West China Hospital. After admission, we first collected demographic information, vital signs, medical history, laboratory test results, and imaging test findings from the database. Hematological indicators including white blood cell (WBC) count, PLT, hemoglobin (Hb) and HCT levels were analyzed using an automated hematology analysis system (Beckman Coulter LH750; Beckman Coulter Inc., Brea, CA, USA). Total bilirubin, albumin, BUN, Cr, serum calcium (Ca), lactate dehydrogenase (LDH), triglyceride (TG), cholesterol (CHOL), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), alanine aminotransferase (AST), and aspartate aminotransferase (ALT) levels were analyzed using an Architect c16000 analyzer (Abbott Diagnostics). D-Dimer, activated partial thromboplastin time (APTT), prothrombin time (PT), and FIB levels were measured using a Sysmex CA-7000 analyzer (Siemens Healthcare Diagnostics). PCT, IL-6, and CRP levels were determined using the Cobas S6000 Hitachi system (Roche Diagnostics). Risk stratification of AP patients based on the APACHE II,<sup>16</sup> SOFA,<sup>17</sup> BISAP<sup>18</sup> and Balthazar CT<sup>19</sup> scores was conducted by physicians according to the patients' baseline clinical characteristics.

## Quality Control

The management team supervised the recording of the data. The data were double-checked, and the medical team verified the data to ensure its authenticity and reliability when data verification was found to be inconsistent. Follow-ups were carried out by dedicated personnel. TH, TC and YL analyzed and interpreted the data. CY carried out quality control on the data.

## Study Follow-Up and Primary Endpoints

All patients with AP underwent a 28-day follow-up. The primary endpoint was all-cause mortality during follow-up. Secondary endpoints were adverse outcomes, including the requirement for both invasive and non-invasive ventilator mechanical ventilation (MV), POF, and admission to the intensive care unit (AICU). All emergency pancreatitis patients underwent structured telephone interviews with emergency doctors to determine the all-cause mortality and other adverse consequences after 28 days. If the patient could not be contacted directly, their family members were contacted. Wrong phone numbers or inability to contact patients despite three calls at different times were defined as a failure to follow-up.

## Establishment of the New System

In the present study, the inflammatory markers (PCT, WBC, CRP, and IL-6) and thrombotic markers (D-dimer, PLT, APTT, PT, and Fib) measured at admission were used to develop the score to predict 28-day mortality. Patients with high-risk values for both the thrombotic and inflammatory biomarkers were assigned a score of 2, whereas patients with high-risk values for only one or none of the parameters were assigned scores of 1 and 0, respectively.

## Statistical Analysis

Continuous variables were tested for normal distribution with the Kolmogorov–Smirnov (K-S) test. Continuous variables were presented as means + standard deviation (SD) for normally distributed data, and the difference between groups was analysed by *t*-test. Other continuous variables that did not conform to the normal distribution were expressed as medians and interquartile range (IQR), and the differences between groups were tested with the Mann–Whitney *U*-test. Categorical variables were presented as frequencies and percentages. Chi-square test was used for categorical variables. We also constructed receiver operating characteristic curves (ROCs) and calculated the area under the curve (AUC) values of the different thrombotic and inflammatory biomarkers (including PCT, WBC, CRP, IL-6, D-dimer, PLT, APTT,

PT, and Fib) to analyse these discriminating abilities for the risk of death in patients with AP and to determine the optimal cutoff points for the different biomarkers. Patient characteristics were then compared based on the TIPS. The APACHE II, SOFA, BISAP and Balthazar CT scores were calculated for each patient. A correlation coefficient heat map was used to display the correlation between TIPS and other prognostic scores in patients with AP. Correlation was determined using Spearman's correlation test. Moreover, we used the DeLong test to compare the AUCs of these scores, comparing the discriminating ability of TIPS and other scores on 28 - day mortality. Multivariable logistic regression models were used to investigate the relationship between the TIPS and the different end points. Subsequently, TIPS was also used to categorize the patients into three subgroups, and the rates of adverse events (including 28-day mortality, AICU, MV and POF) in the three subgroups were compared using the  $\chi^2$  test. A two-sided  $p$ -value  $<0.05$  was considered statistically significant for all tests. Data analyses were performed using SPSS statistical software version 26.0 (IBM Corporation, Armonk, NY), MedCalc<sup>®</sup> Statistical Software version 19 and R V.3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) software.

## Results

### Clinical Characteristics of the Derivation Group

A total of 440 AP patients were enrolled in the derivation group. Their median age was 47.0 years, and this group included 267 male patients (60.7%). Of the 440 patients, 58 (13.2%), 129 (29.3%), and 253 (57.5%) had mild, moderate, and severe disease respectively, according to the revised Atlanta classification. Twenty-seven patients died within the 28-day follow-up period. The clinical characteristics of these patients are summarized in Table 1.

### Establishment of the New System

Inflammatory biomarkers (PCT, WBC, CRP, and IL-6) were measured at admission. For the prediction of 28-day mortality, the AUC of IL-6 (0.731,  $P < 0.001$ ) was larger than that of other inflammatory biomarkers, including WBC count (0.618,  $P = 0.40$ ), CRP levels (0.538,  $P = 0.505$ ), and PCT levels (0.661,  $P = 0.005$ ) (Figure 1). In addition, thrombotic biomarkers (PT, D-dimer, PLT, APTT, and Fib) were also measured at admission. The AUC for PT (0.791,  $P < 0.001$ ) was larger than that for the other thrombotic biomarkers, such as APTT (0.657,  $P = 0.006$ ), Fib (0.554,  $P = 0.349$ ), D-dimer (0.691,  $P = 0.001$ ), and PLT (0.552,  $P = 0.366$ ) (Figure 2). Therefore, the recommended cutoff values for IL-6 (78 pg/mL) and PT (13.65 s), obtained based on the maximum Youden's index from the ROC curves, were used to calculate the TIPS. The method used for calculating the TIPS is shown in Table 2.

