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*Article*

# Platelet-To-Lactate Ratio Predicts In-Hospital Mortality in Patients With Sepsis-Induced Coagulopathy: A Retrospective Cohort Study

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**Abstract**

**Aims/Background:** Sepsis-induced coagulopathy (SIC) is a life-threatening complication with high mortality. The platelet count reflects coagulation status, and the lactate level indicates tissue hypoperfusion, although the prognostic value of these individual parameters is limited. The platelet-to-lactate ratio (PLAC) integrates these parameters, but its prognostic role in SIC is unclear. Here, we investigated the association between the PLAC and in-hospital mortality in patients with SIC. **Methods:** This retrospective cohort study included patients with SIC who were diagnosed after admission to the intensive care unit (ICU) of Chinese PLA General Hospital between December 2017 and October 2025. Multivariate Cox regression was used to assess the association between the PLAC and mortality. Restricted cubic spline (RCS) analysis was used to explore nonlinear relationships and threshold effects. The predictive performance of the PLAC was compared with that of the Sequential Organ Failure Assessment (SOFA) score, the SIC score, and the Charlson comorbidity index score using receiver operating characteristic (ROC) curves and the DeLong test. **Results:** Among 1722 patients with SIC, the in-hospital mortality was 26.2% (n = 452). Nonsurvivors had significantly lower PLAC values than did survivors (13.44 vs. 32.75, $p < 0.001$). Compared with the highest PLAC tertile, the middle and lowest tertiles had significantly higher mortality risk [adjusted hazard ratios (HRs): 1.701 and 3.501, respectively; both $p < 0.05$]. RCS analysis revealed a threshold effect at PLAC = 28. The area under the curve (AUC) for the PLAC was 0.711 (95% CI: 0.683–0.738), which was comparable to that of the SOFA score ($p = 0.135$) and superior to that of the SIC score and Charlson comorbidity index score (both $p < 0.001$). Subgroup analyses revealed a consistent prognostic value across most subgroups, with a significant interaction for coronary artery disease ($p < 0.0001$ for interaction) and Charlson score ($p = 0.042$). **Conclusion:** The PLAC is independently associated with in-hospital mortality in patients with SIC, with a clinically actionable threshold of 28. The PLAC is a simple biomarker that integrates coagulation and perfusion status and is a practical tool for risk stratification. However, multicenter prospective studies are needed to validate these findings.

**Keywords:** sepsis; platelet-to-lactate ratio; mortality; prognosis; risk assessment; intensive care unit

## 1. Introduction

Sepsis is still among the most common causes of mortality in intensive care units (ICUs) worldwide. Sepsis is caused by complex pathophysiological processes such as excessive inflammation, immune dysfunction, and activation of the coagulation cascade [1,2]. One of the most common and serious complications of sepsis is sepsis-induced coagulopathy (SIC), which occurs in approximately 40% to 60% of sepsis-affected individuals [3,4]. The development of SIC significantly increases the risk of multiple organ dysfunction and mortality, and thus its clinical management is challenging [4,5]. The International Society on Thrombosis and Haemostasis (ISTH) has defined the diagnostic criteria for SIC, which allows it to be identified in a clinical setting in a standardized way. However, we cannot detect early SIC and risk-stratify patients who are at risk of poor and adverse outcomes [3,6,7,8]. Therefore, it is important to improve the prognostic tools for SIC to optimize therapeutic interventions and to improve survival.

Platelets are important players that link coagulation and inflammatory processes in sepsis [9,10,11]. In the early phase of sepsis, platelet activation is involved in host defence by contributing to microthrombus formation and thus to pathogen clearance [12,13]. Excessive platelet activation causes consumptive thrombocytopenia and therefore increases bleeding risk and predisposes patients to disseminated intravascular coagulation (DIC) [10,14]. Recently, metabolic reprogramming of platelets in septic states, with a shift in energy metabolism from oxidative phosphorylation to glycolysis, has been investigated [15,16]. This metabolic switch is associated with platelet activation and mitochon-

drial dysfunction and reflects the biological changes that occur in septic coagulopathy [12,16,17]. Platelet counts are not sufficient to reflect the overall dynamics of platelet function and metabolic changes, and thus this value alone is not clinically useful [18,19].

Lactate is a well-established biomarker of tissue hypoperfusion and cellular hypoxia in cases of septic shock, and elevated levels are associated with poor outcomes [20,21]. Elevated levels of lactate, which reflect anaerobic metabolism, have been commonly used to assess the severity of sepsis and for resuscitation [20,22,23]. However, as a measure of clinical significance, the measurement of lactate is prone to confounders such as hepatic clearance, pharmacological agents, and metabolic derangements and may have attenuated specificity when it is used alone for risk stratification [24,25]. As a result, the use of lactate levels alone may not fully capture the multifactorial pathophysiological disturbances in patients with SIC [7,24].

The integration of platelet parameters with lactate measurements may result in a more complete biomarker that considers both coagulation-inflammatory disruption and metabolic-perfusion abnormalities in SIC [16,26]. The platelet-to-lactate ratio (PLAC) is a good composite marker that reflects platelet consumption and metabolic stress and provides a multidimensional view of disease severity [27,28]. An integrative approach may bypass the prognostic limitations of each marker alone and may provide improved sensitivity and specificity for the identification of high-risk patients with SIC [29].

Composite inflammatory and haematologic indices, such as the platelet-to-lymphocyte ratio (PLR), the lactate-to-albumin ratio (LAR) and the neutrophil-to-lymphocyte ratio (NLR), have been investigated for prognostication [30,31,32]. However, use of the PLAC, particularly in the SIC subpopulation, has not been well investigated. The current literature is predominantly focused on broad sepsis cohorts or individual parameters [33], and the data characterizing the nonlinear associations or threshold effects between the PLAC and mortality risk in SIC are limited. Filling these gaps is crucial for the development of personalized risk stratification and the optimization of clinical management.

To fill this knowledge gap, we performed this retrospective study to assess whether the PLAC could predict in-hospital death in 1722 persons admitted with a diagnosis of SIC. We grouped the patient characteristics according to their PLAC measurements to determine the individual relationship between this ratio and survival. In addition, restricted cubic splines were used to assess any nonlinear dynamics and to determine a cut-off point. The prognostic accuracy of the PLAC was also compared with that of the classical severity measures, the Sequential Organ Failure Assessment (SOFA) score, the SIC score and the Charlson comorbidity index score. By focusing on this at-risk population, we hope that our work will provide new insights into easily accessible risk assessment strategies for intensive care settings.

## 2. Methods

### *2.1 Study Design and Population*

Patients with SIC admitted to the ICU of the Chinese PLA General Hospital from December 2017 through October 2025 were retrospectively analysed. Sepsis was identified according to the Sepsis-3 consensus [34], and SIC was classified according to the International Society on Thrombosis and Haemostasis (ISTH) scoring system [3].

The cohort was established according to the following selection criteria: (1) adult patients (18 years or older); (2) SIC was diagnosed according to the ISTH criteria using the first available platelet count and lactate measurements obtained within 24 hours after ICU admission. Candidates were excluded if they (1) were pregnant; (2) had congenital coagulation disorders or malignant tumors; or (3) had missing PLAC index data (defined as the absence of either platelet count or lactate measurement within the first 24 hours of ICU admission, or uncertain admission timing preventing accurate window calculation).

The flowchart of our participant screening is shown in Fig. 1.

### *2.2 Data Collection*

The complete clinical profiles of each patient were obtained from the hospital's electronic medical records databases. The following variables were extracted: patient demographics, underlying comorbidities, laboratory diagnostics, and clinical severity. The baseline demographics collected were age and sex. The chronic comorbidities included hypertension (HTN), diabetes mellitus (DM), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), and chronic kidney disease (CKD).

The laboratory data collected during the initial 24 hours (using the first available value) after ICU admission were divided into the following data panels: complete blood counts (white/red blood cells, haemoglobin, and platelets), systemic inflammation markers (C-reactive protein and interleukin-6), coagulation status [prothrombin time, international normalized ratio (INR), D-dimer, and fibrinogen], and metabolic/organ function indicators (alanine and aspartate aminotransferases, total bilirubin, urea, creatinine, and lactate). For the overall disease burden, we used the Sequential Organ Failure Assessment (SOFA), the SIC score and the Charlson comorbidity index score. These clinical scoring systems are performed within the first 24 hours of ICU admission by trained intensive care physicians.

