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ORIGINAL ARTICLE

Case Control Study

Diagnostic value of tissue plasminogen activator-inhibitor complex in sepsis-induced liver injury: A single-center retrospective case-control study

Ye Zhou, Long-Ping He, Ying-Han Qi, Yu Huang, Bing-Qin Hu, Jia-Ling Liu, Qing-Bo Zeng, Jing-Chun Song

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Abstract

BACKGROUND

Sepsis often causes severe liver injury and leads to poor patient outcomes. Early detection of sepsis-induced liver injury (SILI) and early treatment are key to improving outcomes.

AIM

To investigate the clinical characteristics of SILI patients and analyze the associated risk factors, to identify potential sensitive biomarkers.

METHODS

Retrospective analysis of clinical data from 546 patients with sepsis treated in the intensive care unit of the 908th Hospital of Chinese People's Liberation Army Joint Logistic Support Force between May 2018 and December 2022. The patients were divided into the sepsis group (n = 373) and SILI group (n = 173) based on the presence of acute liver injury within 2 hours of admission. We used the random forest algorithm to analyze risk factors and assessed potential diagnostic markers of SILI using the area under the receiver operating characteristic curve, Kaplan-Meier survival curves, subgroup analysis and correlation analysis.

RESULTS

Compared with the sepsis group, tissue plasminogen activator-inhibitor complex (t-PAIC) levels in serum were significantly higher in the SILI group ($P < 0.05$). Random forest results showed that t-PAIC was an independent risk factor for SILI, with an area under the receiver operating characteristic curve of 0.862 (95% confidence interval: 0.832-0.892). Based on the optimal cut-off value of 11.9 ng/mL, patients at or above this threshold had significantly higher levels of lactate and Acute Physiology and Chronic Health Evaluation II score. The survival rate of these patients was also significantly worse (hazard ratio = 2.2, 95% confidence interval: 1.584-3.119, $P < 0.001$). Spearman's correlation coefficients were 0.42 between t-PAIC and lactate, and 0.41 between t-PAIC and aspartate transaminase. Subgroup analysis showed significant differences in t-PAIC levels between patients with different severity of liver dysfunction.

CONCLUSION

T-PAIC can serve as a diagnostic indicator for SILI, with its elevation correlated with the severity of SILI.

Key Words: Sepsis; Liver injury; Liver diseases; Tissue plasminogen activator-inhibitor complex; Prognosis

Core Tip: Our study showed that tissue plasminogen activator-inhibitor complex levels were significantly higher in patients with sepsis-induced liver injury and differed significantly between patients with different severity of liver dysfunction. Furthermore, our study proposed that tissue plasminogen activator-inhibitor complex may be an effective biomarker for diagnosis of sepsis-induced liver injury, providing a novel tool for its clinical recognition.

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INTRODUCTION

Sepsis refers to life-threatening organ dysfunction caused by a dysregulated host response to infection[1]. Data indicate that in 2017, there were about 11 million deaths attributable to sepsis globally, representing 19.7% of all deaths[2]. Multiorgan dysfunction is associated with a high risk of mortality. Sepsis is caused by a variety of microorganisms that trigger an immune response that fails to restore homeostasis, leading to a sustained hyperinflammatory response, which in turn causes immunosuppression[3]. Dysregulation of the inflammatory response is the most critical factor in sepsis and is characterized by the release of proinflammatory cytokines such as tumor necrosis factor, interleukin (IL)-1 and IL-6, which cause a cytokine storm[4]. The immunosuppressive phase of sepsis is a key factor in the progression of the disease. During this phase, widespread lymphocyte apoptosis occurs across various organs, resulting in significant depletion of immune cell populations (including monocytes, macrophages, dendritic cells, natural killer cells, and B cells)[5,6].

The liver is frequently affected by sepsis, which is associated with various pathogens, toxins and cytokines[7]. This condition can disrupt the microcirculation of the gut, facilitating the translocation of intestinal bacteria and toxins to the liver *via* the portal vein, thereby initiating a cascade of inflammatory responses[8]. As the inflammatory response escalates, the risk of cellular damage and liver injury correspondingly increases. Furthermore, inflammation stimulates the coagulation system, leading to the formation of microthrombi that impair adequate hepatic perfusion[9]. During sepsis, the liver also serves as a hub for oxidative stress reactions, with byproducts that can activate neutrophils and escalate liver injury[10]. For sepsis patients who experience liver failure, the mortality rate can soar to between 54% and 68%[11].

