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RESEARCH ARTICLE

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Prognostic indicators and outcome in patients with acute liver failure, sepsis and with and without shock: a retrospective cohort study

Dan Wang*, Xin Wang*, Jinsong Mu*, Zhidan Kuang, Junchang Zhang, Xianghong Lu, Xuemei Wang and Fang Lin

Department of Critical Care Medicine, The Fifth Medical Center of PLA General Hospital, Beijing, China

ABSTRACT

Background: Sepsis or septic shock is associated with severe morbidity and mortality in patients with acute liver failure (ALF). This study aimed to explore the potential prognostic value of common clinical indicators in patients with ALF, sepsis and with and without shock.

Patients and methods: The clinical, laboratory, and microbiological data of patients with ALF and sepsis or septic shock who were admitted to the intensive care unit from January 2014 to December 2019 were collected retrospectively. Clinical indicators, outcomes and the associations among them were analyzed and defined.

Results: Of 150 patients, 64 (42.7%) and 86 (57.3%) were divided into the shock and non-shock groups, respectively. Plasma procalcitonin (PCT), C-reactive protein (CRP), and creatinine (Cre) levels, aspartate aminotransferase to alanine aminotransferase (AST/ALT) ratio, and prothrombin time (PT) in the shock group and plasma PCT and Cre levels in the non-shock group were positively correlated with 30-day, 60-day, and 90-day mortality. Furthermore, plasma ALT levels were positively correlated with 60-day and 90-day mortality, and PTA showed negative correlations with 30-day, 60-day, and 90-day mortality in both groups. Multivariate logistic regression analysis revealed that the combination of plasma PCT and CRP levels, the combination of plasma PCT and ALT levels, and the combination of plasma ALT levels and PTA were found to be associated with 90-day mortality.

Conclusions: Clinical indicators, especially plasma PCT, CRP, and ALT levels, PTA, and their combinations were associated with poor outcomes in patients with ALF, sepsis and with and without shock.

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Introduction

Acute liver failure (ALF) seriously threatens human health, with a historical mortality rate of approximately 80% [1]. Patients with ALF are often associated with various bacterial and fungal infections, posing a significant challenge for their clinical management. Infection is the main cause of death in ALF, and it is also the cause of late death in at least one-quarter of ALF cases [2]. In ALF, systemic inflammation and susceptibility to sepsis are common, resulting in tissue damage and organ failure. The initial massive pro-inflammatory response leads to the subsequent systemic inflammatory response syndrome, leading to immune cell dysfunction and sepsis through compensatory anti-inflammatory responses [3]. Septic shock is also particularly common in patients with ALF and may exacerbate the initial hypovolemic shock associated with prehospital oral administration, vomiting, and encephalopathy [4].

In recent years, several studies have been conducted to evaluate clinical parameters, such as biochemical and inflammatory parameters, and study the relationship of these parameters with mortality in patients with severe sepsis and septic shock [5,6]. Clinical indicators have been consistently highlighted as potential effective biomarkers for the early diagnosis and prognosis of sepsis in patients with acute-on-chronic liver failure (ACLF) [7]. However, very little information is available on the significance of clinical indicators in predicting the prognosis of sepsis or septic shock in patients with ALF. A previous study conducted by Mallet et al. involving a sample size of 35 patients with ALF demonstrated that, among those who did not undergo liver transplantation, infectious

CONTACT Fang Lin 13811029709@163.com Department of Critical Care Medicine, The Fifth Medical Center of Chinese PLA General Hospital, No. 100, West Fourth Ring Middle Road, Fengtai District, Beijing 100039, China
*These authors contributed equally to this work and share first authorship.
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parameters did not correlate with poorer survival outcomes. Instead, the only clinical indicator associated with worse survival was elevated bilirubin levels [8]. Currently, this remains the sole research examining clinical indicators for prognosis in patients with ALF complicated by sepsis; however, the sample size is deemed insufficient. Therefore, our study aimed to determine the prognostic value of clinical indicators in patients with ALF, sepsis, and with and without shock.

Methods

Patients and study design

This retrospective study included a total of 188 patients with ALF, sepsis, and with and without shock who were admitted to the intensive care unit (ICU) from January 2014 to December 2019; patients who were admitted to the ICU for the first time were included, where those with second ICU admission were not included in the analysis. Patients were excluded based on the following exclusion criteria: (1) age <18 years, (2) ICU stay <24 h, (3) incomplete or poorly reliable clinical data, (4) excessive use of corticosteroids, (5) antibiotic abuse, and (6) immunosuppression.

Definitions

Definitions of ALF, sepsis, and septic shock followed international definitions. ALF was diagnosed based on the 2019 diagnostic criteria developed by the US Acute Liver Failure Study Group (ALFSG) registry [9], which was defined as the synthetic hepatic dysfunction (international normalized ratio [INR] ≥ 1.5 and hepatic encephalopathy) occurring within 26 weeks of treatment initiation in patients without a history of liver disease. Preexisting underlying liver disease was excluded; however, acute manifestations of Wilson's disease, autoimmune hepatitis, Budd-Chiari syndrome, or hepatitis B virus were included.

According to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [10], sepsis was defined as an infection accompanied by organ dysfunction. The quick Sequential Organ Failure Assessment (qSOFA) score (range: 0-3) was used to identify patients at sepsis risk. Systolic blood pressure ≤100 mmHg, respiratory rate ≥ 22 breaths per minute, and any acute changes in the mental state were scored 1 point each. Changes in mental status were assessed using the Glasgow Coma Scale (GCS), with a score of 1 on a GCS of < 13. Generally, a qSOFA score ≥ 2 indicates that patients with sepsis require immediate ICU admission for monitoring and treatment. The diagnostic criteria for septic shock were: (1) sepsis, (2) hypotension requiring vasopressor therapy to maintain mean arterial pressure (MAP) > 65 mmHg, and (3) serum lactate > 2 mmol/L after adequate fluid resuscitation.

Classification

Patients with ALF, sepsis, and with and without shock were divided into the shock (patients who met the diagnostic criteria for septic shock) and non-shock (remaining patients who did not develop septic shock) groups.