In summary, the SOFA score assesses six organ systems (respiratory, coagulation, liver, cardiovascular, central nervous system, and renal). Each component is scored from 0 to 4, and the total score ranges from 0 to 24. Higher scores indicate more severe organ dysfunction. The SIC

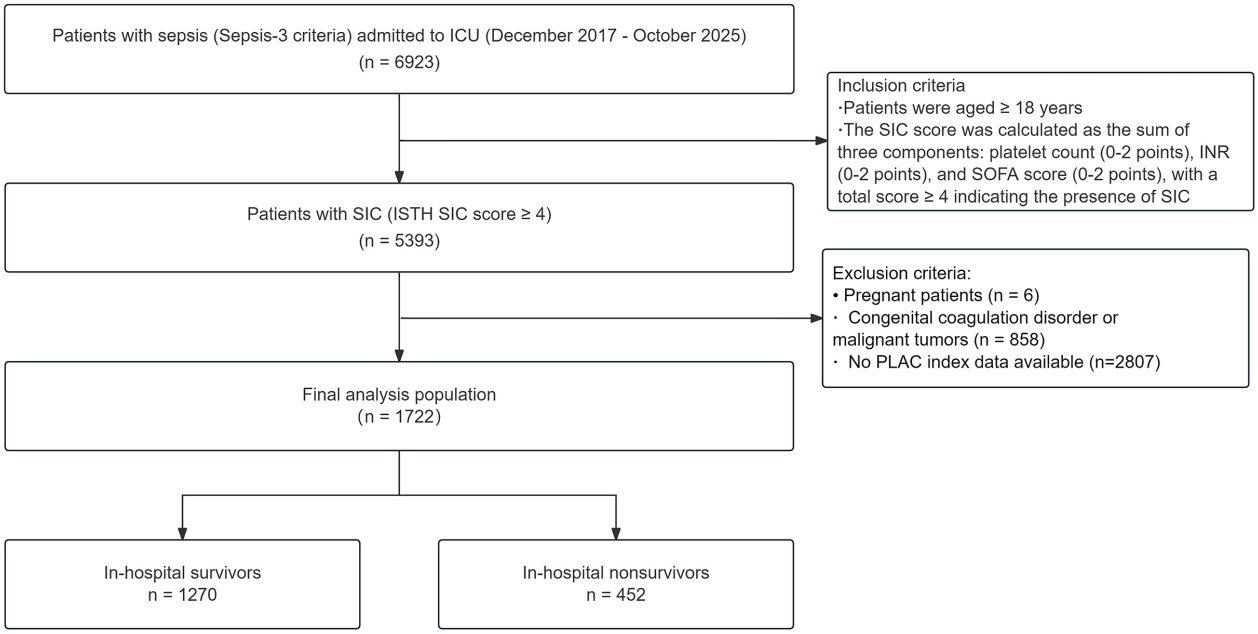


**Fig. 1. Flowchart of patient selection**. SOFA, Sequential Organ Failure Assessment; INR, international normalized ratio; ICU, intensive care unit; ISTH, International Society on Thrombosis and Haemostasis; SIC, sepsis-induced coagulopathy; PLAC, platelet-to-lactate ratio.

score comprises three components (platelet count, INR, and SOFA score). Each component is scored from 0 to 2, and the total score ranges from 0 to 6. A total score of ≥4 indicates the presence of SIC [3]. The Charlson comorbidity index predicts 10-year mortality according to 19 comorbid conditions, each of which receives a weight score [35].

### *2.3 Calculation of Platelet-To-Lactate Ratio*

The platelet-to-lactate ratio (PLAC) was calculated using the following formula:

PLAC = platelet count ($\times 10^9$/L) / lactate level (mmol/L)

The platelet counts and lactate levels were obtained from the first available laboratory tests performed during the first 24 hours after admission to the ICU. To investigate the association of the PLAC with clinical outcomes, patients were divided into tertiles based on their PLAC values (low PLAC group, T1; middle PLAC group, T2; high PLAC group, T3).

### *2.4 Outcome Definition*

The principal clinical endpoint studied in this work was all-cause mortality before hospital discharge. The study population was therefore divided into survivors and nonsurvivors according to their vital status at the end of the index hospitalization. Survival time ranged from ICU admission to in-hospital death or discharge. Those who survived to discharge were censored at discharge.

### *2.5 Statistical Analysis*

The statistical evaluations were performed with R software for statistical computing (version 4.2.1; R Foundation, Vienna, Austria). A two-tailed alpha level of less than 0.05 was considered significant. The normality of the continuous variables was evaluated by the Shapiro–Wilk test, supplemented by visual inspection of histograms and quantile–quantile (Q-Q) plots. Continuous baseline parameters are reported as the means together with standard deviations (SDs) or as medians together with interquartile ranges (IQRs) according to the normality of the distribution of the data. Categorical data are described as count frequencies and corresponding proportions. Differences between the survival and nonsurvival cohorts in terms of continuous measures were evaluated by independent Student's *t*-test or by the Mann–Whitney U test, according to the normality of the data distribution. For categorical comparisons, Pearson's Chi-square analysis or Fisher's exact test was used. For comparisons among the three PLAC tertiles, the Kruskal–Wallis test was used for continuous variables, and the Chi-square test was used for categorical variables. Homogeneity of variances was assessed using Levene's test. Survival analysis was performed using the Kaplan–Meier method and Cox proportional hazards regression. Kaplan–Meier survival curves were generated to compare survival probabilities among patients stratified by PLAC tertiles. Differences between the groups were assessed using the log-rank test. Univariable Cox regression analyses were performed for the PLAC as a continuous vari-

able and by tertiles. On the basis of clinical relevance and previous literature, the multivariable Cox regression model was adjusted for age, sex, SOFA score and Charlson comorbidity index. The SOFA score integrates multiple organ functions (including coagulation, liver, renal, respiratory, cardiovascular, and neurological), while the Charlson comorbidity index captures underlying chronic conditions. Therefore, additional adjustments for individual components (e.g., INR, creatinine, CKD, and CAD) were not performed to avoid collinearity and overfitting. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. The proportional hazards assumption was tested using Schoenfeld residuals. Collinearity among variables was assessed using the variance inflation factor (VIF), with a VIF >5 considered indicative of significant collinearity.

The discriminatory capacity of the PLAC metric for mortality outcomes was evaluated using receiver operating characteristic (ROC) curves. In addition to the area under the curve (AUC), both sensitivity and specificity metrics were obtained, and the Youden index allowed us to determine the best prognostic threshold. The prognostic ability of this new marker was compared with that of several classical tools (SOFA, SIC, and Charlson comorbidity index) by performing pairwise AUC contrasts using the DeLong method. To define possible nonlinear relationships connecting the PLAC with the risk of mortality, restricted cubic spline (RCS) modelling was also added to the multivariable Cox regression to delineate these possible nonlinear relationships. For the RCS technique, we used three different knots placed at the 10th, 50th and 90th percentiles of the data distribution, with the median as a reference. After corrections for age, sex, SOFA score and Charlson comorbidity index, the lack of linearity was tested by likelihood ratio testing. To objectively determine the threshold, segmented Cox regression analysis was performed in addition to visual inspection of the RCS plot. Decision curve analysis (DCA) was also performed using the rmda package to further evaluate the clinical utility of the PLAC. To evaluate whether adding PLAC to SOFA-related models can improve risk reclassification and overall discriminative ability, we also calculated the net reclassification improvement (NRI) and the integrated discrimination improvement (IDI). The NRI and IDI were estimated using bootstrap resampling with 1000 iterations.

Additional stratification analyses were performed to assess the stability of the prognostic results across different subgroups of demographic and clinical characteristics. The cohort was divided according to age (≥60 vs. <60 years), sex, the presence of certain comorbidities (hypertension, diabetes mellitus, chronic kidney disease, coronary artery disease and chronic obstructive pulmonary disease), and clinical severity measures (median SOFA score, SIC score and Charlson score dichotomized at 3 [≥3 vs. <3]). The age cut-off of 60 years is commonly used to define elderly patients in clinical practice and epidemiological studies. The significance of the stratified variations was reported by formal testing for interactions.

## 3. Results

### *3.1 Patient Characteristics*

In all, 1722 patients with sepsis-induced coagulopathy were included in the final analysis, consisting of 1270 in-hospital survivors (73.8%) and 452 nonsurvivors (26.2%) (Fig. 1). The overall in-hospital mortality rate was 26.2% (n = 452). Table 1 summarizes the baseline characteristics stratified by survival status. Nonsurvivors were significantly older than survivors [81.00 (69.00–88.00) vs. 67.00 (53.00–78.00) years, $p < 0.001$]. Nonsurvivors also had significantly higher incidences of CAD, COPD, and CKD (all $p < 0.05$). No significant differences were observed between the groups regarding sex distribution or the incidence of HTN and DM (all $p > 0.05$). The corresponding statistical test methods and test statistics for the comparisons between survivors and nonsurvivors are detailed in **Supplementary Table 1**.