Sepsis-induced liver injury (SILI) patients often present with elevated liver enzyme levels, jaundice, coagulopathy and even consciousness impairment as the main manifestations[7,11]. Early detection and timely intervention of SILI are important for improving the survival rate and prognosis of sepsis patients. Regrettably, there is currently a lack of accurate and sensitive diagnostic marker for SILI. Therefore, this study retrospectively analyzed the clinical data of 546 patients with sepsis admitted to the intensive care unit (ICU) of our hospital, to explore new methods for detection of SILI and provide a novel basis for its clinical identification.

MATERIALS AND METHODS

Study design and patients

This study enrolled sepsis patients who had been admitted to the ICU of the 908th Hospital of Chinese People's Liberation Army Joint Logistic Support Force (Nanchang, China) between May 2018 and December 2022. Patients were required to meet the sepsis 3.0 diagnostic criteria and had complete clinical data. Diagnosis of sepsis needs to meet both of the following: (1) Confirmed or suspected infection; and (2) Sequential Organ Failure Assessment score ≥ 2[1]. Patients were excluded if they were: (1) Younger than 18 years old; (2) If they died or were transferred out within 24 hours of admission to the ICU; (3) If they had chronic liver disease (alcoholic hepatitis, drug-induced hepatitis, autoimmune liver disease, malignant hepatic tumor or cirrhosis); or (4) If they had obstructive jaundice. The diagnostic criteria for alcoholic hepatitis were: (1) Onset of jaundice within the past 8 weeks; (2) Continuous alcohol consumption for ≥ 6 months with < 60 days of abstinence prior to the onset of jaundice; (3) Aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio > 1.5, with both values < 400 IU/L; (4) AST level > 50 IU/L; and (5) Serum total bilirubin level > 3.0 mg/dL[12]. The diagnostic criteria for drug-induced hepatitis were: (1) History of drug use; (2) > 2-fold increase in plasma ALT; and (3) Decrease in plasma ALT levels after drug discontinuation[13]. The diagnostic criteria for autoimmune liver disease were defined according to the American Association for the Study of Liver Diseases clinical guidance in 2008[14]: (1) Elevated serum alkaline phosphatase [> 1.5 folds the upper limit of normal (ULN)] or γ-glutamyl transpeptidase (> 3 ULN); and (2) Positive test for antimitochondrial antibodies (titer > 1:40). Obstructive jaundice was diagnosed based on the following criteria: (1) Confirmation of biliary obstruction by ultrasound, endoscopic retrograde cholangiopancreatography, or computed tomography; and (2) Serum bilirubin level > 17.1[15]. The diagnostic criteria for malignant hepatic tumor need to be in accordance with the Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (2022 Edition)[16]. The diagnostic criteria for cirrhosis are defined according to the Chinese guidelines on the management of liver cirrhosis: The etiology, history, clinical manifestations, complications, course of treatment, tests, imaging and histology need to be considered[17].

Based on the presence of acute liver injury within 2 hours of admission, all enrolled patients were divided into the sepsis group (including those without acute liver injury within 2 hours of admission) and the SILI group (including those with acute liver injury within 2 hours of admission). The diagnostic criteria for acute liver injury were: Total bilirubin level > 34.2 μmol/L or aminotransferases ≥ 2 ULN[18-20]. This study was approved by the Ethics Committee of the 908th Hospital of the Chinese People's Liberation Army Joint Logistics Support Force (No. 908yyLL028). As all participants or their legal guardians had previously given their written consent upon admission, stipulating the use of their anonymized medical data for research, this study was exempt from obtaining additional informed consent.

Data collection

Baseline clinicodemographic data of the two groups were extracted from electronic medical records, including: Age; sex; Glasgow Coma Scale score; Acute Physiology and Chronic Health Evaluation (APACHE) II score; Child-Pugh score within 2 hours of admission; and 90-day outcome. Discharged patients were followed up by phone to confirm their 90-day outcomes. The laboratory test results were also collected upon admission to the ward: White blood cell (WBC) count, red blood cell (RBC) count, hemoglobin, platelet count, ALT, AST, total bilirubin, albumin, creatinine, C-reactive protein (CRP), lactate, prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, thrombin time (TT), fibrin degradation product (FDP), D-dimer, thrombomodulin (TM), thrombin-antithrombin complex (TAT), tissue plasminogen activator-inhibitor complex (t-PAIC), and α2-plasmin inhibitor-plasmin complex.