The clinical characteristics of the patients with different 'TIPS' values are shown in Table 3. Age, temperature, heart rate, breathing rate, WBC count, Cr, BUN, LDH, lipase (LIP), amylase (AMY), PT, APTT, FIB, D-dimer, PCT, CRP, IL-6, and lactate (LAC) significantly increased with an increasing TIPS. Conversely, albumin, CHOL, HDL-C, LDL-C and Ca significantly decreased with an increasing TIPS. The other clinical characteristics did not vary significantly based on the TIPS ( $P > 0.05$ ).

### Correlation Between the TIPS and Other Prognostic Scores in the Derivation Group

In addition, we analyzed TIPS association with APACHE II, SOFA, BISAP, and Balthazar CT scores—the most widely used scoring systems for pancreatitis severity. The correlations between TIPS and clinical prognostic scores are shown in Figure 3 using the Spearman correlation coefficient heat map. A significant positive correlation was observed between the TIPS and APACHE II ( $r=0.40$ ,  $P < 0.001$ ), SOFA ( $r=0.41$ ,  $P < 0.001$ ), BISAP ( $r=0.41$ ,  $P < 0.001$ ) and Balthazar CT ( $r=0.22$ ,  $P < 0.001$ ) scores. These findings confirmed the usefulness of TIPS in assessing AP severity.

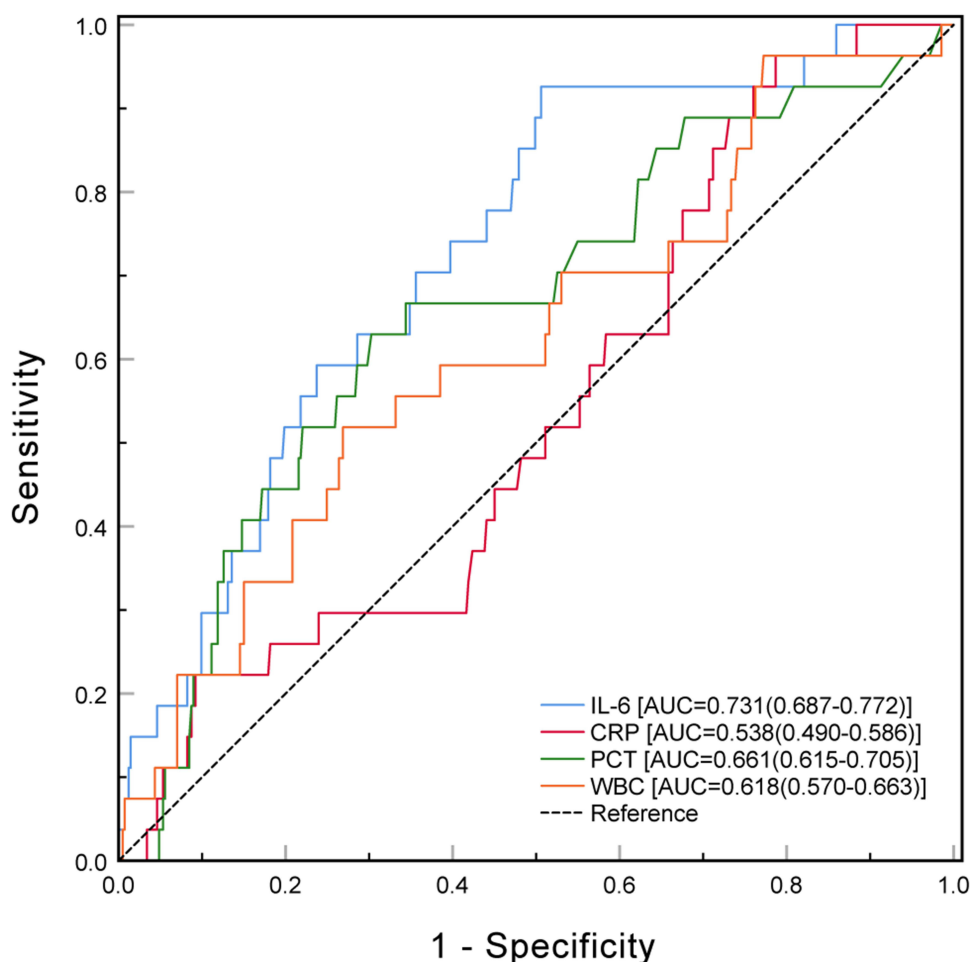
### TIPS and 28-Day Adverse Outcomes in the Derivation Group

The 28-day mortality, AICU, MV, and POF rates gradually increased as the TIPS increased. The 28-day mortality rate of patients with a TIPS of 2 or 1 was significantly higher than that of patients with scores of 0. There were statistical differences among three groups (0 vs 3.2% vs 22.3%,  $P < 0.05$ ) (Figure 4A). There were significant differences in the incidence of AICU among the three groups (6.3% vs 19.1% vs 39.4%,  $P < 0.05$ ) (Figure 4B). There was a statistically