Laboratory parameters revealed a more severe disease profile in nonsurvivors. Compared with survivors, nonsurvivors had significantly higher lactate levels [6.77 (3.90–9.10) vs. 2.95 (2.00–5.04) mmol/L, $p < 0.001$], lower platelet counts [92.00 (70.75–99.00) vs. 94.00 (83.00–99.00) $\times 10^9$/L, $p < 0.001$], and markedly lower PLAC values [13.44 (8.97–29.58) vs. 32.75 (17.57–57.45), $p < 0.001$]. Nonsurvivors also had higher SOFA scores [8.00 (6.00–10.00) vs. 6.00 (4.00–8.00), $p < 0.001$] and significantly different SIC scores ($p < 0.001$). Nonsurvivors had significantly higher Charlson scores than survivors ($p < 0.001$).

### *3.2 Clinical Characteristics Across PLAC Tertiles*

Patients were stratified into three groups based on PLAC tertiles: low (<17.19; n = 574), middle (17.19–39.20; n = 572), and high (>39.20; n = 576) (Table 2). A consistent gradient of disease severity was observed across the PLAC tertiles. **Supplementary Table 2** provides the complete test statistics for the comparisons across the three PLAC tertiles.

Patients in the low PLAC group had the highest lactate levels [7.90 (6.20–9.50) mmol/L], lowest platelet counts [82.00 (53.00–95.00) $\times 10^9$/L], and highest SOFA scores [8.00 (6.00–10.00)]. Conversely, those in the high PLAC group had the most favourable profile, characterized by a median lactate level of 1.90 (1.45–2.40) mmol/L, a median platelet count of 99.00 (93.00–294.25) $\times 10^9$/L, and a median SOFA score of 4.00 (4.00–6.00) (all $p < 0.001$). Charlson scores did not differ significantly across PLAC tertiles ($p = 0.202$). The proportion of patients with an SIC score of 6 decreased dramatically from 90.94% in the low PLAC group to 29.86% in the high PLAC group ($p < 0.001$).

Notably, compared with the low PLAC group (11.67%), the high PLAC group had a higher incidence

**Table 1. Baseline characteristics of patients with SIC stratified by in-hospital survival status.**

| Variables | All patients (n = 1722) | In-hospital survivors (n = 1270) | In-hospital nonsurvivors (n = 452) | *p*-value |
|---|---|---|---|---|
| Demographic characteristics | | | | |
| Age, years | 71.00 (56.00–82.00) | 67.00 (53.00–78.00) | 81.00 (69.00–88.00) | <0.001 |
| Sex, n (%) | | | | 0.780 |
| Female | 573 (33.28) | 425 (33.46) | 148 (32.74) | |
| Male | 1149 (66.72) | 845 (66.54) | 304 (67.26) | |
| Comorbidities | | | | |
| CAD, n (%) | | | | 0.001 |
| No | 1357 (78.80) | 1026 (80.79) | 331 (73.23) | |
| Yes | 365 (21.20) | 244 (19.21) | 121 (26.77) | |
| HTN, n (%) | | | | 0.240 |
| No | 1318 (76.54) | 963 (75.83) | 355 (78.54) | |
| Yes | 404 (23.46) | 307 (24.17) | 97 (21.46) | |
| COPD, n (%) | | | | 0.001 |
| No | 1568 (91.06) | 1174 (92.44) | 394 (87.17) | |
| Yes | 154 (8.94) | 96 (7.56) | 58 (12.83) | |
| CKD, n (%) | | | | 0.028 |
| No | 1485 (86.24) | 1109 (87.32) | 376 (83.19) | |
| Yes | 237 (13.76) | 161 (12.68) | 76 (16.81) | |
| DM, n (%) | | | | 0.418 |
| No | 1464 (85.02) | 1085 (85.43) | 379 (83.85) | |
| Yes | 258 (14.98) | 185 (14.57) | 73 (16.15) | |
| Laboratory parameters | | | | |
| WBC, $\times 10^9$/L | 9.53 (8.60–9.88) | 9.49 (8.50–9.85) | 9.63 (8.91–9.95) | <0.001 |
| IL-6, pg/mL | 89.75 (9.97–638.70) | 81.87 (9.66–98.45) | 598.05 (85.03–5000.00) | <0.001 |
| CRP, mg/dL | 8.22 (4.93–9.55) | 7.96 (4.61–9.46) | 8.80 (6.20–9.74) | <0.001 |
| HGB, g/L | 99.00 (96.00–99.00) | 99.00 (96.00–99.00) | 99.00 (95.00–99.00) | 0.011 |
| RBC, $\times 10^{12}$/L | 3.61 (3.18–4.11) | 3.62 (3.19–4.13) | 3.52 (3.13–4.07) | 0.077 |
| PLT, $\times 10^9$/L | 94.00 (81.00–99.00) | 94.00 (83.00–99.00) | 92.00 (70.75–99.00) | <0.001 |
| D-dimer, mg/L | 7.77 (4.20–11.25) | 7.55 (3.90–9.91) | 8.55 (5.03–20.00) | <0.001 |
| PT, seconds | 20.10 (17.40–27.60) | 19.00 (16.90–24.80) | 25.10 (19.80–38.20) | <0.001 |
| Fibrinogen, g/L | 4.90 (3.62–6.16) | 4.97 (3.75–6.29) | 4.68 (3.24–5.88) | <0.001 |
| INR | 1.71 (1.42–2.55) | 1.59 (1.36–2.23) | 2.28 (1.67–3.75) | <0.001 |
| AST, U/L | 68.85 (34.15–93.70) | 65.90 (31.60–92.00) | 77.00 (44.35–98.03) | <0.001 |
| ALT, U/L | 33.90 (9.50–90.00) | 35.10 (9.50–89.20) | 28.85 (9.20–92.18) | 0.006 |
| Creatinine, μmol/L | 95.00 (80.80–129.50) | 94.15 (77.82–99.77) | 97.75 (87.50–219.40) | 0.194 |
| Urea, mmol/L | 9.56 (8.61–9.97) | 9.49 (8.37–9.93) | 9.74 (9.03–26.51) | <0.001 |
| TBIL, μmol/L | 9.90 (9.20–54.10) | 9.80 (9.30–49.80) | 9.90 (9.10–66.43) | 0.116 |
| Lactate, mmol/L | 3.54 (2.20–6.80) | 2.95 (2.00–5.04) | 6.77 (3.90–9.10) | <0.001 |
| PLAC | 27.46 (12.43–48.95) | 32.75 (17.57–57.45) | 13.44 (8.97–29.58) | <0.001 |
| Disease severity scores | | | | |
| SOFA score | 6.00 (4.00–8.00) | 6.00 (4.00–8.00) | 8.00 (6.00–10.00) | <0.001 |
| Charlson score | 2.00 (0.00–3.00) | 2.00 (0.00–3.00) | 2.00 (1.00–3.00) | <0.001 |
| SIC score, n (%) | | | | <0.001 |
| 4 | 415 (24.10%) | 344 (27.09%) | 71 (15.71%) | |
| 5 | 255 (14.81%) | 227 (17.87%) | 28 (6.19%) | |
| 6 | 1052 (61.09%) | 699 (55.04%) | 353 (78.10%) | |

Data are presented as mean ± standard deviation (SD), median [interquartile range, (IQR)], or number (percentage), as appropriate. The IL-6 value of 5000 pg/mL represents the upper detection limit of the assay, with 15.7% of patients reaching this limit. CAD, coronary artery disease; HTN, hypertension; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; DM, diabetes mellitus; WBC, white blood cell; IL-6, interleukin-6; CRP, C-reactive protein; HGB, haemoglobin; RBC, red blood cell; PLT, platelet count; PT, prothrombin time; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TBIL, total bilirubin; PLAC, platelet-to-lactate ratio; SOFA, Sequential Organ Failure Assessment; SIC, sepsis-induced coagulopathy.