Statistical analysis

All statistical analyses were performed using SPSS version 26.0 (IBM, Chicago, IL, United States) and R4.1.3 software (Chicago, IL, United States), and all analyses were two-sided. Normality tests were performed on all continuous data. Normally distributed data were expressed as mean ± SD and intergroup differences in the two groups were assessed for significance using Student's *t* test. Skewed data were expressed as median (interquartile range), and intergroup differences were assessed using the Mann-Whitney *U* test. Categorical data were expressed as numbers (percentages), and intergroup differences were assessed using the χ^2 test. Random forests were used to identify potential risk factors for SILI and the relative importance of diagnostic variables assessed. Important diagnostic variables were selected after variable screening, and receiver operating characteristic curves were analyzed. Kaplan-Meier methods were used to draw survival curves, and log-rank tests were used to compare differences between groups. Spearman's rank correlation was used to assess associations of serum t-PAIC with serum lactate and AST levels. Subgroup analysis was performed to assess differences in t-PAIC levels among patients with different Child-Pugh classifications. $P < 0.05$ was considered significant.

RESULTS

Patient characteristics

From May 2018 to December 2022, 632 patients with sepsis were admitted to our ICU. We excluded three patients under the age of 18 years; 44 who died or were transferred out within 24 hours; 35 with alcoholic hepatitis, drug-induced hepatitis, autoimmune liver disease, malignant hepatic tumor or cirrhosis and four with obstructive jaundice. The remaining 546 patients were included, and 173 (31.7%) were diagnosed with SILI (Figure 1). There was no significant

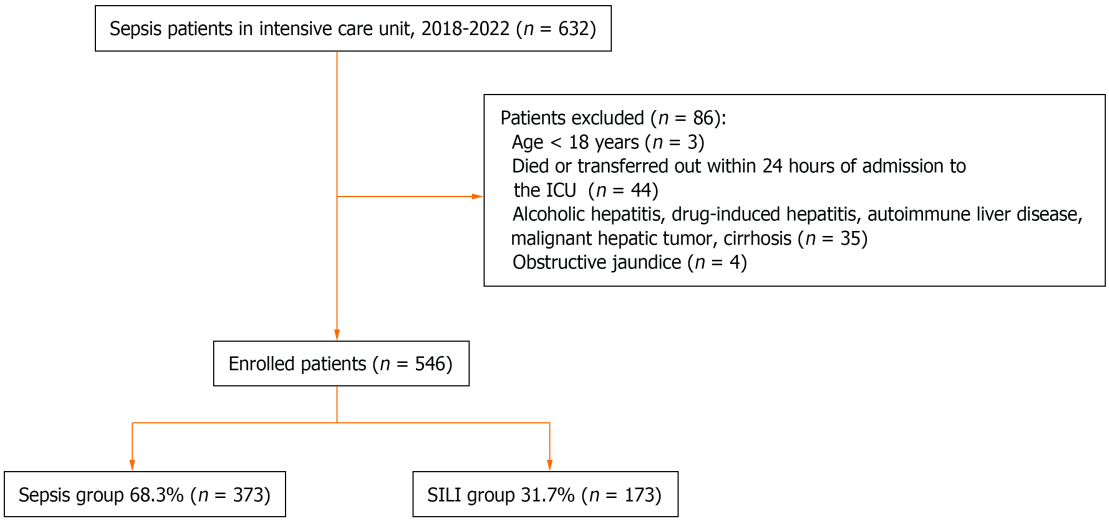

Figure 1 Patient flow diagram. SILI: Sepsis-induced liver injury; ICU: Intensive care unit.

difference in age, gender, RBC count and hemoglobin level between the two groups ($P > 0.05$). However, compared with the sepsis group, the Glasgow Coma Scale score, platelet count, albumin and fibrinogen levels in the SILI group were significantly lower ($P < 0.05$). On the contrary, the APACHE II score, Child-Pugh score, serum WBC count, ALT, AST, total bilirubin, creatinine, CRP, lactate, PT, APTT, TT, FDP, D-dimer, TM, TAT, t-PAIC and α2-plasmin inhibitor-plasmin complex concentrations in the SILI group were significantly higher ($P < 0.05$) (Table 1).