**Table I** Characteristics of Patients in the Derivation Group According to the Severity of Acute Pancreatitis

Variable	MAP (n=58)	MSAP (n=129)	SAP (n=253)	P-value
<b>Baseline variables</b>				
Age (years)	47.0 (39.8–58.3)	46.0 (38.0–55.0)	48.0 (39.5–59.0)	0.518
Male, n (%)	32 (55.2%)	75 (58.1%)	160 (63.2%)	0.410
Etiology, n (%)				0.108
Gallstone	15 (25.9%)	44 (34.1%)	95 (37.6%)	
Hyperlipemia	25 (43.1%)	53 (41.1%)	85 (33.6%)	
Alcohol abuse	3 (5.1%)	13 (10.1%)	34 (13.4%)	
Unknown	15 (25.9%)	19 (14.7%)	39 (15.4%)	
BMI	24.6 (22.3–27.3)	26.0 (23.4–28.2)	25.8 (23.2–27.7)	0.175
Temperature (°C)	36.6 (36.4–37.0)	36.7 (36.4–37.1)	36.8 (36.5–37.3)	0.109
Heart rate (beats/min)	93.0 (±19.6)	97.3 (±21.5)	110.0 (±24.1)	<0.001
Breathing rate (beats/min)	20.0 (20.0–21.0)	20.0 (20.0–22.0)	22.0 (20.0–26.0)	<0.001
MAP (mmHg)	97.8 (±14.8)	97.4 (±14.1)	99.0 (±15.6)	0.590
SPO <sub>2</sub> (%)	96.0 (94.0–98.0)	96.0 (93.0–97.5)	95.0 (92.0–97.0)	0.006
WBCs (10 <sup>9</sup> /L)	11.10 (8.38–14.51)	13.61 (9.71–16.62)	13.45 (10.48–17.48)	0.012
PLT (10 <sup>9</sup> /L)	165.00 (122.75–212.75)	160.00 (125.00–201.50)	159.00 (120.50–209.50)	0.916
Hb (g/L)	130.97 (±22.44)	134.41 (±20.99)	131.08 (±32.45)	0.528
HCT (%)	39 (35–42)	39 (36–42)	39 (33–45)	0.823
TBIL (μmol/L)	17.80 (12.85–24.65)	19.40 (12.05–28.70)	21.30 (13.60–38.35)	0.014
ALT (IU/L)	29.00 (18.75–52.50)	27.00 (16.50–50.00)	37.00 (18.00–76.00)	0.091
AST (IU/L)	27.00 (19.00–39.25)	28.00 (19.00–46.50)	42.00 (25.00–88.00)	<0.001
Albumin (g/L)	41.70 (36.25–45.10)	38.90 (34.20–42.55)	34.60 (29.75–39.00)	<0.001
Cr (μmol/L)	63.50 (53.50–79.00)	65.00 (49.50–81.50)	72.00 (57.00–107.00)	<0.001
BUN (mg/dL)	4.61 (3.24–5.37)	4.28 (2.93–5.90)	5.40 (3.74–8.33)	<0.001
CHOL (mmol/L)	4.61 (3.24–5.37)	4.28 (2.93–5.90)	5.40 (3.74–8.33)	0.011
HDL-C (mmol/L)	1.00 (0.72–1.30)	0.97 (0.76–1.20)	0.66 (0.40–1.09)	<0.001
LDL-C (mmol/L)	1.60 (0.75–2.41)	1.61 (0.92–2.36)	1.33 (0.66–2.21)	0.146
LIP (IU/L)	132.50 (57.00–557.25)	212.00 (94.50–647.50)	329.00 (92.00–1071.00)	0.001
AMY (IU/L)	126.00 (68.50–312.25)	174.00 (87.50–473.50)	310.00 (90.00–922.50)	0.001
Ca (mmol/L)	2.17 (2.05–2.33)	2.15 (2.02–2.28)	2.01 (1.82–2.17)	<0.001
PT (s)	12.10 (11.55–12.95)	12.70 (11.95–13.40)	13.40 (12.20–14.70)	<0.001
APTT (s)	30.35 (27.25–33.43)	29.70 (27.15–33.60)	31.20 (28.10–36.45)	0.016
Fib (g/L)	3.73 (3.05–4.77)	4.38 (3.06–6.72)	4.51 (3.35–6.96)	0.060
D-dimer (mg/L)	1.19 (0.40–2.62)	2.59 (1.00–5.00)	4.41 (2.19–8.69)	<0.001
CRP (mg/L)	88.40 (28.40–157.25)	135.00 (49.50–230.00)	189.00 (118.00–289.00)	<0.001
PCT (ng/mL)	0.14 (0.07–0.41)	0.28 (0.09–0.92)	0.70 (0.29–2.58)	<0.001
IL-6 (pg/mL)	41.84 (16.76–91.25)	55.19 (16.79–143.05)	109.40 (55.37–223.95)	<0.001
Lac (mmol/L)	1.30 (1.20–1.80)	1.40 (1.20–1.90)	1.70 (1.30–2.60)	<0.001
<b>Scores</b>				
APACHE II	4 (3–7)	5 (3–7)	8 (5–11)	<0.001
SOFA	2 (1–3)	2 (1–4)	4 (2–6)	<0.001
BISAP	1 (1–2)	2 (1–2)	2 (2–3)	<0.001
<b>Outcomes</b>				
Death, n (%)	0 (0.0%)	1 (0.8%)	26 (10.3%)	<0.001
MV, n (%)	0 (0.0%)	4 (3.1%)	130 (51.4%)	<0.001
ICU admission, n (%)	0 (0.0%)	4 (3.1%)	79 (31.2%)	<0.001

**Abbreviations:** BMI, body Mass Index; SPO<sub>2</sub>, oxygen saturation; WBC, white blood cell; PLT, platelets; HB, hemoglobin; HCT, hematocrit; TBIL, total bilirubin; Cr, creatinine; BUN, blood urea nitrogen; CHOL, cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LIP, lipase; AMY, amylase; Ca, calcium; PT, prothrombin time; APTT, activated partial thromboplastin time; Fib, fibrinogen; PCT, procalcitonin (PCT); CRP, C-reactive protein; IL-6, interleukin-6; LAC, lactate; APACHE II, Acute physiology and chronic health evaluation scoring system; SOFA, Sequential Organ Failure Assessment; BISAP, bedside index for severity in AP; MV, Mechanical ventilation; ICU, Intensive Care Unit.