**Table 2. Baseline characteristics of patients with SIC stratified by PLAC tertiles.**

| Variables | Low PLAC (<17.19, n = 574) | Middle PLAC (17.19–39.20, n = 572) | High PLAC (>39.20, n = 576) | *p*-value |
|---|---|---|---|---|
| Demographic characteristics | | | | |
| Age, years | 71.00 (57.00–83.00) | 72.00 (59.00–83.00) | 69.00 (54.00–81.00) | 0.016 |
| Sex, n (%) | | | | 0.375 |
| Female | 202 (35.19) | 179 (31.29) | 192 (33.33) | |
| Male | 372 (64.81) | 393 (68.71) | 384 (66.67) | |
| Comorbidities | | | | |
| CAD, n (%) | | | | 0.684 |
| No | 455 (79.27) | 455 (79.55) | 447 (77.60) | |
| Yes | 119 (20.73) | 117 (20.45) | 129 (22.40) | |
| HTN, n (%) | | | | <0.001 |
| No | 480 (83.62) | 444 (77.62) | 394 (68.40) | |
| Yes | 94 (16.38) | 128 (22.38) | 182 (31.60) | |
| COPD, n (%) | | | | 0.076 |
| No | 527 (91.81) | 529 (92.48) | 512 (88.89) | |
| Yes | 47 (8.19) | 43 (7.52) | 64 (11.11) | |
| CKD, n (%) | | | | 0.003 |
| No | 507 (88.33) | 504 (88.11) | 474 (82.29) | |
| Yes | 67 (11.67) | 68 (11.89) | 102 (17.71) | |
| DM, n (%) | | | | 0.144 |
| No | 496 (86.41) | 492 (86.01) | 476 (82.64) | |
| Yes | 78 (13.59) | 80 (13.99) | 100 (17.36) | |
| Laboratory parameters | | | | |
| WBC, $\times 10^9$/L | 9.50 (8.56–9.91) | 9.57 (8.69–9.88) | 9.49 (8.58–9.84) | 0.098 |
| IL-6, pg/mL | 93.55 (68.50–535.27) | 79.16 (9.48–96.66) | 64.25 (9.12–92.47) | <0.001 |
| CRP, mg/dL | 8.75 (5.98–9.73) | 8.27 (4.96–9.54) | 7.42 (3.76–9.28) | <0.001 |
| HGB, g/L | 99.00 (96.00–99.00) | 99.00 (97.00–99.00) | 99.00 (96.00–99.00) | 0.048 |
| RBC, $\times 10^{12}$/L | 3.47 (3.10–4.02) | 3.67 (3.22–4.20) | 3.64 (3.20–4.10) | <0.001 |
| PLT, $\times 10^9$/L | 82.00 (53.00–95.00) | 94.00 (85.00–98.00) | 99.00 (93.00–294.25) | <0.001 |
| D-dimer, mg/L | 9.03 (5.89–20.00) | 7.70 (4.29–9.97) | 6.27 (2.99–9.62) | <0.001 |
| PT, seconds | 25.60 (20.20–35.50) | 19.00 (16.80–24.50) | 18.30 (16.80–22.08) | <0.001 |
| Fibrinogen, g/L | 4.49 (3.00–5.73) | 4.93 (3.80–6.22) | 5.21 (4.10–6.46) | <0.001 |
| INR | 2.32 (1.72–3.45) | 1.59 (1.36–2.15) | 1.52 (1.35–1.94) | <0.001 |
| AST, U/L | 85.40 (52.97–99.50) | 66.90 (32.30–91.30) | 56.00 (25.80–82.50) | <0.001 |
| ALT, U/L | 50.40 (9.60–94.50) | 34.20 (9.50–88.80) | 24.65 (9.30–83.23) | <0.001 |
| Creatinine, μmol/L | 95.10 (83.20–99.85) | 95.10 (81.40–99.47) | 94.80 (77.10–239.80) | 0.453 |
| Urea, mmol/L | 9.57 (8.83–9.98) | 9.61 (8.79–9.96) | 9.50 (8.20–9.96) | 0.047 |
| TBIL, μmol/L | 26.60 (9.50–78.45) | 9.90 (9.30–43.65) | 9.70 (8.90–30.82) | <0.001 |
| Lactate, mmol/L | 7.90 (6.20–9.50) | 3.30 (2.69–4.40) | 1.90 (1.45–2.40) | <0.001 |
| Disease severity scores | | | | |
| SOFA score | 8.00 (6.00–10.00) | 6.00 (4.00–8.00) | 4.00 (4.00–6.00) | <0.001 |
| Charlson score | 2.00 (1.00–3.00) | 2.00 (0.00–3.00) | 2.00 (0.00–3.00) | 0.202 |
| SIC score, n (%) | | | | <0.001 |
| 4 | 13 (2.26) | 95 (16.61) | 307 (53.30) | |
| 5 | 39 (6.79) | 119 (20.80) | 97 (16.84) | |
| 6 | 522 (90.94) | 358 (62.59) | 172 (29.86) | |

Data are presented as mean ± standard deviation (SD), median (IQR), or number (percentage), as appropriate. PLAC tertiles were defined based on the distribution of platelet-to-lactate ratio in the overall cohort. Abbreviations: SIC, sepsis-induced coagulopathy; CAD, coronary artery disease; HTN, hypertension; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; DM, diabetes mellitus; WBC, white blood cell; IL-6, interleukin-6; CRP, C-reactive protein; HGB, haemoglobin; RBC, red blood cell; PLT, platelet count; PT, prothrombin time; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TBIL, total bilirubin; PLAC, platelet-to-lactate ratio; SOFA, Sequential Organ Failure Assessment.

**Table 3. Cox regression analysis for in-hospital mortality.**

| Variables | Univariable model | | | Multivariable model | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *p*-value | HR | 95% CI | *p*-value |
| PLAC (as continuous) | 0.984 | 0.980–0.989 | <0.001 | 0.977 | 0.971–0.983 | <0.001 |
| PLAC tertiles | | | | | | |
| High | Reference | | | Reference | | |
| Middle | 1.752 | 1.307–2.347 | <0.001 | 1.701 | 1.216–2.377 | 0.002 |
| Low | 4.530 | 3.488–5.882 | <0.001 | 3.501 | 2.487–4.928 | <0.001 |

HRs and 95% CIs were estimated using Cox proportional hazards regression models. Multivariable models were adjusted for age, sex, SOFA score, and Charlson score. PLAC was analyzed as both a continuous variable (per unit increase) and a categorical variable based on tertiles (High tertile as reference). Abbreviations: PLAC, platelet-to-lactate ratio; HR, hazard ratio; CI, confidence interval; SOFA, Sequential Organ Failure Assessment.

of CKD (17.71%), which may seem counterintuitive given that CKD typically affects lactate clearance. These unexpected findings may be explained by the more intensive supportive care received by CKD patients or selection bias, as patients with severe CKD and critical illness may have been excluded. Further studies are needed to explore this association.

### *3.3 Association Between PLAC and Mortality*

In the univariable analysis, each unit increase in the PLAC was associated with a 1.6% reduction in mortality risk (HR = 0.984; 95% CI: 0.980–0.989; $p < 0.001$; Table 3). After adjustments for age, sex, SOFA score, and Charlson comorbidity index score, the association remained significant, as each unit increase in the PLAC resulted in a 2.3% reduction in mortality risk (HR = 0.977; 95% CI: 0.971–0.983; $p < 0.001$; Table 3).

When the PLAC levels were categorized into tertiles, a dose–response relationship was observed. Compared with the high PLAC tertile, the middle and lowest tertiles were associated with a significantly increased risk of mortality, with an adjusted HR of 1.701 (95% CI 1.216–2.377, $p = 0.002$) for the middle tertile and an adjusted HR of 3.501 (95% CI 2.487–4.928, $p < 0.001$) for the lowest tertile (Table 3).

The proportional hazards assumption was tested using Schoenfeld residuals. The global test yielded a non-significant result [$\chi^2 = 5.33$, degrees of freedom (df) = 5, $p = 0.377$], indicating that the proportional hazards assumption was satisfied. The VIFs for all variables in the multivariable model ranged from 1.02 to 1.28, all well below the conventional threshold of 5, confirming that collinearity did not significantly distort the estimates. Specifically, the VIFs for PLAC and SOFA score were 1.17 and 1.18, respectively. A sensitivity analysis excluding the SOFA score from the adjustment model yielded essentially unchanged results (HR = 0.976, 95% CI: 0.972–0.981, $p < 0.001$), as presented in **Supplementary Table 3**.

### *3.4 Survival Analysis*

Kaplan–Meier survival curves were generated to compare survival probabilities among patients stratified by PLAC tertiles (Fig. 2). A distinct gradient in survival probability was evident across the three groups. Patients in the high PLAC tertile (>39.20) demonstrated the most favourable prognosis, with a 90-day survival probability of approximately 88%. In contrast, patients in the low PLAC tertile (<17.19) had the poorest prognosis, with a 90-day survival probability of 56%. The middle PLAC tertile (17.19–39.20) followed an intermediate survival trajectory, yielding a 90-day survival probability of 80%. The differences among the three groups were highly significant (log-rank test, $p < 0.0001$). The separation of survival curves was evident within the first 5–7 days of ICU admission, which underscores the early prognostic value of the PLAC.