Table 1 Demographic characteristics of sepsis patients with or without liver injury

Characteristics	Normal range	Total (*n* = 546)	Sepsis (*n* = 373)	SILI (*n* = 173)	*P* value
Age, year, median (IQR)	-	65 (51-81)	66 (50.5-81.5)	63 (51-76)	0.166
Male, *n* (%)	-	380 (69.6)	258 (69.2)	122 (70.5)	0.749
WBC, × 10^9/L, median (IQR)	3.5-9.5	11.0 (7.9-15.2)	10.8 (7.7-14.6)	12.1 (8.2-16.4)	0.047
RBC, × 10^{12}/L, mean ± SD	3.8-5.1	3.4 ± 0.9	3.4 ± 0.9	3.5 ± 1.1	0.212
HGB, g/L, mean ± SD	115-150	103.7 ± 28.9	103.3 ± 27.3	104.7 ± 32.0	0.624
Platelet, × 10^9/L, median (IQR)	125-350	163.5 (109.8-230.3)	172.0 (124.0-237.5)	136.0 (73.0-215.5)	< 0.001
ALT, U/L, median (IQR)	0-40	26.8 (14.2-60.7)	18.6 (12.0-32.4)	98.0 (42.4-217.7)	< 0.001
AST, U/L, median (IQR)	8-40	37.3 (20.9-75.1)	27.1 (18.7-42.8)	116.8 (74.6-333.2)	< 0.001
TBIL, mmol/L, median (IQR)	3.42-20.5	13.3 (7.8-24.4)	10.4 (6.8-16.4)	35.0 (14.7-63.4)	< 0.001
Albumin, g/L, mean ± SD	38-51	31.9 ± 6.8	33.0 ± 6.6	29.4 ± 6.6	< 0.001
Cr, mmol/L, median (IQR)	44-80	84.2 (59.9-152.0)	76.1 (56.0-118.8)	110.1 (73.4-193.8)	< 0.001
CRP, mg/L, median (IQR)	0-5	41.2 (8.5-100.2)	34.1 (8.3-85.6)	53.9 (11.2-117.8)	0.003
Lac, mmol/L, median (IQR)	0.5-1.6	1.7 (1.0-3.6)	1.4 (0.9-2.7)	3.2 (1.7-5.5)	< 0.001
PT, s, median (IQR)	10-14	14.3 (12.9-16.4)	13.9 (12.7-15.4)	15.4 (13.6-19.6)	< 0.001
APTT, s, median (IQR)	22-38	31.2 (26.8-36.9)	30.4 (26.6-35.4)	33.5 (27.7-41.5)	< 0.001
FIB, g/L, median (IQR)	2-4.5	2.7 (1.8-3.5)	2.8 (2.0-3.6)	2.3 (1.5-3.3)	< 0.001
TT, s, median (IQR)	10-16	16.1 (14.7-17.9)	15.7 (14.5-17.4)	17.4 (15.2-19.6)	< 0.001
FDP, mg/L, median (IQR)	0-5	7.5 (3.1-19.3)	5.9 (2.5-14.6)	13.0 (5.5-31.8)	< 0.001
D-dimer, mg/L, median (IQR)	0-0.5	2.5 (1.0-6.1)	2.0 (0.8-4.8)	4.2 (1.7-9.4)	< 0.001
TM, TU/mL, median (IQR)	3.82-13.35	10.8 (7.7-16.9)	10.0 (7.3-14.5)	13.3 (9.3-23.1)	< 0.001
TAT, ng/mL, median (IQR)	0-4.07	10.1 (4.6-29.1)	7.5 (4.0-20.4)	18.4 (7.5-53.3)	< 0.001

t-PAIC, ng/mL, median (IQR)	Female: 0-10.5. Male: 0-17.0	12.2 (7.4-18.9)	9.8 (5.9-14.4)	20.6 (14.9-29.9)	< 0.001
PIC, μg/mL, median (IQR)	0-0.85	1.3 (0.7-2.4)	1.2 (0.7-2.1)	1.6 (0.7-3.3)	0.021
GCS score, median (IQR)	15	8 (4-12)	9 (5-12)	7 (3-12)	0.032
APACHE II score, median (IQR)	0	21 (16-27)	20 (16-26)	23 (18-28)	0.001
Child-Pugh score, median (IQR)	5	8 (7-9)	7 (7-8)	9 (8-11)	< 0.001