Data collection

Patient characteristics (age, sex, etiology, key baseline conditions, treatment modalities, and the Model for End-stage Liver Disease (MELD) score) and clinical indicator data (inflammatory, biochemical, and coagulation parameters) were collected retrospectively. Blood samples were collected within 24 h of ICU admission. The MELD score, derived from serum creatinine (Cre), bilirubin, and INR, has been evaluated as a general predictive tool for perioperative risks, postoperative complications, duration of hospitalization, and mortality [11]. Therefore, alongside assessing inflammatory paremeters, our research concentrated on significant biochemical parameters and indicators of coagulation function. White blood cell (WBC) counts, plasma procalcitonin (PCT) and C-reactive protein (CRP) levels, and platelet (PLT) counts were used as inflammatory parameters, whereas biochemical parameters included plasma levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), direct bilirubin (DBil), total bilirubin (TBil), and Cre, AST to ALT (AST/ALT) ratio, DBil to TBil (DBil/TBil) ratio, and levels of blood urea nitrogen (BUN) and blood ammonia (BLA). Prothrombin time (PT), prothrombin activity (PTA), and INR were the main coagulation parameters. WBC and PLT counts were evaluated through the utilization of a Sysmex XT-2000i automatic five-category analyzer, which is specifically designed for blood cell analysis. Additionally, PCT, CRP, and various biochemical parameters were examined using a SEBIA automatic enzyme-linked immunoassay detector. For the assessment of coagulation function parameters, a fully automatic coagulation tester was employed. Once admitted to the ICU, routine testing of all clinical indicators was conducted daily by the laboratory department. The primary outcome was 30-day, 60-day, and 90-day mortality, which was defined as all deaths occurring

within 30, 60, and 90 days of ICU admission, respectively.

Statistical analysis

GraphPad Prism 8.0.2 software was used for data analysis. Categorical and continuous variables are presented as counts (percentages) and medians (25-75 percentiles), respectively. All nonparametric data were log-transformed. Chi-square tests were used to analyze differences in categorical variables between the two groups. Continuous variables were analyzed using a two-tailed Mann-Whitney test. Survival curves were constructed to determine 30-day mortality and compared using the log-rank test (Mantel-Cox). Furthermore, the associations among clinical indicators and 30-day, 60-day and 90-day mortality were analyzed using Spearman's rank correlation analysis. To investigate the predictive value of combined indicators in determining the 90-day mortality of patients with ALF, sepsis, and with and without shock, a multivariate logistic regression analysis was performed using the results obtained from Spearman's rank correlation analysis. In this study, the multiple imputation by Chained Equations procedure [12] was implemented to address missing data. This method allows for the imputation of missing values by using observed data to estimate plausible values for the missing data points. Statistical significance was defined as a p-value of < 0.05.

Results

A total of 188 patients with ALF, sepsis, and with and without shock were admitted to the ICU during the study period. Of these, two were <18 years old, 11 received ICU treatment for <24 h, four had incomplete or unreliable clinical data, six had corticosteroid overuse, 10 had antibiotic abuse, and five were identified with immunosuppression. After these exclusions, the final cohort ($n = 150$ patients) was divided into shock (patients with septic shock; 64 [42.7%]) and non-shock (patients without septic shock; 86 [53.3%]) groups (Figure 1).

Patient characteristics

Table 1 summarizes the patients' characteristics. No significant differences were observed in age, sex, etiology, and MELD score > 25 and > 40 between the two groups (all $p \geq 0.05$). The proportion of patients with bleeding was higher in the shock group than that in the non-shock group ($p = 0.009$), whereas no significant difference was observed in the proportion of patients with hepatic coma between the two groups. The number of patients requiring mechanical ventilator or central venous catheter was higher in the shock group than that in the non-shock group ($p < 0.001$ and $p = 0.024$, respectively); however, no significant difference was observed between the two groups in terms of the number of patients receiving corticosteroids or ≥ 3 antibiotics.

Clinical indicators

Plasma PCT and CRP levels were higher in the shock group than those in the non-shock group ($p = 0.007$ and $p = 0.033$, respectively). However, no significant differences were observed in WBC and PLT counts between the two groups (Figure 2A). In terms of biochemical parameters, plasma Cre levels and AST/ALT ratio were higher in the shock group than those in the non-shock group ($p = 0.048$ and $p = 0.002$, respectively), with no significant differences in other biochemical parameters between the two groups (Figure 2B). The coagulation parameters, such as PT, PTA, and INR were higher in the shock group than those in the non-shock group (Figure 2C) ($p = 0.035$, $p = 0.014$, and $p = 0.034$, respectively).

Outcomes

The 30-day and 60-day mortality was significantly higher in the shock group than that in the non-shock group (30-day: 78.5% vs. 38.4%, respectively, $p < 0.001$; 60-day: 89.1% vs. 47.7% respectively, $p < 0.001$; 90-day: 93.7% vs. 54.6% respectively, $p < 0.001$) (Table 1). The 30-day survival curves demonstrated death peaks on days 3 to 7 and on day 30 in the shock group, whereas the frequency of death was evenly distributed over the 30 days in the non-shock group (Figure 3A). The log-rank test revealed a significant difference in the 30-day survival between the two groups ($p < 0.001$). Furthermore, both groups had fewer subsequent deaths as per the 60-day and 90-day survival curves, with a flattening of the curves observed (Figure 3B,C).

Correlations between clinical indicators and outcomes

Table 2 shows the correlations between clinical indicators (including inflammatory, biochemical, and coagulation parameters) and 30-day mortality. The plasma levels of PCT (odds ratio [OR] = 0.322, $p = 0.009$), CRP (OR = 0.312, $p = 0.011$), and Cre (OR = 0.393, $p = 0.001$), AST/ALT ratio (OR = 0.258, $p = 0.039$), and PT (OR = 0.260, $p = 0.038$) were positively correlated with the 30-day mortality in the shock group; however, PTA (OR = −0.338,