### *3.5 Nonlinear Relationship and Threshold Effect*

To characterize the association between the PLAC and mortality, we performed an RCS analysis adjusted for age, sex, SOFA score, and Charlson comorbidity index score (Fig. 3). The three knots were placed at the 10th, 50th, and 90th percentiles of the PLAC distribution, corresponding to PLAC values of 7.59, 27.46, and 100.25, respectively. The median PLAC value (27.46) served as the reference. The analysis demonstrated a statistically significant nonlinear association between the PLAC values and in-hospital mortality ($p$ for nonlinearity <0.0001).

Notably, we identified a distinct threshold effect at a PLAC value of 28. Segmented Cox regression analysis objectively confirmed the threshold at PLAC = 28.4, which is consistent with the visual inspection. Below this threshold, the HR for mortality sharply and progressively increased as the PLAC decreased. Conversely, when the PLAC value is above 28, the curve continues to decline but the trend is significantly flatter, indicating that further increases in the PLAC value only result in a slight reduction in the risk of death. This threshold effect has direct clinical implications: patients with a PLAC ≤28 represent a distinct high-

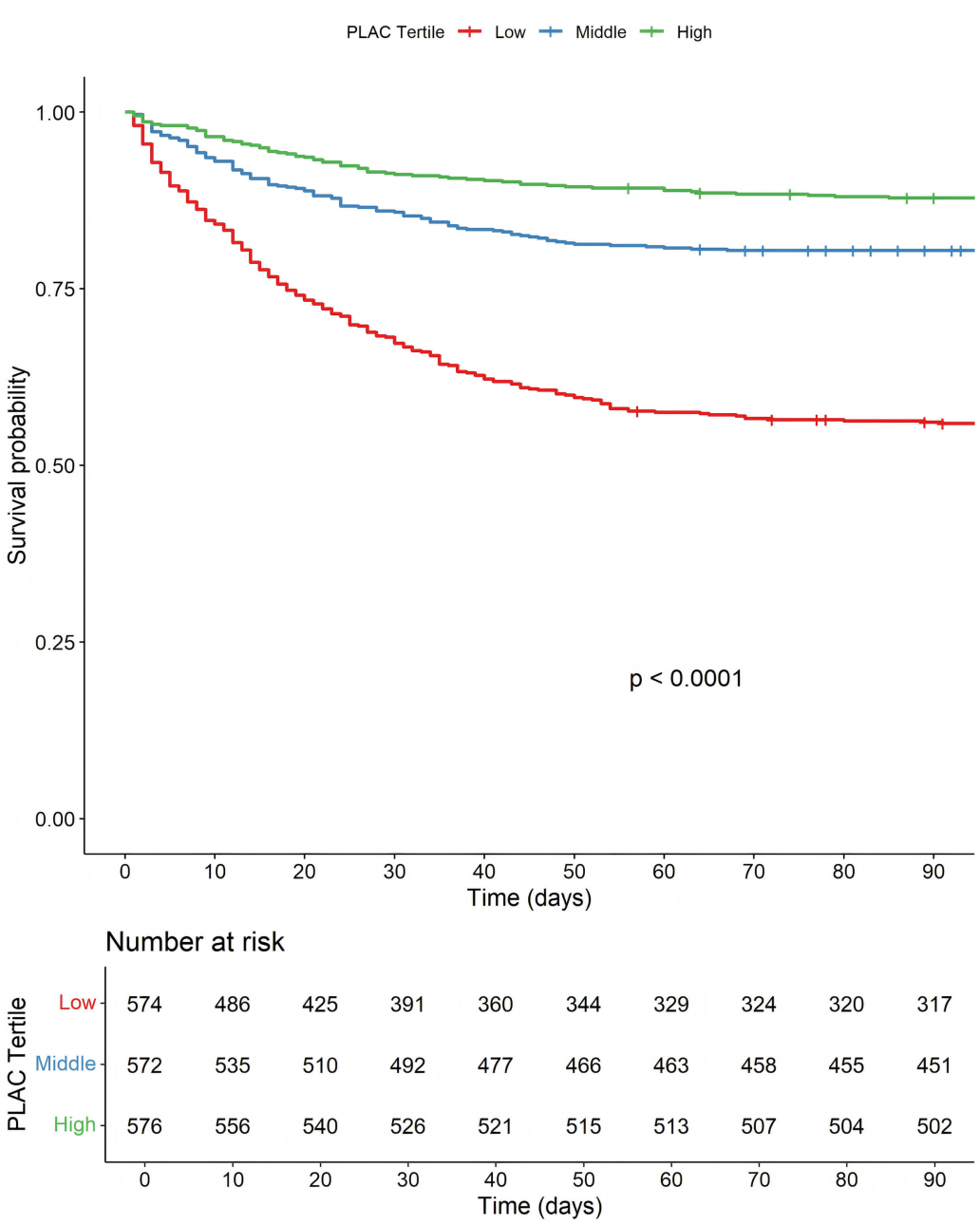


**Fig. 2. Kaplan–Meier survival curves for patients with SIC stratified by PLAC tertiles**. The curves show in-hospital all-cause survival among patients with SIC stratified by PLAC tertiles (Low: <17.19, Middle: 17.19–39.20, High: >39.20). The x-axis is truncated at 90 days. Log-rank test $p < 0.0001$.

risk phenotype that requires urgent attention, whereas those with a PLAC >28 may be considered relatively stable.

### *3.6 Predictive Performance*

ROC curve analysis was performed to evaluate the performance of the PLAC for predicting in-hospital mortality (Fig. 4). The AUC for the PLAC was 0.711 (95% CI: 0.683–0.738), yielding an optimal cut-off value of 18.3, with a sensitivity of 60.6% and a specificity of 74.0%.

Compared with current clinical scoring systems, the PLAC demonstrated comparable predictive performance to the SOFA score (AUC 0.687, $p = 0.135$) and significantly outperformed both the SIC score (AUC 0.610, $p < 0.001$) and the Charlson comorbidity index (AUC 0.575, $p < 0.001$). Detailed AUC values and pairwise comparisons are presented in Table 4.

To further evaluate the clinical utility of the PLAC, we performed decision curve analysis (DCA). The DCA demonstrated that the PLAC provided a positive net benefit across a range of threshold probabilities, confirming its clinical utility in risk stratification (Fig. 5). Additionally, we assessed whether adding PLAC to the SOFA score

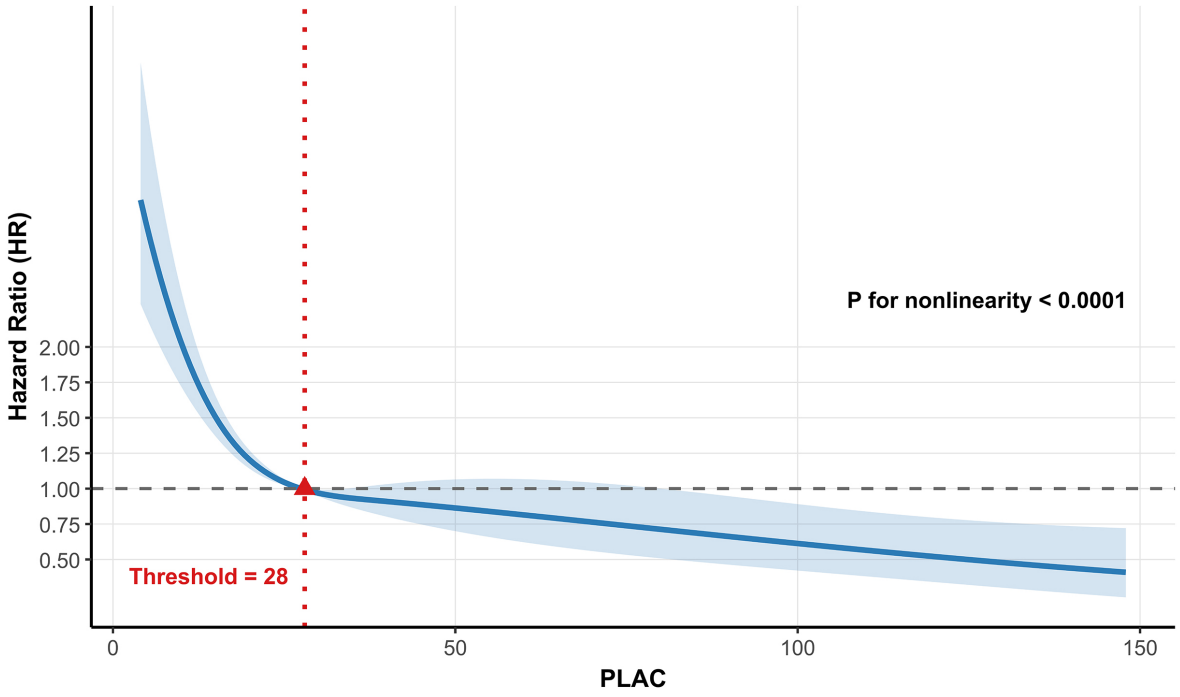


**Fig. 3. Restricted cubic spline analysis of the association of PLAC with in-hospital mortality**. Restricted cubic spline (RCS) analysis adjusted for age, sex, SOFA score, and Charlson score. The solid line represents adjusted HRs, and the shaded area denotes the 95% CIs. The analysis revealed a nonlinear relationship with a threshold effect at PLAC = 28 ($p$ for nonlinearity <0.0001). The reference point (HR = 1) corresponds to the median PLAC value of 27.46. The slight offset in the figure is due to the smoothing algorithm.