SILI: Sepsis-induced liver injury; IQR: Interquartile range; WBC: White blood cell; RBC: Red blood cell; HGB: Hemoglobin; ALT: Alanine transaminase; AST: Aspartate transaminase; TBIL: Total bilirubin; Cr: Creatinine; CRP: C-reaction protein; Lac: Lactate; PT: Prothrombin time; APTT: Activated partial thrombin time; FIB: Fibrinogen; TT: Thrombin time; FDP: Fibrinogen degradation product; TM: Thrombomodulin; TAT: Thrombin-antithrombin complex; t-PAIC: Tissue plasminogen activator-inhibitor complex; PIC: α2-plasmin inhibitor-plasmin complex; GCS: Glasgow Coma Scale; APACHE II: Acute physiological and chronic health evaluation II.

Random forest analysis

Random forest analysis identified the following significant variables in descending order: T-PAIC, lactate, creatinine, PT, albumin, TAT, FDP, D-dimer, TM, platelet count, TT, age, fibrinogen, CRP, RBC count and APTT (Figure 2A and B).

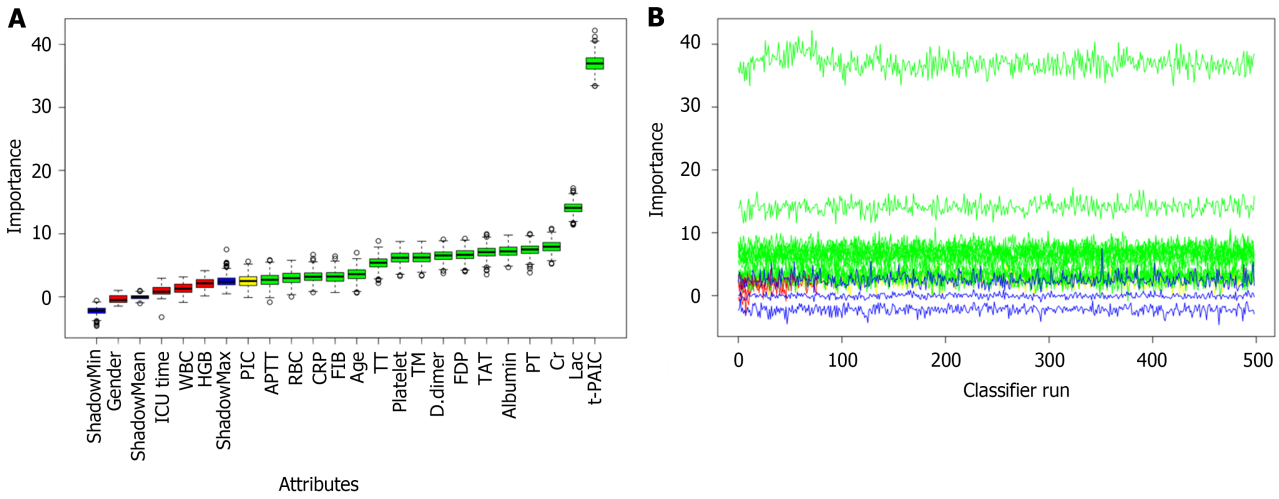

Figure 2 Investigation of the most valuable variables using random forests analysis. A: Boxplot for all features in random forest analysis. Green indicates important variables; red, blue, or yellow, rejected variables; B: Rejection or acceptance of factors during random forest classification runs. ICU: Intensive care unit; WBC: White blood cell; HGB: Hemoglobin; PIC: α2-plasmin inhibitor-plasmin complex; APTT: Activated partial thrombin time; RBC: Red blood cell; CRP: C-reaction protein; FIB: Fibrinogen; TT: Thrombin time; TM: Thrombomodulin; FDP: Fibrinogen degradation product; TAT: Thrombin-antithrombin complex; PT: Prothrombin time; Cr: Creatinine; Lac: Lactate; t-PAIC: Tissue plasminogen activator-inhibitor complex.

Diagnostic value of t-PAIC for SILI by receiver operating characteristic analysis

The area under the receiver operating characteristic curve for t-PAIC to diagnose SILI among the 546 patients was 0.862 [95% confidence interval (CI): 0.832-0.892] for the optimal cut-off value of 11.9 ng/mL, which gave sensitivity of 88.4%, specificity of 65.4%, positive predictive value of 54.3% and negative predictive value of 92.4% (Figure 3).