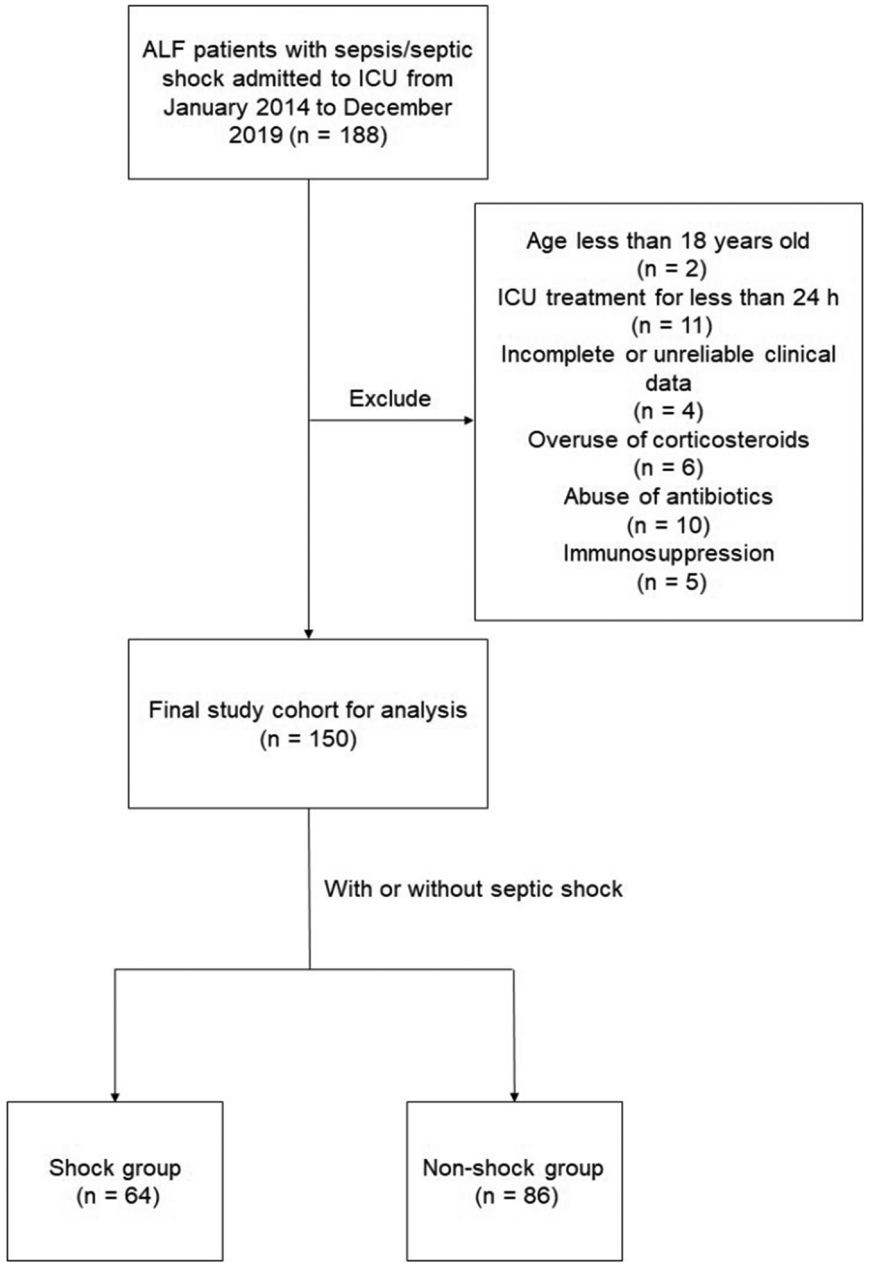

Figure 1. Study flow chart.

$p=0.006$) was negatively correlated. In contrast, in the non-shock group, only the plasma levels of PCT (OR = 0.219, $p=0.042$) and Cre (OR = 0.214, $p=0.047$) were significantly correlated with the 30-day mortality, and the correlation between PTA and the 30-day mortality (OR=−0.237, $p=0.028$) was also negative.

Table 3 shows the correlations between clinical indicators (including inflammatory, biochemical, and coagulation parameters) and 60-day mortality. In the shock group, the plasma levels of PCT (OR = 0.355, $p=0.004$), CRP (OR = 0.276, $p=0.027$), ALT (OR = 0.266, $p=0.035$), and Cre (OR = 0.358, $p=0.004$), and AST/ALT ratio (OR = 0.273, $p=0.029$) demonstrated positive correlations with the 60-day mortality, whereas PTA (OR=−0.322, $p=0.009$) was negatively correlated. The non-shock group also had positive correlations of plasma PCT (OR = 0.238, $p=0.027$), ALT (OR = 0.255, $p=0.018$), and Cre (OR = 0.330, $p=0.002$) levels and negative correlation of PTA (OR=−0247, $p=0.022$) with the 60-day mortality.

Table 4 shows the correlations between clinical indicators (including inflammatory, biochemical, and coagulation parameters) and 90-day mortality. In the shock group, there were positive correlations observed between plasma levels of PCT (OR = 0.336, $p=0.007$), CRP (OR = 0.264, $p=0.035$), ALT (OR = 0.252, $p=0.045$), and Cre (OR = 0.256, $p=0.041$), as well as the AST/ALT ratio (OR = 0.254,

Table 1. Patient characteristics.

Characteristics	Shock group ($n=64$)	Non-shock group ($n=86$)	p-value
Age, median (IQR)	47 (31-62)	43 (29-57)	0.186
Male gender, n (%)	28 (43.7)	40 (46.5)	0.743
Etiology, n (%)			
Hepatitis virus	13 (20.3)	25 (29.1)	0.257
Drugs	42 (65.6)	46 (53.5)	0.179
Others	9 (14.1)	15 (17.4)	0.656
Key baseline conditions, n (%)			
Hepatic coma	44 (68.7)	51 (59.3)	0.304
Bleeding	21 (32.8)	12 (13.9)	0.009
Treatment modalities, n (%)			
Mechanical ventilator	35 (54.6)	21 (24.4)	< 0.001
Central venous catheter	62 (96.9)	73 (84.9)	0.024
Corticosteroids	24 (37.5)	28 (32.6)	0.603
Antimicrobial agents (≥ 3 types)	22 (34.4)	26 (30.2)	0.600
MELD score ≥ 25, n (%)	52 (81.3)	65 (75.6)	0.433
MELD score ≥ 40, n (%)	18 (28.1)	24 (27.9)	> 0.999
30-day mortality, n (%)	51 (78.5)	33 (38.4)	< 0.001
60-day mortality, n (%)	57 (89.1)	41 (47.7)	< 0.001
90-day mortality, n (%)	60 (93.7)	47 (54.6)	< 0.001

n: number; IQR: interquartile range (25–75 percentile); qSOFA: quick Sequential Organ Failure Assessment; MELD: model for end-stage liver disease. Data are presented as mean (standard deviation) or No. (%). p-value < 0.05 means statistically significant.