**Table 4. Predictive performance of PLAC and clinical scoring systems for in-hospital mortality.**

| Variable | AUC (95% CI) | Cut-off value | Sensitivity | Specificity | Youden index |
|---|---|---|---|---|---|
| PLAC | 0.711 (0.683–0.738) | 18.30 | 0.606 | 0.740 | 0.346 |
| SOFA score | 0.687 (0.658–0.715) | 7.50 | 0.566 | 0.723 | 0.289 |
| SIC score | 0.610 (0.585–0.634) | 5.50 | 0.781 | 0.450 | 0.231 |
| Charlson score | 0.575 (0.546–0.605) | 1.50 | 0.639 | 0.481 | 0.120 |

Data are presented as AUC with 95% CI. Pairwise comparisons of AUCs using the DeLong test showed that PLAC was comparable to the SOFA score (ΔAUC = +0.024, $p$ = 0.135), and significantly superior to the SIC score (ΔAUC = +0.101, $p$ < 0.001) and the Charlson score (ΔAUC = +0.136, $p$ < 0.001). Abbreviations: PLAC, platelet-to-lactate ratio; SOFA, Sequential Organ Failure Assessment; AUC, area under the curve; CI, confidence interval.

model improved risk stratification. The addition of PLAC (along with age and sex) to the SOFA model significantly improved risk reclassification (categorical NRI = 0.068; 95% CI: 0.026–0.115; $p$ = 0.003) and overall discrimination (IDI = 0.0273; 95% CI: 0.0138–0.0465; $p$ < 0.001). A sensitivity analysis adding only PLAC to the SOFA model (without age and sex) yielded consistent results (categorical NRI = 0.076; 95% CI: 0.029–0.126; $p$ = 0.002; IDI = 0.0304; 95% CI: 0.0171–0.0483; $p$ < 0.001; **Supplementary Table 4**), confirming that the incremental value of PLAC is independent of these covariates.

### *3.7 Subgroup Analysis*

Subgroup analyses were conducted to evaluate potential heterogeneity in the association between the PLAC and mortality across different patient populations (Fig. 6). The protective effect of a higher PLAC was consistently observed across most subgroups, as HRs ranged from 0.963 to 0.992.

Notably, significant interactions were observed for coronary artery disease status ($p$ for interaction <0.0001) and Charlson score ($p$ = 0.042). In patients without CAD, a higher PLAC was significantly associated with reduced mortality risk (HR 0.975; 95% CI: 0.968–0.982; $p$ < 0.001), whereas no significant association was observed in patients with CAD (HR 0.997; 95% CI: 0.991–1.002; $p$ = 0.255).

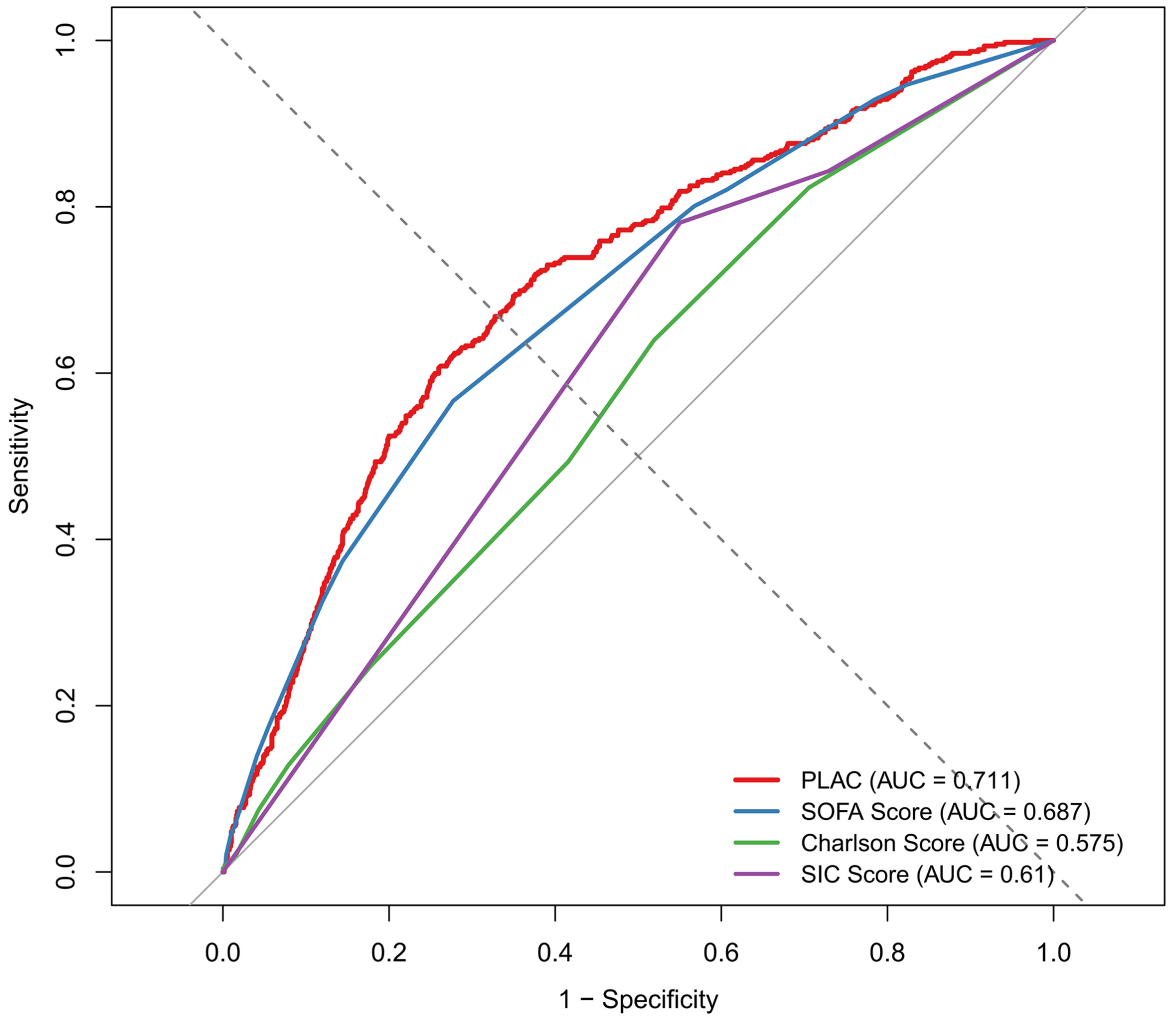


**Fig. 4. Receiver operating characteristic (ROC) curves of PLAC and clinical scoring systems for predicting in-hospital mortality**. AUC, area under the curve.

No other significant interactions were detected across the remaining subgroups (all other *p* for interaction >0.05), indicating that the prognostic value of PLAC is robust across diverse patient populations, with the exception of CAD status and Charlson score.

## 4. Discussion

In this rather large cohort of patients with SIC, we have shown a nonlinear association between the PLAC and in-hospital mortality and determined a threshold. This composite marker, which combines haemostatic and metabolic information, has a similar predictive value in different subsets of patients and could add to the classical indicators used in risk stratification. The observed threshold effect identified the point above which concomitant thrombocytopenia and lactic acidosis worsened organ dysfunction [26]. Below the threshold, the steep increase in mortality probably reflects the passage from compensated platelet activation to consumptive coagulopathy plus progressive tissue hypoxia [3]. This nonlinear pattern is different from the linear correlation that is usually reported for lactate alone [36,37], and thus it seems that the PLAC captures the two axes of coagulation failure and metabolic distress more globally. To our knowledge, this threshold effect has not been described in any SIC cohorts, and we believe that the observed threshold effect can be identified using restricted cubic spline analysis, as this type of analysis can yield a cut-off that is more clinically useful than that of the usual linear model.