Comparison of disease severity and survival rates of SILI patients based on t-PAIC stratification

A total of 546 SILI patients were stratified based on the optimal t-PAIC threshold of 11.9 ng/mL. Patients with sepsis were divided into a t-PAIC-elevated group (n = 282) and t-PAIC-normal group (n = 264) based on whether serum t-PAIC level was > 11.9 ng/mL. Patients with levels at or above this threshold had significantly higher lactate levels and APACHE II score (Figure 4A and B), as well as significantly worse 90-day survival rates (Figure 4C).

Correlation analysis

Serum t-PAIC levels correlated moderately with lactate (r = 0.42, P < 0.001) and AST (r = 0.41, P < 0.001) levels (Figure 5). Other variables had weak correlations with t-PAIC levels including TM, PT, ALT and total bilirubin.

Subgroup analysis

Subgroup analysis based on the Child-Pugh classification[21], which categorized patients into those with normal or mildly liver dysfunction (Class A, n = 89), moderate liver dysfunction (Class B, n = 375), and severe liver dysfunction

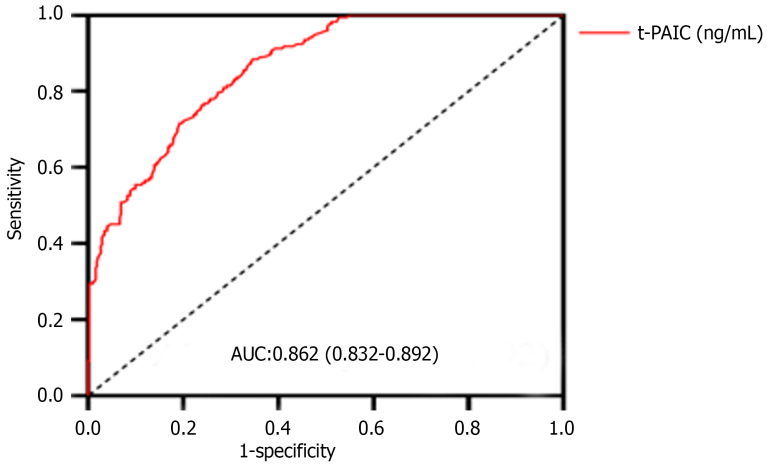

Figure 3 Receiver operating characteristic curve to assess the ability of tissue plasminogen activator-inhibitor complex to diagnose sepsis-induced liver injury. t-PAIC: Tissue plasminogen activator-inhibitor complex; AUC: Area under the receiver operating characteristic curve.