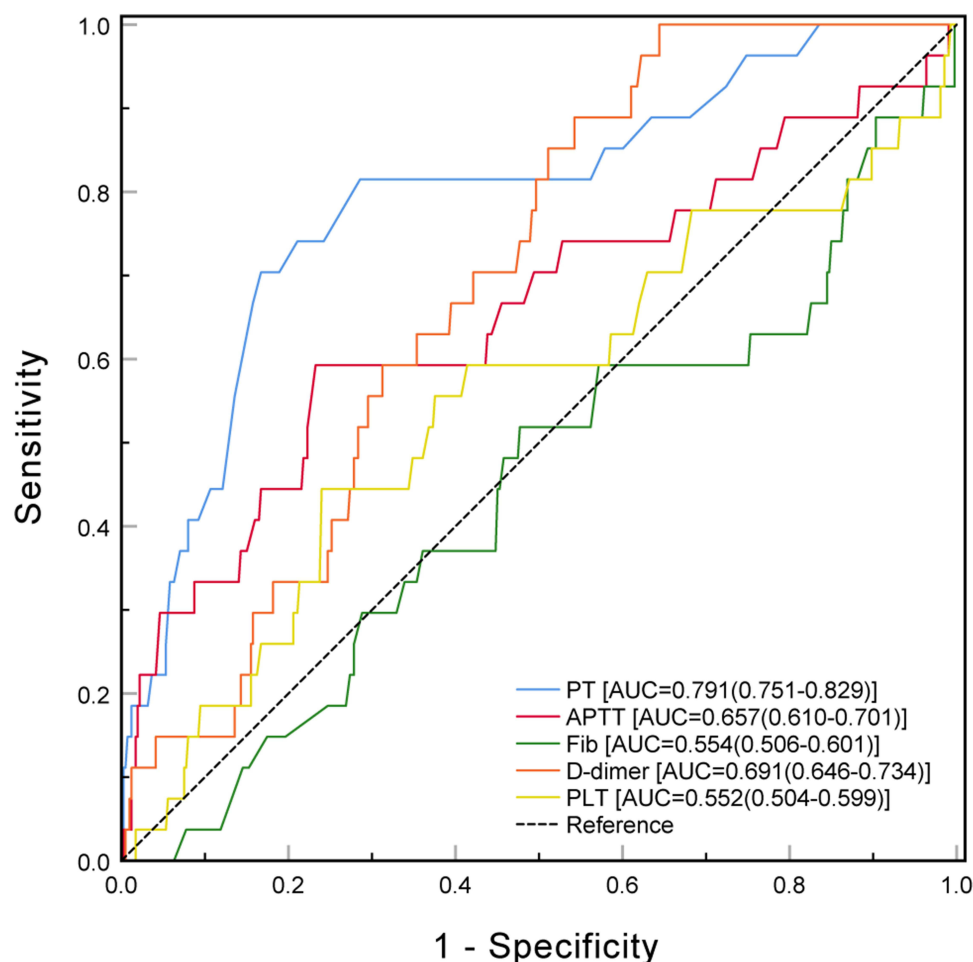
**Figure 1** Receiver operating characteristic curve analysis of the prediction of 28-day mortality using inflammatory biomarkers (IL-6, CRP, PCT and WBC).

significant difference in the incidence of MV among the three groups (11.9% vs 35.1% vs 53.2%,  $P < 0.05$ ) (Figure 4C). Moreover, regarding the incidence POF, the differences among the three groups remained statistically significant (36.1% vs 64.9% vs 79.8%,  $P < 0.05$ ) (Figure 4D). The results of univariable logistic regression analyses indicated that the TIPS was positively associated with the risks of 28-day mortality, AICU, MV and POF (Table 4). After adjusting for these potential confounders in the multivariate logistic regression analysis, the TIPS was independently associated with 28-day mortality (OR = 11.796, 95% CI: 4.414~24.866,  $P < 0.001$ ), AICU (OR = 2.922, 95% CI: 2.026~4.215,  $P < 0.001$ ), MV (OR = 2.874, 95% CI: 2.095~3.941,  $P < 0.001$ ) and POF (OR = 2.761, 95% CI: 2.051~3.717,  $P < 0.001$ ) (Table 4).

## Comparison Between the TIPS and Other Prognostic Scores in the Prediction of 28-Day Mortality in AP

We also assessed the performances of TIPS, APACHE II, SOFA, BISAP and Balthazar CT scores in the prediction of 28-day mortality. As shown in Figure 5, the AUC values of the APACHE II, SOFA, BISAP and Balthazar CT were 0.841 (95% CI 0.780 to 0.901), 0.797 (95% CI 0.692 to 0.901), 0.762 (95% CI 0.664 to 0.860) and 0.655 (95% CI 0.552 to 0.757), respectively; however, the TIPS obtained an AUC value of 0.843 (95% CI 0.782 to 0.904). Additionally, we found that the predictive performance of TIPS is comparable to that of the APACHE II ( $P = 0.9486$ ), SOFA ( $P = 0.3634$ ) and BISAP ( $P = 0.0882$ ) in predicting 28-day mortality. However, its predictive value is better than that of Balthazar CT score and the difference is statistically significant ( $P = 0.0026$ ) (Figure 5).





**Figure 2** Receiver operating characteristic curve analysis of the prediction of 28-day mortality using thrombotic biomarkers (PT, APTT, Fib, D-dimer and PLT).

## Validation of the Ability of the TIPS to Predict the Prognosis of AP

To validate the ability of the TIPS to predict the 28-day clinical outcomes of AP patients, 358 patients with AP (validation cohort) were divided into three groups based on the TIPS: group 1, TIPS=0; group 2, TIPS=1; and group 3, TIPS=2. Next, we analyzed the major 28-day clinical outcomes in these three groups (Table 5). We found that the 28-day mortality, MV, AICU, and POF rates gradually increased in patients with AP as the TIPS increased. Among patients with a TIPS of 0, 1, and 2, the mortality rates were 0.0%, 9.7%, and 21.3%, respectively ( $P < 0.001$ ). In these patients, the incidence of MV was 7.2%, 27.1%, and 57.3%, respectively ( $P < 0.001$ ), the incidence of AICU was 5.0%, 15.3%, and 34.7%, respectively ( $P < 0.001$ ), and the incidence of POF was 6.5%, 34.0%, and 70.7%, respectively ( $P < 0.001$ ).