The close relationship we observed between platelet counts and lactate levels in sepsis patients supports the prognostic value of the PLAC. Actually, in sepsis, platelets undergo metabolic reprogramming from oxidative phosphorylation to glycolysis, which is related to the impairment of mitochondria and to an improvement in procoagulant activity [15,27]. These metabolic alterations lead to functional exhaustion and consumption, thrombocytopenia and microvascular thrombosis [15,38]. Lactate accumulation reflects tissue hypoxia but is also associated with hepatic clearance and systemic inflammation, thereby compro-

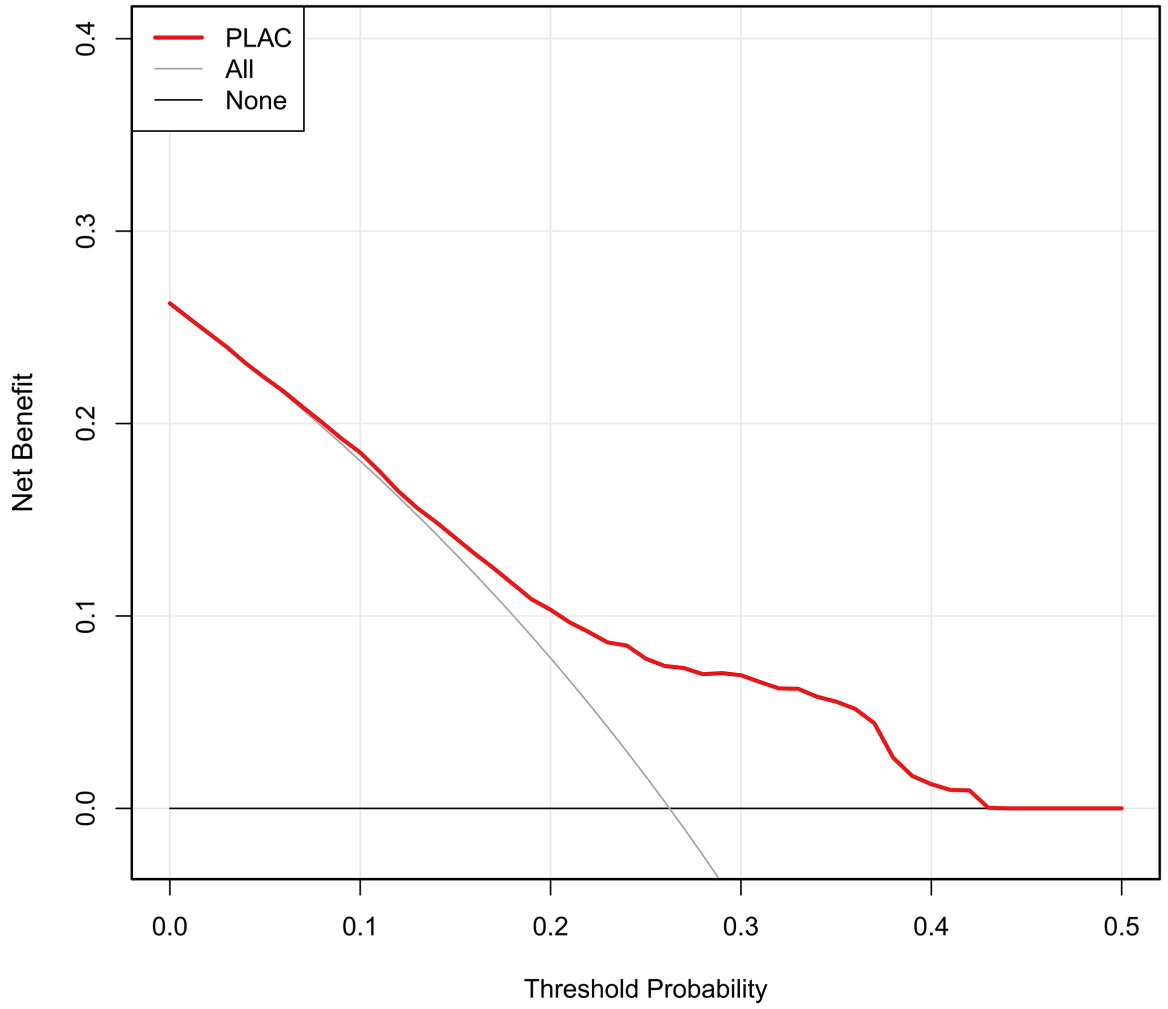


**Fig. 5. Decision curve analysis (DCA) for PLAC**. The DCA curve shows the net benefit of PLAC across a range of threshold probabilities. The PLAC model provided a positive net benefit, confirming its clinical usefulness for risk stratification.

mising its specificity [36,39,40]. Therefore, by combining these two dimensions, the PLAC can characterize the crossing of coagulation collapse and perfusion failure. This mechanistic synergy is consistent with the high mortality rate we observed in patients with low platelet counts and high lactate levels. These results support that the PLAC is a composite biomarker that could provide prognostic information that is more complementary than isolated information provided by other composite markers, such as the C-reactive protein–albumin–lymphocyte (CALLY) index [29].

Compared with the above-established clinical scoring systems, the PLAC has several advantages. First, the prognostic performance of the PLAC was comparable to that of the SOFA score, which is a more complicated scoring system with six parameters, including laboratory tests, vital signs and neurological assessment [41], whereas the PLAC is derived from only two laboratory parameters that are routinely obtained (platelet count and lactate level). Second, the PLAC demonstrated a much better performance than both the SIC score and the Charlson comorbidity index. The better performance of the PLAC compared with the SIC score is interesting because the SIC score is intended for the diagnosis of SIC, even though it only contains the weighted components of platelet count, INR and the SOFA score; however, the SIC score does not capture the synergism of coagulation failure and tissue hypoxia, which may explain why its predictive performance is not as good as that of the PLAC [3,8]. These results suggest that the integration of both platelet consumption and metabolic stress into the PLAC may better reflect the pathophysiology of SIC than the above scoring systems. Since the PLAC requires only two parameters that are commonly measured, it would be very clinically practical for this scoring system to be used for rapid bedside risk stratification, especially when a comprehensive scoring system is not readily available [42].