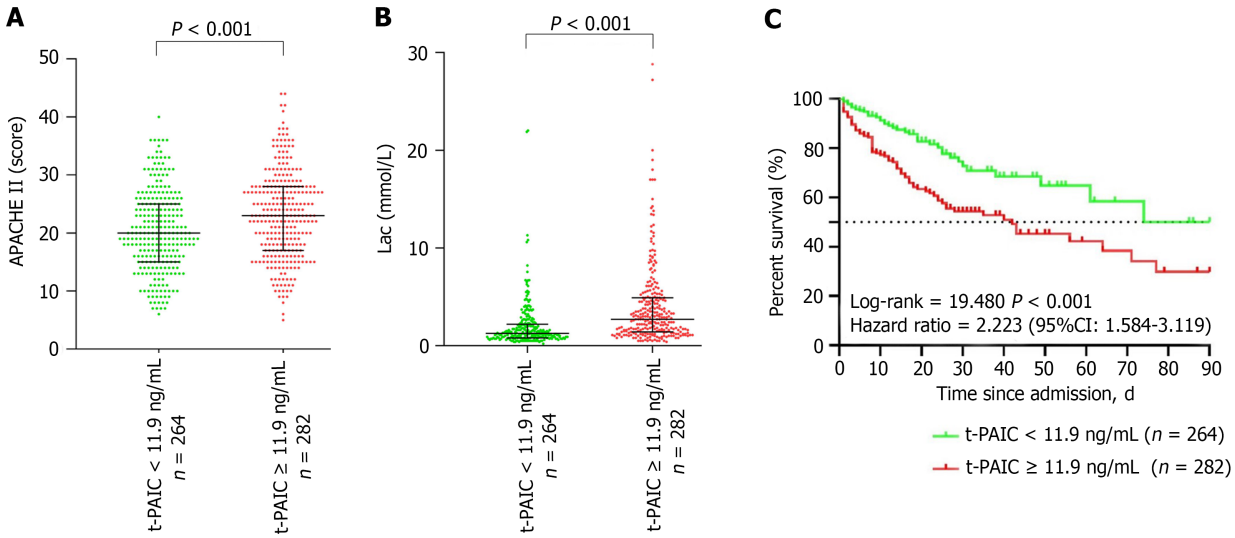

Figure 4 Comparison of patients stratified based on an optimal tissue plasminogen activator-inhibitor complex cutoff of 11.9 ng/mL. A: Acute Physiology and Chronic Health Evaluation II score; B: Lactate levels; C: Kaplan-Meier survival curves. APACHE II: Acute Physiology and Chronic Health Evaluation II; t-PAIC: Tissue plasminogen activator-inhibitor complex; Lac: Lactate; CI: Confidence interval.

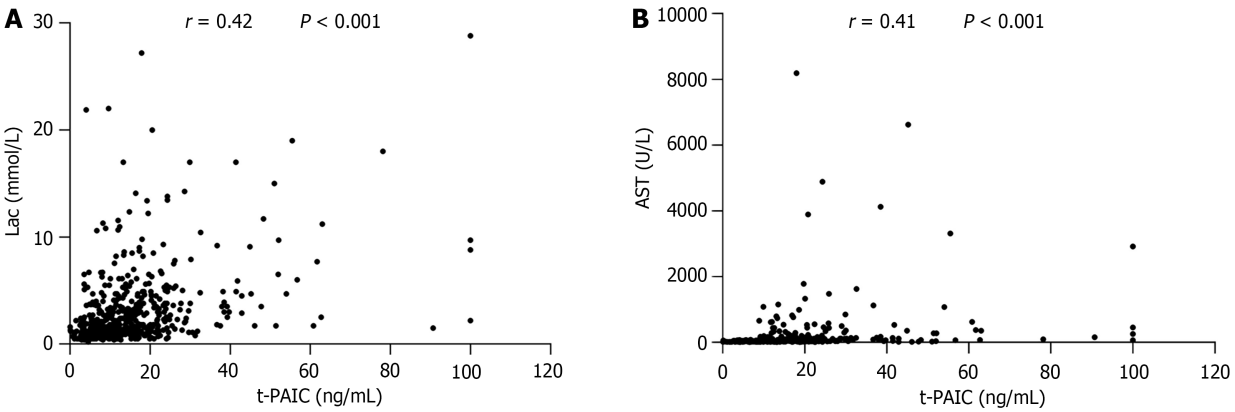

Figure 5 Analysis of correlations of tissue plasminogen activator-inhibitor complex with lactate and aspartate aminotransferase. A: Lactate; B: Aspartate aminotransferase. AST: Aspartate aminotransferase; Lac: Lactate; t-PAIC: Tissue plasminogen activator-inhibitor complex.

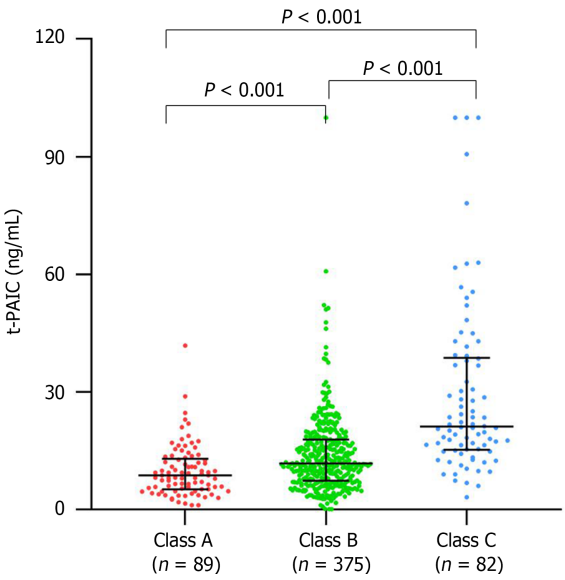

Figure 6 Analysis of tissue plasminogen activator-inhibitor complex levels in patients with different Child-Pugh classifications. t-PAIC: Tissue plasminogen activator-inhibitor complex.

(Class C, n = 82), was conducted to assess t-PAIC levels across varying degrees of liver impairment. Patients in Class C patients had higher t-PAIC levels than Class B patients, who also presented with higher t-PAIC levels than Class A patients, with significant differences (P < 0.001) (Figure 6).