$p=0.043$) and PT (OR = 0.261, $p=0.037$), with the 90-day mortality. On the other hand, in the non-shock group, plasma levels of PCT (OR = 0.277, $p=0.009$), ALT (OR = 0.250, $p=0.020$), and Cre (OR = 0.346, $p=0.001$) showed positive correlations with the 90-day mortality. Additionally, both groups exhibited a negative correlation between PTA and the 90-day mortality ([OR=−0.278, $p=0.026$] and [OR=−0.288, $p=0.007$], respectively).

Multivariate logistic regression analysis of combined indicators for outcomes

Based on the results of Spearman's rank correlation analysis, plasma levels of PCT, CRP, ALT, and Cre, AST/ALT ratio, PT and PTA were found to be significantly correlated with outcomes. To assess their combined predictive values for outcomes in patients with ALF, sepsis, and with and without shock, a multivariate logistic regression analysis was performed. The results indicated that the combination of plasma PCT and CRP levels (OR = 0.950, $p=0.025$), the combination of plasma PCT and ALT levels (OR = 1.000, $p=0.008$), and the combination of plasma ALT levels and PTA (OR = 0.952, $p=0.042$) were found to be associated with 90-day mortality (Table 5).

Discussion

In general, ALF results in cardiovascular instability, renal failure, cerebral edema, and death, which may be associated with marked systemic inflammation and severe hemodynamic disturbances, such as increased cardiac output, peripheral vasodilation, decreased systemic vascular resistance, and secondary shock [4]. Sepsis or septic shock remains the leading cause of death in the ICU; this is particularly because patients admitted to the ICU often have underlying non-communicable diseases, such as diabetes and cancer, and disease- or treatment-related immunosuppression [13]. Previously, it was reported that liver failure with sepsis or septic shock is closely related to mortality [3]. The present study examined patients with ALF and sepsis or septic shock who were admitted to the ICU over the past six years and compared the differences in clinical indicators and outcomes of patients with and without septic shock. Furthermore, we evaluated the prognostic value of clinical indicators in ALF complicated with sepsis or septic shock by analyzing the correlations between clinical indicators and 30-day, 60-day, and 90-day mortality in ICU.

The ALF etiology varies widely due to socioeconomic factors, exposures, and genetic predisposition. Acetaminophen poisoning, other drug-related injuries, and viral hepatitis have been confirmed to account for the majority of ALF cases [14]. Consistently, the present study also demonstrated that drugs and hepatitis viruses are the main causes of ALF in ICU patients. Hepatic encephalopathy is a complication of liver failure characterized by neuropsychiatric disturbances ranging from disorientation to coma [15]. In the present study, we did not observe a significant difference in the proportion of hepatic coma between the shock and non-shock groups. Furthermore, the risk of bleeding is the most common concern in patients with ALF; bleeding may occur spontaneously, originate in capillaries, and be associated with gastrointestinal mucosal injury [16]. Siddiqui et al. found that the incidence of gastrointestinal bleeding in patients with septic shock was 5.4% [17], which was higher than that reported in critically ill patients in other previous studies. The present study also demonstrated an increased risk of bleeding in patients with ALF and septic shock. More than 70% of patients with septic shock receive intubation and invasive mechanical ventilation due to respiratory failure [18]. The current study showed that more than 50% of patients with ALF and septic shock received mechanical ventilation during ICU admission; this percentage was much more than that of patients without shock. Central venous catheters, which are usually placed after admission, are of critical importance in the ICU settings, where the treatment needs of patients