**Table 2** Method for Calculating the Thrombo-Inflammatory Prognostic Score (TIPS) Using PT and IL-6 Levels

PT (s)	IL-6 (pg/mL)	TIPS
<13.65	<78	0
<13.65	≥78	1
≥13.65	<78	1
≥13.65	≥78	2

**Abbreviations:** TIPS, thrombo-inflammatory prognostic score; PT, prothrombin time; IL-6, interleukin-6.

**Table 3** Comparison Among Patients with Different “TIPS” Values (Derivation Group)

Variable	TIPS 0 (n=158)	TIPS 1 (n=188)	TIPS 2 (n=94)	P-value
General information				
Age (years)	46.0 (36.0–57.3)	45.0 (39.0–55.0)	51.5 (42.8–62.3)	0.017
Male, n (%)	87 (55%)	117 (62%)	31 (67%)	0.145
BMI	25.8 (23.4–28.2)	25.6 (22.5–27.6)	25.7 (24.1–27.7)	0.186
Temperature (°C)	36.6 (36.4–37)	36.8 (36.5–37.2)	36.8 (36.5–37.3)	0.002
Heart rate (beats/min)	92.66 (±22.05)	107.84 (±21.90)	115.52 (±22.75)	<0.001
Breathing rate (beats/min)	20.0 (20.0–22.0)	22.0 (20.0–25.0)	23.0 (20.0–28.0)	<0.001
MAP (mmHg)	98.43 (±15.00)	99.11 (±15.33)	96.94 (±14.61)	0.520
SPO <sub>2</sub> (%)	96.00 (93.00–97.25)	95.00 (92.00–97.00)	95.00 (93.00–97.00)	0.118
Laboratory examination				
WBCs (10 <sup>9</sup> /L)	11.43 (8.42–15.25)	14.01 (10.63–17.38)	14.31 (10.62–19.05)	<0.001
PLT (10 <sup>9</sup> /L)	169.00 (128.75–221.50)	159.50 (123.25–199.75)	146.00 (99.75–202.50)	0.069
Hb (g/L)	128.98 (±22.06)	133.85 (±30.00)	133.59 (±33.50)	0.235
HCT (%)	0.38 (0.35–0.42)	0.39 (0.34–0.44)	0.40 (0.33–0.46)	0.202
TBIL (μmol/L)	18.25 (12.13–28.05)	20.80 (13.40–32.50)	23.65 (14.10–43.58)	0.058
ALT (IU/L)	31.00 (17.83–94.25)	28.50 (18.00–51.75)	35.00 (16.00–78.75)	0.426
AST (IU/L)	31.00 (21.00–72.75)	32.00 (22.00–56.00)	44.00 (24.50–89.25)	0.080
Albumin (g/L)	39.45 (34.75–43.85)	35.60 (30.70–39.88)	34.40 (29.78–37.70)	<0.001
Cr (μmol/L)	64.00 (51.00–75.25)	65.50 (52.00–89.00)	104.50 (67.00–166.25)	<0.001
BUN (mg/dL)	4.56 (3.12–5.52)	4.69 (3.21–6.57)	7.70 (4.51–11.71)	<0.001
CHOL (mmol/L)	4.42 (3.50–5.53)	4.00 (3.19–7.00)	3.48 (2.37–5.49)	0.002
HDL-C (mmol/L)	0.98 (0.60–1.32)	0.80 (0.48–1.11)	0.71 (0.39–1.06)	<0.001
LDL-C (mmol/L)	1.94 (1.27–2.62)	1.26 (0.63–2.10)	1.04 (0.52–1.59)	<0.001
LDH (U/L)	243.50 (181.75–386.75)	348.50 (247.50–512.00)	397.00 (243.50–620.00)	<0.001
LIP (IU/L)	177.50 (77.00–748.00)	243.00 (88.50–764.75)	450.50 (140.75–1069.50)	0.017
AMY (IU/L)	151.50 (81.50–424.25)	228.00 (80.00–634.00)	476.50 (103.00–934.25)	0.003
Ca (mmol/L)	2.19 (2.04–2.30)	2.05 (1.88–2.18)	1.96 (1.78–2.14)	<0.001
PT (s)	12.30 (11.50–12.90)	12.80 (12.00–13.80)	14.65 (14.00–16.20)	<0.001
APTT (s)	29.00 (26.80–31.65)	30.85 (28.03–34.20)	35.40 (30.45–39.63)	<0.001
Fib (g/L)	4.07 (2.94–6.17)	4.55 (3.46–6.96)	4.66 (3.46–6.96)	0.018
D-dimer (mg/L)	2.12 (0.85–4.83)	3.79 (1.62–6.77)	4.60 (2.66–10.28)	<0.001
CRP (mg/L)	77.95 (25.10–148.50)	195.00 (125.25–306.50)	227.50 (146.50–309.75)	<0.001
PCT (ng/mL)	0.17 (0.08–0.44)	0.62 (0.27–1.58)	1.46 (0.32–5.84)	<0.001
IL-6 (pg/mL)	25.81 (12.24–51.02)	125.20 (71.67–212.90)	191.95 (113.43–306.00)	<0.001
Lac (mmol/L)	1.35 (1.10–1.60)	1.70 (1.30–2.50)	2.00 (1.50–2.93)	<0.001