DISCUSSION

This study reported the value of t-PAIC for SILI, proposing that t-PAIC (area under the receiver operating characteristic curve = 0.862) may be an effective diagnostic biomarker. Our results showed that patients with SILI with t-PAIC ≥ 11.9 had more severe disease and a higher mortality rate within 90 days. Previous studies have reported the construction of a predictive model for liver injury, including procalcitonin, AST-platelet ratio index, blood urea nitrogen and lactate, but the predictive ability is insufficient[22]. Woźnica-Niesobska *et al*[23] found that plasminogen activator inhibitor (PAI)-1, a predictor of sepsis-associated liver dysfunction, may be a prognostic biomarker, but its specificity is low, and the test is not currently available in clinical practice in China.

The liver is not only the primary site for the synthesis of coagulation factors, but also participates in the host immune response and tissue repair. Previous studies have shown that inflammatory reactions can consume coagulation factors, causing coagulation disorders, while coagulation disorders can also promote the development of inflammatory reactions. Therefore, when SILI occurs, a decrease in coagulation substances and endothelial cell damage induced by inflammatory reactions activate platelets and coagulation, promote the formation of microthrombi, and aggravate coagulation failure [10,24]. Strnad *et al*[9] showed that during sepsis, the liver acts as the second line of defense against pathogenic microorganisms, triggering the acute phase response, producing and releasing acute phase proteins, such as CRP, to promote the clearance of pathogenic microorganisms[25,26]. Our results showed that compared with the sepsis group, the levels of lactate and CRP in the SILI group were significantly increased, indicating that infection severity of SILI group patients was aggravated.

In response to infection or inflammatory stimuli, platelets can promote immune responses by forming aggregates with WBCs and interacting with dendritic cells, thereby forming immune thrombi, which inhibit the spread of pathogenic microorganisms. However, excessive formation of immune thrombi can promote organ dysfunction[27,28]. The production of platelets is mainly regulated by thrombopoietin, which is primarily produced by the liver. In instances of liver damage, there is a reduction in thrombopoietin secretion, consequently leading to a decrease in platelet production. The results of this study showed that compared with the sepsis group, the PT and APTT in the SILI group were prolonged, the levels of FDP, D-dimer, and t-PAIC were significantly increased, and the platelet count was significantly decreased, indicating that SILI patients had already developed severe coagulation system imbalance.

t-PAIC is a complex formed by the 1:1 combination of tissue-type plasminogen activator (t-PA) and PAI-1. t-PA is mainly produced by endothelial cells, converting plasminogen in the blood into plasmin to promote fibrinolysis. In contrast, PAI-1 can inhibit t-PA and play an inhibitory role in fibrinolysis. Therefore, t-PAIC can be used as an evaluation index for the balance of the fibrinolytic system[29,30]. In the presence of SILI, endotoxin causes vascular endothelial damage, continuously stimulating endothelial cells to synthesize and release t-PA, PAI-1 and tissue factor into the blood. However, the ability of the liver to degrade t-PA and urokinase-type PA is reduced, resulting in a significant increase in t-PAIC levels, which also suggests the aggravation of coagulation and fibrinolysis disorders[31,32]. Oxidative stress plays a role in exacerbating sepsis by intensifying inflammatory pathways, which in turn worsens liver damage. When

hepatocytes are severely damaged, AST is released from the subcellular structure of the mitochondria into the blood, resulting in an increase in AST levels. However, AST is not only found in the liver, but is also widely distributed in many organs and tissues such as the heart, skeletal muscle and brain[33,34]. Our study found that serum t-PAIC levels correlated moderately with lactate and AST levels. The subgroup analysis revealed that there was a positive association between the Child-Pugh classification and t-PAIC levels: As the classification increases, there is a corresponding increase in t-PAIC levels.

The present study had some limitations. Firstly, the constraints of available clinical data resulted in an absence of continuous monitoring for clinical indicators, which precluded a dynamic analysis of patient condition fluctuations. Secondly, the study was unable to fully capture the typical clinical signs, complete liver function test indicators, and the dynamics of radiographic parameters, indicating that the data gathered may not provide a complete picture of the patients' conditions. Lastly, as a single-center retrospective study, our findings have yet to be corroborated by multicenter research; a gap we aim to address in our upcoming research agenda.

CONCLUSION

Our study provides the first evidence that t-PAIC levels may be an independent risk factor for SILI and its elevation correlated with the severity of SILI.

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FOOTNOTES

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