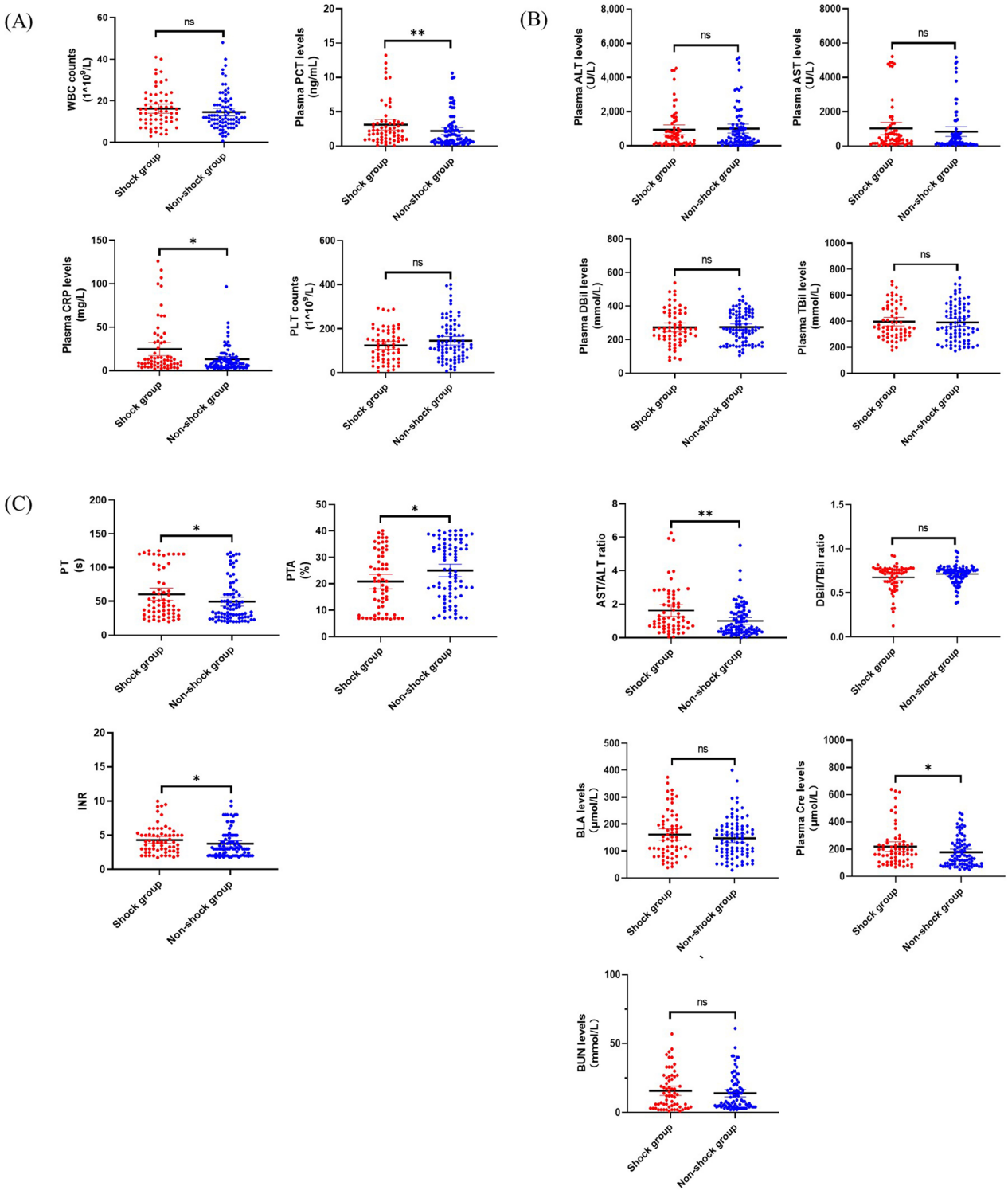

Figure 2. Comparison of clinical indicators between the shock and non-shock groups. Inflammatory parameters (A) include white blood cell (WBC) and platelet (PLT) counts and plasma procalcitonin (PCT) and C-reactive protein (CRP) levels; biochemical parameters (B) include plasma alanine aminotransferase (ALT), aspartate aminotransferase (AST), direct bilirubin (DBil), total bilirubin (TBil), and creatinine (Cre), levels and levels of blood ammonia (BLA), and blood urea nitrogen (BUN), AST/ALT ratio, and DBil/TBil ratio; coagulation parameters (C) include prothrombin time (PT), prothrombin activity (PTA), and international normalized ratio (INR). *, ** represent p <0.05 and p <0.01, respectively.

with shock are complex [19]. In the present study, the rates of central venous catheterization were also significantly higher in the shock group than those in the non-shock group. It has been well-established that the proper use of antibiotics and corticosteroids is crucial in the successful

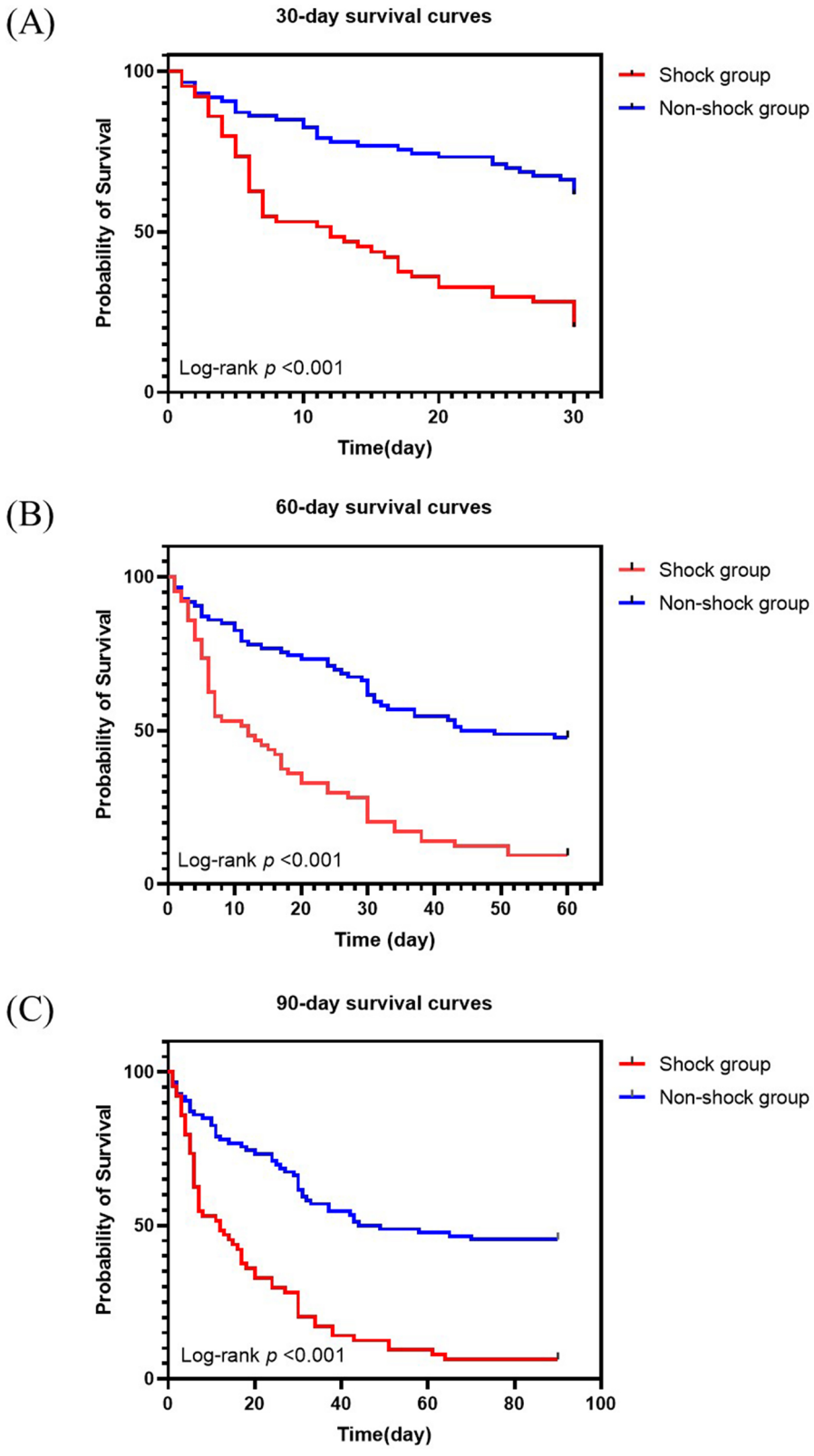

Figure 3. 30-day, 60-day and 90-day survival curves for patients in the shock and non-shock groups. Black and red lines represent 30-day (a), 60-day (B), and 90-day (C) survival curves for the shock and non-shock groups, respectively.

management of patients with sepsis or septic shock [20]. However, in the current study, no significant differences were observed between the two groups in terms of antibiotic or corticosteroid use. We also did not observe significant differences between the two groups in terms of the MELD score, which was

Table 2. Correlation of clinical indicators with 30-day mortality.