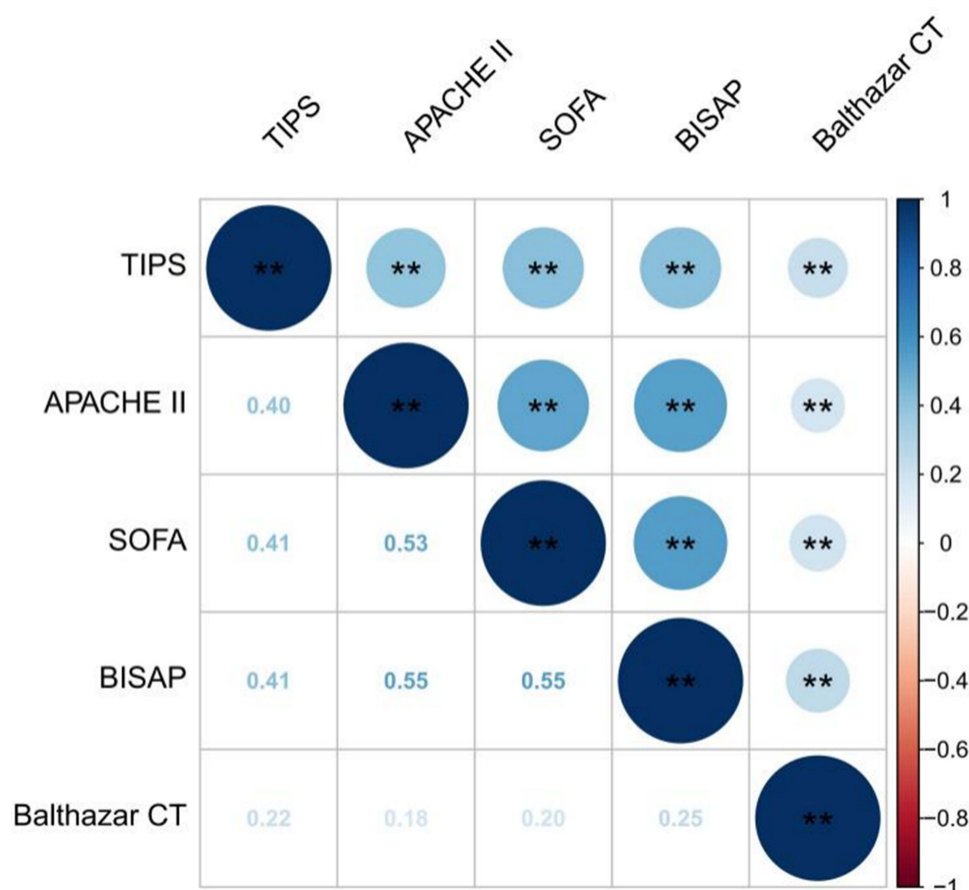
**Abbreviations:** BMI, body Mass Index; SPO<sub>2</sub>, oxygen saturation; WBC, white blood cells; PLT, platelets; HB, hemoglobin; HCT, hematocrit; TBIL, total bilirubin; Cr, creatinine; BUN=blood urea nitrogen; CHOL, cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LDH, lactic dehydrogenase; LIP, lipase; AMY, amylase; Ca, calcium; PT, prothrombin time; APTT, activated partial thromboplastin time; Fib, fibrinogen; PCT, procalcitonin (PCT); CRP, C-reactive protein; IL-6, interleukin 6; LAC, lactate.

## Discussion

We performed a large retrospective single-center study to assess the ability of the TIPS, a score developed based on a thrombotic and an inflammatory biomarker, to predict adverse outcomes among AP patients in the ED. We found that the TIPS was effective in identifying patients at increased risk for multiple 28-day adverse outcomes, including 28-day mortality, MV, POF, and AICU. Moreover, the TIPS is easier and faster to calculate, can be calculated promptly after admission, and can be repeatedly calculated. Therefore, our results suggest that the TIPS is a useful tool for identifying high-risk AP patients during early ED admission.

AP is a multifactorial disease.<sup>20</sup> Most AP patients present with MAP and have a good prognosis; however, 15–20% of AP patients develop SAP, resulting in significant morbidity and mortality. An increase in the annual incidence of AP has been observed in most recent studies.<sup>21</sup> Early severity-based stratification and prognostic prediction are crucial for reducing the rates of mortality among patients with AP.<sup>22</sup> However, the quick and effective screening of AP patients at