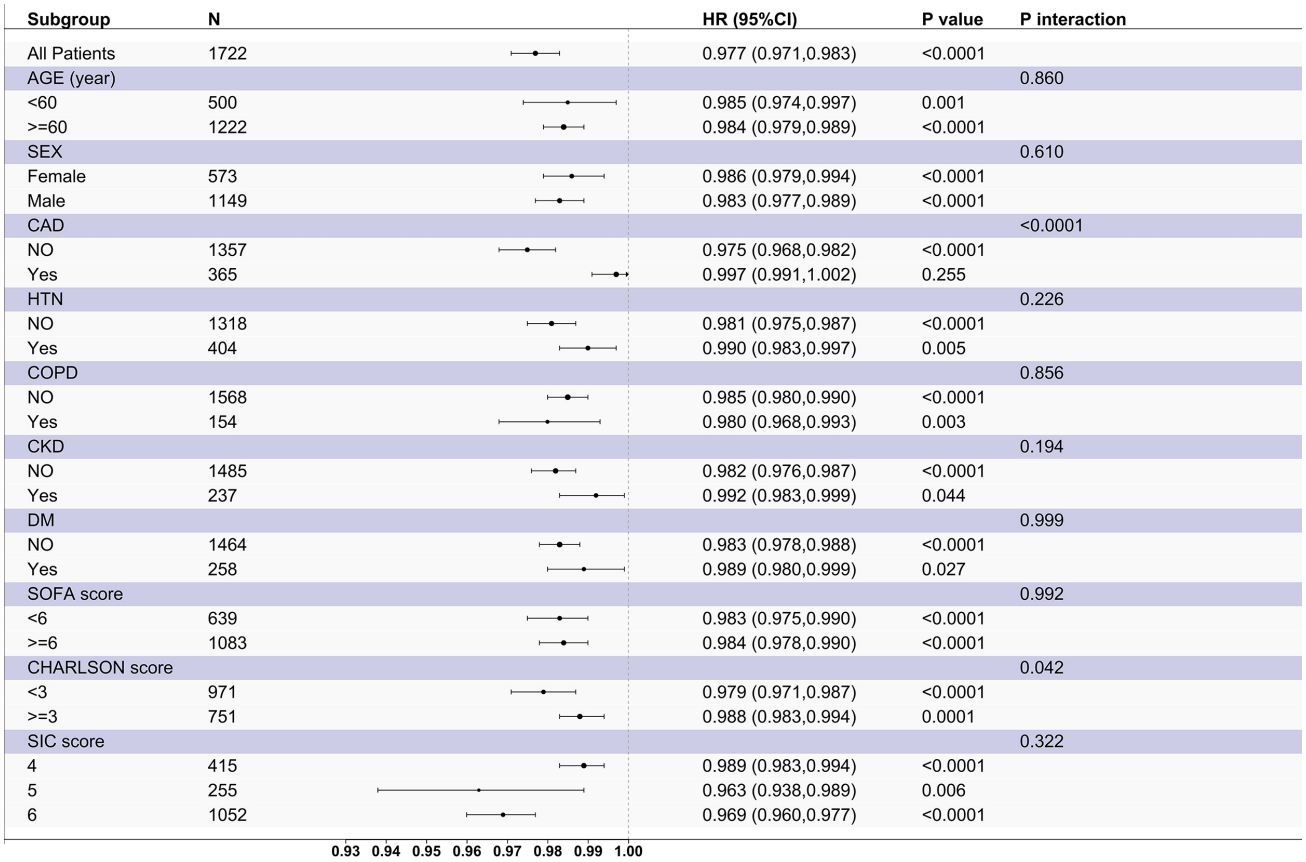


**Fig. 6. Subgroup analyses of the association between PLAC and in-hospital mortality**. Forest plot showing the association between PLAC and in-hospital mortality across predefined subgroups. HRs were adjusted for age, sex, SOFA score, and Charlson score (excluding the respective stratification variable). Black dots represent HRs, and horizontal lines denote 95% CIs. The vertical dashed line represents the null value at HR = 1.00.

Compared with other platelet-related ratios, such as the PLR (which reflects only the inflammatory status [30]), the PLAC is a reflection of the coagulation-perfusion crosstalk, which is the main factor in the pathogenesis of SIC. The nonlinear relationship observed here is a novel finding because a previous study on lactate-related composite indices has primarily focused on nutritional status rather than the coagulation interplay, with limited data available on this specific aspect in SIC patients [31]. The large sample size and the use of spline modelling support these findings, and thus the PLAC could be useful as a biomarker for risk stratification of patients with SIC.

According to the results of the subgroup analysis, the prognostic value of the PLAC was modified by the CAD status. Actually, higher PLAC was associated with lower mortality risk in patients without CAD but not in patients with pre-existing CAD. This may be explained by the use of antiplatelet agents in patients with CAD, which is common in clinical practice. Long-term antiplatelet therapy, such as aspirin or P2Y12 inhibitors (a class of antiplatelet agents targeting the platelet P2Y12 receptor), can modulate platelet function and possibly attenuate the prognostic impact of platelet-related biomarkers [43,44]. In patients with CAD, the protective effect of higher PLAC may be cancelled by the therapeutic effect of the antiplatelet agent, which independently reduces platelet activation and thrombotic risk [43]. Alternatively, the presence of CAD may represent a different pathophysiological state in which the interplay between coagulation and metabolic stress changes in a different way [45,46,47,48]. These findings show that the clinical usefulness of the PLAC may be in this context and that its use should consider underlying cardiovascular comorbidities and concomitant antiplatelet therapy.

Additionally, we observed a counterintuitive finding: the high PLAC group had a higher prevalence of CKD (17.71%) compared with the low PLAC group (11.67%). Typically, a higher PLAC indicates a more favourable prognosis, so a lower CKD prevalence would be expected in the high PLAC group. The reason for this unexpected association remains unclear. It is possible that unmeasured confounding factors or selection bias contributed to this observation. Further studies are needed to explore the relationship between PLAC and CKD in patients with SIC.

The distinct threshold effect at PLAC = 28 serves as a clear, actionable cut-off for the identification of high-risk patients with SIC who could benefit from intensified moni-

toring or therapeutic interventions, a strategy supported by studies demonstrating improved outcomes with risk-guided management in SIC populations [49,50]. This cut-off is consistent with the two dimensions of platelet-mediated microthrombosis and lactate-indicated hypoxia that are captured by the PLAC and indicates that interventions that aim to modulate coagulation but also metabolic resuscitation may be warranted in patients whose PLAC values are below the threshold [51]. The identification of these high-risk patients may help guide clinical decisions and support more targeted management in SIC. It is important to note that the RCS-derived threshold of 28 represents the inflection point where mortality risk begins to increase sharply, whereas the ROC-derived optimal cut-off of 18.3 maximizes sensitivity and specificity for predicting mortality. These two values serve complementary purposes: the RCS threshold (28) identifies the onset of high risk, while the ROC cut-off (18.3) optimizes diagnostic accuracy. Clinically, a PLAC value below 18.3 indicates extremely high risk, while values between 18.3 and 28 indicate moderate risk, and values above 28 indicate relatively low risk.

Some limitations of the present investigation should be noted. First, the single-center, retrospective design and the exclusion of 2807 patients due to missing PLAC data may introduce selection bias and limit the generalizability of our findings. Patients with missing laboratory records might represent a different subgroup (e.g., those with shorter ICU stays or less severe illness). Additionally, the newly identified risk cut-off requires independent external validation in multicenter cohorts or publicly available critical care databases [e.g., MIMIC-IV (https://mimic.physionet.org/) or eICU (https://eicu-crd.mit.edu/)] before clinical application. Second, we only assessed biomarkers at ICU admission (within the first 24 hours) and lacked data on their dynamic trajectories. Furthermore, detailed data on allogeneic blood transfusions (including platelet transfusions), 24-hour fluid balances, infection site, presence of shock or shock index, and treatment-related factors such as anticoagulant therapy and vasoactive drug use were not available due to the retrospective design. These unmeasured variables could influence platelet counts, lactate levels, and patient outcomes, and should be systematically collected in future prospective studies. Third, initial height and weight records were missing in many cases, preventing analysis of body mass index (BMI) as a potential confounder. The relatively low variability of C-reactive protein (CRP), WBC, and urea observed in our cohort may reflect early-phase measurements that had not yet peaked. Finally, despite extensive adjustments for recognized clinical variables, the possibility of unobserved residual confounding cannot be excluded.

## 5. Conclusion

In conclusion, we have shown in this study that the PLAC is independently associated with in-hospital mortality in patients with SIC, with a nonlinear relationship and a clinically actionable threshold. Although this is a simple readily available biomarker that reflects both coagulation and perfusion status, multiple prospective studies are needed to confirm our findings and to assess PLAC-guided therapeutic strategies.

## Key Points

• We retrospectively evaluated the prognostic value of the PLAC, a new biomarker of coagulation status and tissue perfusion, in a cohort of 1722 patients with SIC.

• The PLAC was independently associated with in-hospital mortality, such that patients in the lowest tertile had 3.5 times the risk of mortality than did those in the highest tertile.

• Restricted cubic spline analysis revealed a nonlinear effect and a clear threshold effect at PLAC = 28, below which the risk of mortality increased sharply.

• Although the PLAC is based on only two parameters that are routinely available (platelet count and lactate level), this ratio also has a prognostic performance similar to that of the SOFA score (AUC 0.711 vs. 0.687; $p = 0.135$).

• The prognostic value of the PLAC was the same in most of the subgroups, but the interaction was significant for the status of coronary artery disease and Charlson score, thus indicating that the clinical utility of the PLAC could differ based on context.

## Abbreviations

CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DIC, disseminated intravascular coagulation; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; ICU, intensive care unit; IL-6, interleukin-6; INR, international normalized ratio; IQR, interquartile range; ISTH, International Society on Thrombosis and Haemostasis; LAR, lactate-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; PLAC, platelet-to-lactate ratio; PLR, platelet-to-lymphocyte ratio; PLT, platelet count; PT, prothrombin time; RCS, restricted cubic spline; ROC, receiver operating characteristic; SIC, sepsis-induced coagulopathy; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell.

## Availability of Data and Materials

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

## Author Contributions

TY and YX designed the research study. SM, XZ, and SSW performed the data collection and methodology. SM, SSW, and YFW conducted the statistical analysis and interpretation of data. YZZ, YZY, CL, and YYW contributed to data validation and interpretation. TY and YX acquired funding. SM, CL, and YFW wrote the original draft. All authors critically revised the manuscript for important intellectual content. All authors reviewed and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

This study protocol was approved by the Institutional Review Board of the Chinese PLA General Hospital in 2024 (Approval No. [S2024-442-02]). Data collection continued through October 2025 under this approved protocol. Since we only used deidentified pre-existing electronic medical records and this study does not introduce any risk to the participants, the Institutional Review Board waived the requirement for informed consent in accordance with the Declaration of Helsinki and local regulations.


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## Conflicts of Interest

The authors declare no conflicts of interest.

## Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used a large language model (LLM)-based AI tool to assist with language polishing, grammar checking, and formatting of the manuscript. Following the use of this tool, the authors critically reviewed and revised the content to ensure accuracy and completeness. The authors take full responsibility for the final content of this publication.

## Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/BJHM52277.

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