	Shock group ($n = 64$)		Non-shock group ($n = 86$)	
Parameters	OR (95% CI)	p-value	OR (95% CI)	p-value
WBC	0.106 (-0.151 to 0.350)	0.403	0.079 (-0.105 to 0.293)	0.465
PCT	0.322 (0.076 to 0.532)	0.009	0.219 (-0.001 to 0.417)	0.042
CRP	0.312 (0.065 to 0.524)	0.011	0.146 (-0.074 to 0.353)	0.179
PLT	−0.144 (-0.383 to 0.112)	0.245	−0.076 (-0.289 to 0.144)	0.484
ALT	0.119 (-0.140 to 0.363)	0.352	0.105 (-0.116 to 0.316)	0.336
AST	0.089 (-0.169 to 0.332)	0.482	0.080 (-0.140 to 0.293)	0.463
AST/ALT ratio	0.258 (0.006 to 0.480)	0.039	0.115 (-0.107 to 0.326)	0.296
DBil	0.066 (-0.189 to 0.314)	0.601	0.057 (-0.163 to 0.272)	0.601
TBil	0.093 (-0.163 to 0.338)	0.463	0.064 (-0.156 to 0.278)	0.557
DBil/TBil ratio	0.080 (-0.176 to 0.327)	0.527	0.068 (-0.152 to 0.282)	0.531
BLA	0.189 (-0.067 to 0.421)	0.134	0.079 (-0.142 to 0.292)	0.471
Cre	0.393 (0.155 to 0.587)	0.001	0.214 (-0.004 to 0.413)	0.047
BUN	0.157 (-0.099 to 0.395)	0.158	0.140 (-0.080 to 0.347)	0.198
PT	0.260 (0.008 to 0.481)	0.038	0.095 (-0.126 to 0.306)	0.385
PTA	−0.338 [-0.544 to (-0.093)]	0.006	−0.237 [-0.433 to (-0.020)]	0.028
INR	0.224 (-0.030 to 0.451)	0.075	0.142 (-0.078 to 0.349)	0.191

n: number; CI: confidence interval; OR: odds ratio; WBC: white blood cell; PCT: procalcitonin; CRP: C-reactive protein; PLT: platelet; ALT: alanine aminotransferase; AST: aspartate aminotransferase; DBil: direct bilirubin; TBil: total bilirubin; BLA: blood ammonia; Cre: creatinine; BUN: blood urea nitrogen; PT: prothrombin time; PTA: prothrombin activity; INR: international normalized ratio. p-value < 0.05 means statistically significant.

proposed to be a prognostic tool for ALF [21]. Liver failure with sepsis or septic shock has been shown to impose a significant impact on mortality [13]. In the present study, patients in the shock group had a higher 30-day, 60-day, and 90-day mortality than that in the non-shock group, with a sharp drop in survival during the first week of ICU admission. Altogether, the results of this study revealed that sepsis or septic shock poses a serious threat to the survival of patients with ALF admitted to the ICU.

The main objective of this study is to investigate prognostic indicators for outcomes in patients with ALF, sepsis and with and without shock. Sepsis can be categorized into two distinct phases. The initial phase, known as the hyper-inflammatory phase, is marked by systemic inflammatory response syndrome (SIRS). This phase often presents with compensatory anti-inflammatory responses and immunosuppression, leading to multiple organ dysfunction [22]. The clinical indicators selected for our study were chosen based on the underlying pathophysiological process and focused on the clinical characteristics of ALF. These indicators included inflammatory parameters, liver and kidney function parameters, and coagulation parameters.

The inflammatory storm caused by liver failure and sepsis is one of the current research hotspots [23]. PCT, the prohormone of calcitonin, and CRP, an acute-phase response protein, are important biomarkers for predicting the prognosis of ICU patients with sepsis and septic shock. CRP is primarily synthesized by the liver, while PCT can originate from various tissues such as thyroid cells, adipose tissue, and white blood cells. Although there are reports of hepatic synthesis, it is not considered the main or sole source of PCT [8]. Elevated PCT levels have been shown to differentiate sepsis from septic shock [24]. On the other hand, research has indicated that during ALF, the acute phase protein PCT is elevated in the liver and is produced by liver macrophages [25]. This emphasizes the significance of inflammatory indicators in ALF when accompanied by sepsis. In the present study, plasma PCT and CRP levels were significantly higher in the shock group than those in the non-shock group. Furthermore, we found that plasma PCT and CRP levels were positively correlated with 30-day, 60-day, and 90-day mortality in the shock group, whereas only plasma PCT levels showed positive correlations with outcomes in the non-shock group. This could be

Table 3. Correlation of clinical indicators with 60-day mortality.

	Shock group ($n=64$)		Non-shock group ($n=86$)	
Parameters	OR (95% CI)	p-value	OR (95% CI)	p-value
WBC counts	0.118 (-0.139 to 0.360)	0.352	0.105 (-0.115 to 0.316)	0.335
Plasma PCT levels	0.355 (0.112 to 0.557)	0.004	0.238 (-0.022 to 0.434)	0.027
Plasma CRP levels	0.276 (0.025 to 0.494)	0.027	0.133 (-0.087 to 0.341)	0.221
PLT counts	−0.068 (-0.315 to 0.188)	0.595	−0.123 (-0.332 to 0.098)	0.261
Plasma ALT levels	0.266 (0.012 to 0.488)	0.035	0.255 (0.040 to 0.448)	0.018
Plasma AST levels	0.187 (-0.068 to 0.420)	0.139	0.120 (-0.101 to 0.329)	0.272
AST/ALT ratio	0.273 (0.021 to 0.491)	0.029	0.067 (-0.153 to 0.281)	0.538
Plasma DBil levels	0.129 (-0.128 to 0.370)	0.309	0.034 (-0.185 to 0.250)	0.753
Plasma TBil levels	0.076 (-0.181 to 0.322)	0.552	0.039 (-0.180 to 0.255)	0.719
DBil/ TBil ratio	0.145 (-0.112 to 0.384)	0.253	0.112 (-0.109 to 0.322)	0.305
BLA levels	0.170 (-0.086 to 0.405)	0.178	0.112 (-0.108 to 0.322)	0.303
Plasma Cre levels	0.358 (0.115 to 0.559)	0.004	0.330 (0.121 to 0.512)	0.002
BUN levels	0.109 (-0.148 to 0.352)	0.391	0.131 (-0.089 to 0.340)	0.228
PT	0.305 (-0.056 to 0.518)	0.014	0.104 (-0.1117 to 0.315)	0.342
PTA	−0.322 [-0.531 to (-0.075)]	0.009	−0.247 [-0.441 to (-0.031)]	0.022
INR	0.214 (-0.041 to 0.443)	0.089	0.133 (-0.087 to 0.341)	0.223

n: number; CI: confidence interval; OR: odds ratio; WBC: white blood cell; PCT: procalcitonin; CRP: C-reactive protein; PLT: platelet; ALT: alanine aminotransferase; AST: aspartate aminotransferase; DBil: direct bilirubin; TBil: total bilirubin; BLA: blood ammonia; Cre: creatinine; BUN: blood urea nitrogen; PT: prothrombin time; PTA: prothrombin activity; INR: international normalized ratio. p-value < 0.05 means statistically significant.