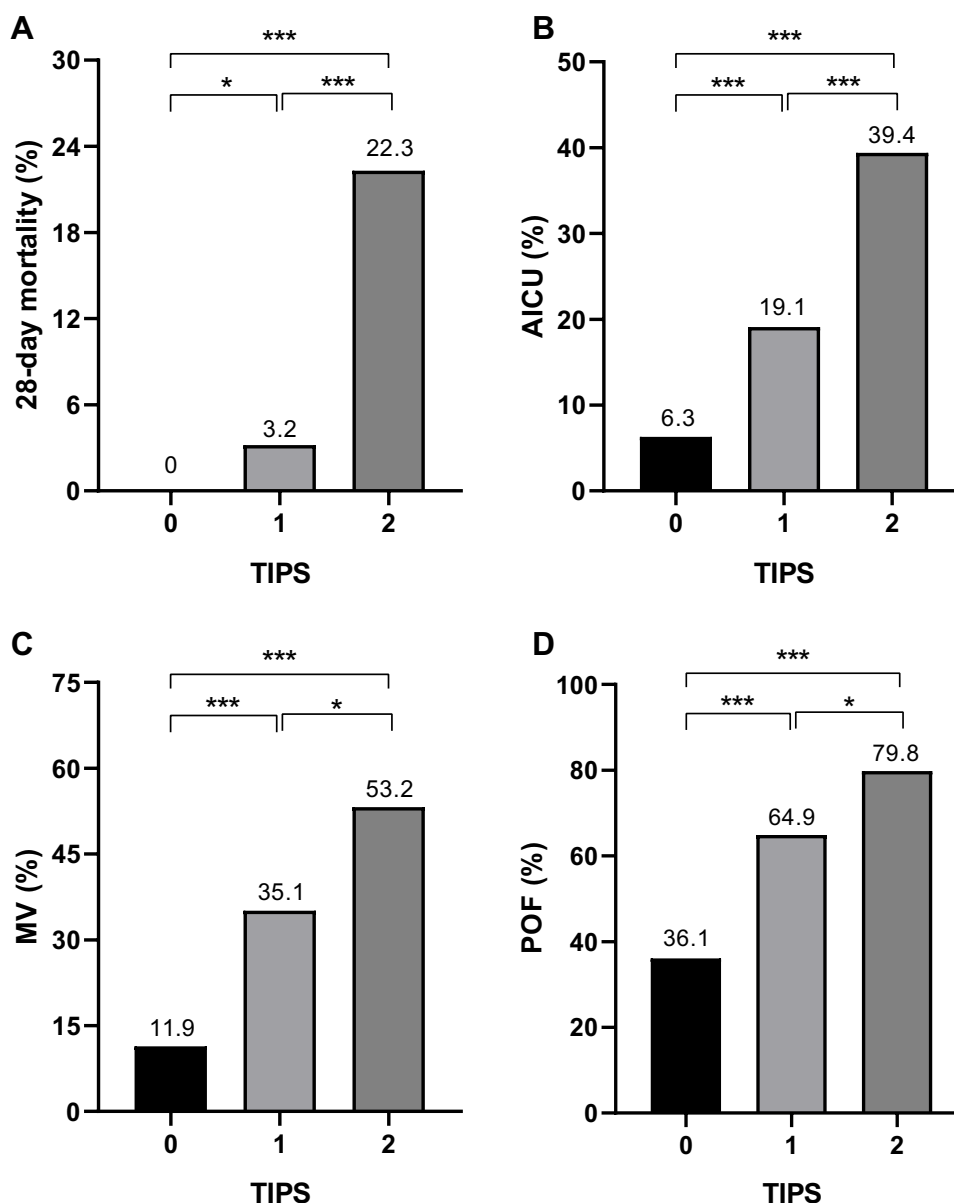


**Figure 3** Correlation coefficient heat map of APACHE II, SOFA, BISAP and Balthazar CT scores with the TIPS. \*\* $P < 0.001$ .

**Abbreviations:** APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; BISAP=bedside index for severity in acute pancreatitis; TIPS, thrombo-inflammatory prognostic score.

a high risk of adverse outcomes is challenging during clinical management in the ED. Given the adverse prognosis and increased mortality associated with necrotizing pancreatitis, a number of scoring systems have been designed to assess the severity of AP.<sup>23</sup> These scoring systems for the prediction of severe AP usually have a sensitivity and specificity ranging from 55% to 90%, but these systems are too complex to allow immediate calculation in an actual clinical situation. Hence, a new predictive tool that allows an estimation of adverse AP outcomes in a simpler manner is required.

Inflammation and thrombosis are closely related. Inflammation not only leads to the initiation and spread of thrombosis activity but also causes a further increase in inflammation via synergistic WBC and PLT activity. In our study, we analyzed whether a thrombotic inflammatory state could be a predictor of adverse outcomes in AP patients.<sup>24</sup> In recent years, the relationship between the severity of AP and the level of thrombotic and inflammatory biomarkers has been studied extensively. Although the exact mechanism underlying AP is not fully understood, increasing evidence has implicated certain factors in the occurrence and development of AP. In serious diseases such as AP, a close interaction between thrombosis and inflammation is observed, and this interaction contributes to disease development. Thrombosis and inflammation are considered ticking bombs in SAP and can lead to multiple organ dysfunction and diffuse intravascular coagulation in the most extreme conditions. Oxidative stress and inflammatory mediators play an important role in the pathophysiology of AP.<sup>9</sup> It has been proposed that in AP, the activation of inflammatory cells results in the release of inflammatory mediators such as TNF- $\alpha$ , IL-6, and IL-1 $\beta$ , leading to severe disease.<sup>25,26</sup> These signals allow the recruitment of other inflammatory cells and amplify signals in order to promote local and extrapancreatic multi-organ injury. AP severity depends on whether the inflammatory response gets resolved or becomes amplified and causes multi-organ failure.<sup>27</sup> Previous studies have found that the inflammatory response associated with AP is accompanied by an



**Figure 4** The 28-day mortality (A), AICU (B), MV (C), and POF (D) rates in individuals with different TIPS values. \* $P < 0.05$ , \*\*\* $P < 0.001$ .

**Abbreviations:** AICU, admission to intensive care unit; MV, mechanical ventilation; POF, persistent organ failure; TIPS, thrombo-inflammatory prognostic score.

increase in IL-6 levels, which is primarily released by activated mononuclear phagocytes and is the key mediator for acute-phase protein synthesis in the liver.<sup>28</sup> In the present study, the AUC of IL-6 for the prediction of 28-day mortality was larger than that of other inflammatory biomarkers. IL-6 has been implicated in initiating an inflammatory response during the course of AP.<sup>9</sup> When acute inflammation occurs, IL-6 levels increase rapidly, leading to the initiation of an inflammatory cytokine cascade; hence, IL-6 is an important indicator of the degree of the inflammatory response.<sup>29</sup> High levels of IL-6 indicate the potential development of multi-organ failure at an early stage of AP.<sup>30</sup> Hence, IL-6 has substantial value in determining disease severity AP.

Several experimental studies have suggested that the thrombosis system plays an important role in the pathophysiology of AP. Microcirculatory dysfunction is a pivotal mechanism in the pathogenesis of pancreatitis and is proportional to disease severity in AP.<sup>31</sup> Disseminated intravascular coagulation is a life-threatening condition that frequently occurs in patients with severe sepsis, AP, trauma, solid tumors, and hematologic malignancies. Pancreatitis affects both the systemic and pancreatic vasculature.<sup>31</sup> Systemic alterations in thrombosis are associated with complications in AP

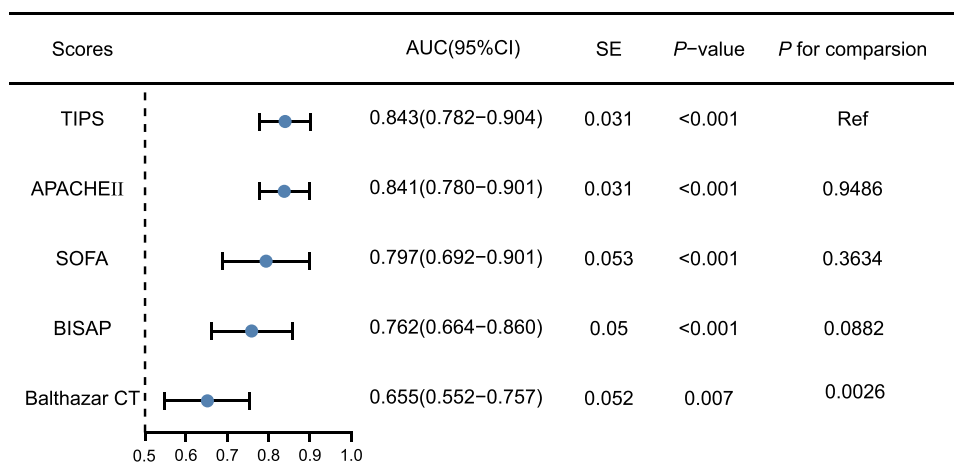
**Table 4** Logistic Regression Analysis Regarding Correlations Between Clinical Outcomes and TIPS

Clinical Outcomes	TIPS			
	OR	95% CI for OR		P-value
		Lower	Upper	
28-day mortality				
Unadjusted	10.476	4.414	24.866	<0.001
Adjusted <sup>a</sup>	11.796	4.695	29.637	<0.001
AICU				
Unadjusted	3.023	2.116	4.320	<0.001
Adjusted <sup>a</sup>	2.922	2.026	4.215	<0.001
MV				
Unadjusted	2.896	2.135	3.927	<0.001
Adjusted <sup>a</sup>	2.874	2.095	3.941	<0.001
POF				
Unadjusted	2.774	2.071	3.714	<0.001
Adjusted <sup>a</sup>	2.761	2.051	3.717	<0.001

**Note:** <sup>a</sup>Risk factors adjustment included age, gender, BMI, etiology.

**Abbreviations:** TIPS, thrombo-inflammatory prognostic score; AICU, admission to intensive care unit; MV, mechanical ventilation; POF, persistent organ failure; OR, odds ratio; CI, confidence interval.

and are one of the causes underlying the high mortality rate of AP.<sup>15</sup> In one study, clinically significant hemorrhagic and thrombotic disorders were observed among 6% and 7% of patients who died due to AP, respectively.<sup>32</sup> Changes to microvascular circulation may also affect the gastrointestinal tract, liver, lungs, kidneys, and skeletal muscle.<sup>31</sup> Some researchers have suggested that microcirculatory disorders are a mechanism of multiple organ dysfunction.<sup>33</sup> Derangement in the coagulation cascade is likely to be at least partially caused by systemic inflammation.<sup>31</sup> In SAP, systemic inflammation leads to endothelial dysfunction and the activation of coagulation.<sup>34</sup> Microcirculatory

**Figure 5** AUCs of the prediction of 28-day mortality based on the TIPS, APACHE II, SOFA, BISAP and Balthazar CT scores.

**Abbreviations:** TIPS, thrombo-inflammatory prognostic score; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; BISAP, bedside index for severity in acute pancreatitis.

**Table 5** Comparison Among Patients with Different “TIPS” Values (Validation Group, n = 358)

28-Day Clinical Outcomes of AP	TIPS 0 (n=139)	TIPS 1 (n=144)	TIPS 2 (n=75)	p-value
Proportion of mortality, % (n)	0 (0)	9.7% (14)	21.3% (16)	<0.001
Proportion of MV, % (n)	7.2% (10)	27.1% (39)	57.3% (43)	<0.001
Proportion of AICU, % (n)	5.0% (7)	15.3% (22)	34.7% (26)	<0.001
Proportion of POF, % (n)	6.5% (9)	34.0% (49)	70.7% (53)	<0.001

**Abbreviations:** TIPS, thrombo-inflammatory prognostic score; MV, mechanical ventilation; AICU, admission to intensive care unit; POF, persistent organ failure.

disturbances and microvascular thromboses appear to play an important role in both pancreatic inflammation and remote OF. PT, INR, APTT, and FIB are commonly used to examine blood coagulation function, and alterations in parameters such as PT, APTT, D-dimer, and FIB levels have been reported during AP. In the present study, the thrombosis measure used was PT, as its AUC for the prediction of 28-day mortality was larger than that of other thrombotic biomarkers. PT is a sensitive index that has commonly been used as an indicator of microcirculatory dysfunction in recent years, and its persistent increase indicates a poor prognosis. Hence, PT is valuable for predicting the severity of AP and related mortality.

## Limitations

There are several limitations to the present study. First, while special care was taken to avoid sources of bias and confusion, this was a single-center, retrospective cohort study and therefore included a homogenous population. With 5000 beds, the West China Hospital of Sichuan University is the largest tertiary A hospital in Western China, and the patients admitted to this center are in a relatively serious condition. Therefore, the proportion of SAP in our study population was relatively high. Hence, multicenter prospective studies with a large sample size are necessary to validate our findings in the future. Second, although we examined the biomarkers upon admission to the ED, these markers may show changes across different time points that may allow improved prognosis prediction. However, these data were unavailable for our study.

## Conclusions

In conclusion, we developed a novel and simple scoring system (TIPS) for severity assessment in AP based on a thrombotic and an inflammatory biomarker. A higher TIPS on admission was associated with increased 28-day mortality, AICU, MV, and POF rates among AP patients. Hence, this low-cost, easy-to-obtain, quick score may be useful in the identification of high-risk AP patients who could benefit from intensive management and thereby help reduce the mortality rate of AP.

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## Disclosure

The authors have no potential conflicts of interest to disclose.

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