attributed to the fact that an exaggerated systemic inflammatory response is causing further harm to the liver. As the source of PCT is not exclusive to the liver, it can more accurately indicate the severity of inflammation and is closely linked to prognosis [26]. These findings provided further evidence that PCT is a more beneficial biomarker than CRP in assessing clinical symptoms and prognostic changes in patients with sepsis. This result is consistent with those reported by Samsudin et al. [27]. Additionaly, the combination of plasma PCT and CRP levels showed a positive association with 90-day mortality in patients with ALF, sepsis, and with and without shock, indicating using both these markers together can potentially provide a more accurate prediction of long-term outcomes. In our study, other inflammatory indicators, such as WBC and PLT counts, showed no significant difference between the two groups and were not correlated with 30-day mortality. Consistently, a previous study also showed that WBC and PLT counts are not independent factors for the diagnosis of sepsis and severe sepsis [28]. In the present study, data were collected within 24 h of ICU admission; however, patients may not have reached their peak disease severity at the time of ICU admission. These results suggested that a severe inflammatory response may contribute to poor outcomes in patients with ALF, sepsis, and with and without shock. Plasma PCT and CRP levels were identified as representative inflammatory parameters for prognostic evaluation.

Patients with liver failure and septic shock show an increased risk of developing renal insufficiency, and decreased MAP may alter renal perfusion [4]. A retrospective study conducted by Tujios et al. found that up to 70% of patients with ALF had acute kidney injury (AKI) symptoms and 30% required renal replacement therapy, which was associated with increased mortality [29]. In the present study, only plasma Cre levels were significantly different between the two study groups, with the shock group showing high Cre levels. We also found that plasma Cre levels were positively correlated with 30-day and 60-day mortality in both groups. Plasma ALT and AST levels are commonly used clinical biochemical indicators of liver function and can also be used for the early diagnosis of sepsis-related liver injury [30]. The AST/ALT ratio is a reliable tool for diagnosing septic shock and predicting 30-day mortality in

Table 4. Correlation of clinical indicators with 90-day mortality.

Parameters	Shock group ($n=64$)		Non-shock group ($n=86$)	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
WBC counts	0.036 (-0.219 to 0.286)	0.777	0.164 (-0.056 to 0.369)	0.132
Plasma PCT levels	0.336 (0.091 to 0.543)	0.007	0.277 (0.063 to 0.467)	0.009
Plasma CRP levels	0.264 (0.012 to 0.485)	0.035	0.191 (-0.028 to 0.392)	0.079
PLT counts	−0.030 (-0.281 to 0.224)	0.814	−0.116 (-0.326 to 0.105)	0.288
Plasma ALT levels	0.252 (-0.001 to 0.475)	0.044	0.250 (0.034 to 0.444)	0.020
Plasma AST levels	0.050 (-0.205 to 0.299)	0.694	0.092 (-0.129 to 0.304)	0.400
AST/ALT ratio	0.254 (0.001 to 0.476)	0.043	0.099 (-0.121 to 0.311)	0.361
Plasma DBil levels	0.116 (-0.141 to 0.358)	0.361	0.061 (-0.159 to 0.275)	0.577
Plasma TBil levels	0.034 (-0.221 to 0.284)	0.790	0.062 (-0.158 to 0.276)	0.571
DBil/ TBil ratio	0.152 (-0.105 to 0.389)	0.230	0.113 (-0.107 to 0.323)	0.298
BLA levels	0.124 (-0.133 to 0.365)	0.329	0.126 (-0.094 to 0.335)	0.246
Plasma Cre levels	0.256 (0.003 to 0.478)	0.041	0.346 (0.138 to 0.524)	0.001
BUN levels	0.084 (-0.172 to 0.330)	0.508	0.138 (-0.082 to 0.346)	0.205
PT	0.261 (0.008 to 0.482)	0.037	0.082 (-0.139 to 0.294)	0.455
PTA	−0.278 [-0.496 to (-0.027)]	0.026	−0.288 [-0.476 to (-0.075)]	0.007
INR	0.214 (-0.041 to 0.443)	0.089	0.136 (-0.084 to 0.344)	0.212

n: number; CI: confidence interval; OR: odds ratio; WBC: white blood cell; PCT: procalcitonin; CRP: C-reactive protein; PLT: platelet; ALT: alanine aminotransferase; AST: aspartate aminotransferase; DBil: direct bilirubin; TBil: total bilirubin; BLA: blood ammonia; Cre: creatinine; BUN: blood urea nitrogen; PT: prothrombin time; PTA: prothrombin activity; INR: international normalized ratio. *p*-value < 0.05 means statistically significant.

Table 5. Multivariate logistic regression analysis of combined indicators for 90-day mortality.

Parameters	OR (95% CI)	*p*-value
Plasma PCT levels + plasma CRP levels	0.950 (0.904 to 0.991)	0.025
Plasma PCT levels + plasma ALT levels	1.000 (0.999 to 1.001)	0.008
Plasma ALT levels + PTA	0.992 (0.982 to 1.004)	0.042

The study conducted multivariate logistic regression analysis on all included patients and only reported significant results.
CI: confidence interval; OR: odds ratio; PCT: procalcitonin; CRP: C-reactive protein; ALT: alanine aminotransferase; PTA: prothrombin activity. *p*-value < 0.05 means statistically significant.

patients with sepsis and septic shock, but neither AST nor ALT are independent predictors [31]. In this study, we consistently found a positive correlation between AST/ALT ratio and 30-day, 60-day and 90-day mortality. However, we did not observe a significant correlation between plasma ALT levels and 30-day mortality. Interestingly, we did find a positive association between plasma ALT levels and 60-day and 90-day mortality, suggesting a potential link to exacerbated liver injury in sepsis. Our study also found that the combination of plasma PCT and ALT levels was positively associated with 90-day mortality in patients with ALF, sepsis, and with and without shock. This suggests that severe inflammatory response contribute to further damage to liver function, which is a significant factor in long-term mortality. Continuous hemofiltration can significantly reduce TBil, DBil, and BLA levels and improve 28-day mortality in children with bacterial sepsis and hepatic insufficiency, but a study in adults is lacking [32]. A previous study demonstrated that an increase in the levels of BUN above the cut-off value of 41.1 mg/dL in patients with sepsis was significantly associated with the risk of death [33]. In the current study, plasma TBil, DBil, TBil/DBil ratio, and BLA levels did not correlate with 30-day, 60-day, and 90-day mortality. Based on these findings, we hypothesized that AST/ALT ratio and plasma Cre levels in patients with ALF may have greater significance than other biochemical parameters in distinguishing sepsis from septic shock, and could also directly indicate prognosis. Additionally, we identified plasma ALT levels as a representative biochemical parameter for evaluating the prognosis of patients with ALF, sepsis, and with and without shock. The biochemical indicators analyzed in this study are commonly used. However,

due to limitations in sample size, other clinical indicators such as the albumin to globulin ratio were not included in the analysis. Future research should aim to address this issue.

A markedly impaired hemostatic system is one of the typical features of patients with ALF and is associated with a bleeding tendency [34]. INR ≥ 1.5 is also one of the diagnostic criteria for ALF, which is associated with prognosis and progression [9]. Furthermore, disseminated intravascular coagulation (DIC) is one of the manifestations of severe septic shock, which is characterized by elevated PT and INR [35]. In the present study, the shock group had significantly prolonged PT, increased INR, and decreased PTA compared with the non-shock group. Furthermore, PTA was negatively correlated with 30-day, 60-day, and 90-day mortality in both groups, whereas PT was positively correlated with outcomes in the shock group. Hence, coagulation parameters, particularly PTA, were associated with the outcomes of patients with ALF, sepsis, and with and without shock. Additionally, the combination of plasma PCT levels and PTA revealed a positive correlation with 90-day mortality. This suggests that a severe inflammatory response, leading to impaired coagulation function, may contribute to a higher long-term mortality. Whether a patient is suffering from ALF or sepsis, their coagulation function is likely to be diminished. In cases where both conditions are present concurrently, inflammation can exacerbate the already compromised coagulation function. This can lead to more severe consequences for the patient and may require special attention and treatment to manage the complications effectively.

To our knowledge, our study is the first to investigate the clinical significance of common clinical indicators in patients with ALF, sepsis, and with and without shock. The findings reported here provide new insights into the ICU management of this unique patient population. Compared to patients with ACLF and sepsis or septic shock, in addition to inflammatory response and coagulation dysfunction, hepatic and renal dysfunction was closely associated with short-term and long-term mortality in patients with ALF, sepsis, and with and without shock. Paying necessary attention to inflammatory, biochemical, and coagulation parameters, and their combinations may change the prognosis to a certain extent.

This study had a few limitations. First, this study was conducted at a single center and included only ICU patients. As a result, external comparison and validation were lacking, potentially leading to an overestimation of the association between predictors and outcomes. Second, this study mainly focused on a few important clinical indicators; hence, other potentially important indicators were not identified. Third, due to limitations in sample size, it is currently not feasible to conduct separate etiological classification studies on patients with ALF, sepsis, and with and without shock. However, future multicenter studies should be undertaken to address this gap in knowledge.

This study examined the screening of clinical prognostic indicators in patients with ALF, sepsis, and with and without shock, highlighting the significance of inflammatory, biochemical, and coagulation indicators in managing these patients. Utilizing a combination of indicators allows for a more precise assessment of patient prognosis. The study revealed that combining plasma PCT with plasma CRP or ALT levels, and plasma ALT levels with PTA, could predict 90-day mortality. This suggests that clinical practice should consider multiple factors rather than relying solely on a single indicator. The potential explanation for their associations could be that the severe inflammation caused by septic shock resulting from infection exacerbates liver injury in ALF patients [13]. Subsequently, liver failure contributes to coagulation abnormalities [36], resulting in diminished long-term survival rates among patients. This series of clinical changes underscores the necessity for clinicians to closely monitor alterations in inflammatory indicators when managing patients with ALF and sepsis. In addition to enhancing liver and coagulation function, clinicians should promptly modify anti-infection regimens and proactively implement blood purification and other therapeutic interventions to mitigate the inflammatory response. While acknowledging the potential bias of a single-center study, multi-center studies are recommended for their ability to rapidly gather a large number of cases, shorten retrospective analysis time, and mitigate the impact of evolving treatment drugs on study outcomes. Future multicenter studies could incorporate additional clinical indicators and consider the original infection focus and pathogenic bacteria classification of sepsis. Therefore, multi-center studies are crucial for validation, and the findings of this study warrant further verification. Moreover, various studies have validated that pro-inflammatory cytokines, such as interleukin (IL)-6, IL-8, and tumor necrosis factor-α (TNF-α), can serve as predictors for the severity of sepsis in patients within the ICU [37,38]. Owing to the constraints of our current conditions, including research on the aforementioned pro-inflammatory cytokines in our current study is not feasible; this gap will need to be addressed by future investigations.

Conclusion

In conclusion, the outcomes of patients with ALF, sepsis, and with and without shock admitted to the ICU were relatively poor, with high 30-day, 60-day, and 90-day mortality. Severe inflammatory response, hepatic and renal dysfunction, and coagulation dysfunction were identified as the leading causes of death in patients with ALF, sepsis, and with and without shock. Clinical indicators, such as plasma PCT, CRP, ALT, and Cre levels, AST/ALT ratio, PT and PTA, were associated with outcomes of these patients. Hence, these biomarkers may be used as potential prognostic indicators in clinical management. Among them, plasma PCT, CRP, and ALT levels, PTA, and their combinations were associated with long-term mortality.

Ethics approval

The study was approved by the Medical Ethics Committee of The Fifth Medical Center of Chinese PLA General Hospital [ky-2020-8-18]. Since this study was retrospective, informed consent was waived and data sources were anonymized.

Authors contributions

Fang Lin contributed to the study conception and design. Zhidan Kuang, Xianghong Lu, Junchang Zhang and Xuemei Wang performed data collection. Dan Wang and Jinsong Mu performed statistical analysis. Dan Wang, Xin Wang and Jinsong Mu drafted the manuscript. Fang Lin approved and revised the manuscript. All authors have read and approved the final manuscript.

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The authors report there are no competing interests to declare.

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ORCID

Fang Lin http://orcid.org/0000-0003-4549-8757

Data availability statement

All data generated or analyzed during this study are included in this article.

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