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Original Article

Changes in TNF-α, IL-33, and MIP-1α before and after artificial liver support treatment and their prognostic value

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Abstract: Objective: To investigate the effect of ALST (artificial liver support treatment) on inflammatory factors and prognosis in patients with ACLF (acute-on-chronic liver failure). Methods: Data of ACLF patients admitted to the No. 2 People's Hospital of Lanzhou from June 2020 to January 2023 were retrospectively analyzed. Patients were compared before and after ALST in terms of ALT (Alanine Aminotransferase), AST (Aspartate Aminotransferase), TBil (Total Bilirubin), Cr (Creatinine), INR (International Normalized Ratio), MELD (Model for End-Stage Liver Disease) scores, as well as TNF-α (Tumor Necrosis Factor-α), IL-33 (Interleukin-33), and MIP-1α (Macrophage Inflammatory Protein-1 α) levels. The ROC (receiver operating characteristic) curve was used to analyze the efficacy of the above indicators in predicting 90-day mortality in patients. Results: After the treatment, the levels of ALT, AST, TBil, Cr, INR, and MELD score were significantly lower than those before treatment (all P<0.001). Also, the levels of TNF-α, IL-33, and MIP-1α were substantially lower than those before treatment (all P<0.001). TNF-α, IL-33, and MIP-1α were positively correlated with MELD score before and after the treatment (all P<0.01). TNF-α, IL-33, MIP-1α, and MELD score were significantly higher in the death group than in the survival group (all P<0.01). The ROC curves showed that MELD (AUC=0.857), TNF-α (AUC=0.836), IL-33 (AUC=0.749), and MIP-1α (AUC=0.746) had high efficacy in predicting patients' 90-day mortality. Conclusion: ALST can significantly reduce TNF-α, IL-33, and MIP-1α levels in patients with ACLF, and postoperative TNF-α, IL-33, and MIP-1α levels have a high predictive value for patients' prognosis.

Keywords: TNF-α, IL-33, MIP-1α, artificial liver therapies, acute on chronic liver failure

Introduction

Liver failure is a severe impairment of liver function with various causes, including viruses, alcohol, drugs, and autoimmune reactions [1]. Patients may or may not have pre-existing liver disease and often present with symptoms such as malaise, nausea, vomiting, and poor appetite. Serious complications include yellowing of the skin (jaundice), ascites, coagulation disorders, hydroelectrolyte disorders, and hepatic encephalopathy [2]. ACLF (acute-on-chronic liver failure) is a specific type of liver failure [3], characterized by a relatively slower progression of liver injury and failure, typically over a few weeks to a few months [4]. This contrasts with acute liver failure, which exhibits a rapidly progressive course, often revealing severe liver impairment within days.

In treating ACLF, ALST (Artificial Liver Support Treatment) has emerged as a significant advancement [5]. ALST involves removing toxic substances from the body of ACLF patients through an extracorporeal circulatory device, supplementing coagulation factors and albumin. This approach not only replaces the function of the damaged liver but also promotes the recovery of hepatocytes and slows disease progression [6]. The current prognosis for ALST patients is cautiously optimistic, with improved survival rates and disease management. However, the effectiveness of ALST can vary based on the severity of liver failure and an individual's condition. This variability highlights the need for effective prognostic indicators to predict treatment outcome [7].

Recent research underscores the importance of cytokine levels as predictors of patient prog-

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nosis in liver failure [8]. When hepatocytes are injured, the body initiates a cellular immune response, producing pro-inflammatory and anti-inflammatory factors [9]. An accumulation of pro-inflammatory cytokines in the liver can trigger an inflammatory cascade, causing secondary liver injury and ultimately leading to liver failure [10]. Cytokines include the interleukin family, tumor necrosis factor, colony-stimulating factor, interferon, chemokines, and growth factors [11]. Clinical observations have shown that serum cytokine levels in patients with liver failure can reflect the severity of the disease earlier than traditional biochemical markers [12]. Key cytokines such as TNF (Tumor necrosis factor)-α, IL (interleukin)-33, and MIP (Macrophage inflammatory protein)-1α play crucial roles in the immune response and inflammation [13]. TNF-α, primarily produced by macrophages, is essential in liver disease development, especially in regulating inflammation and cell death [14]. IL-33, a member of the IL-1 family, is a critical nuclear factor in inflammation and immune regulation, particularly in allergic reactions and liver fibrosis [15]. MIP-1α, a member of the CC chemokine family, is essential for attracting immune cells to the sites of inflammation [16].

The innovation of this study lies in its in-depth examination of the changes in three key cytokines - TNF-α, IL-33, and MIP-1α - before and after ALST in ACLF patients and their potential role in prognostic evaluation. While the importance of cytokines in the pathogenesis of liver failure has been widely recognized, this study uniquely focuses on analyzing the dynamic changes in these specific inflammatory factors during ACLF. This perspective contributes to a better understanding of the pathophysiology of ACLF and can enhance clinical therapeutic strategies, offering a more promising outlook for patient treatment and prognosis.

Materials and methods

Ethical information

The study was conducted with the approval of the Medical Ethics Committee of the No. 2 People's Hospital of Lanzhou.

Sample size assessment

Based on previous literature, we found that the mortality rate of ACLF patients is about 10-30%, and we used 20% as the sample size assessment criterion, which was calculated by the sample size formula:

$$n = \left(\frac{Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}}{\delta} \right)^2 \times p \times (1 - p)$$

n is the required sample size, $Z_{1-\frac{\alpha}{2}}$ is the Z-value corresponding to the level of significance (α), and for a 5% significance level, this value is usually 1.96. $Z_{1-\beta}$ is the Z-value that corresponds to the statistical efficacy (power); for 80% statistical efficacy, this value is about 0.84. δ is the minimum effect size we wish to detect, and here we used 10%. p is the expected proportion; we used 10% in this case. Z-value, which is about 0.84 for 80% statistical power. δ is the minimum effect size we wish to detect; we use 10% here. p is the expected proportion; we adjusted it to 20% in this case. In the end, we statistically found that 124 samples were needed, and taking into account the 10% of patients who were lost or had incomplete information, a total of 140 patients were required for the study, but the actual situation was based on clinical data collection.

Sample collection

The clinical data of ACLF patients admitted to the No. 2 People's Hospital of Lanzhou from June 2020 to January 2023 for treatment were retrospectively analysed.

Clinical data collection

Clinical data collected from patients included age, gender, BMI, comorbid cirrhosis, history of hypertension, diabetes mellitus, and cardiovascular disease, INR (International Normalized Ratio), and MELD (Model for End-Stage Liver Disease) score. Laboratory data were collected, including ALT (Alanine Aminotransferase), AST (Aspartate Aminotransferase), TBil (Total Bilirubin), Cr (Creatinine), TNF-α (Tumor Necrosis Factor-α, Shanghai Enzyme Biotech, China, Cat ID: ml077385), IL-33 (Interleukin-33, Shanghai Enzyme Biotech, China, Cat ID: ml058087) and MIP-1α (Macrophage Inflammatory Protein-1α, Shanghai Enzyme Biotech, China, Cat ID: ml060004).

Inclusion exclusion criteria

Inclusion criteria: ① Patients meeting the Guidelines for the Diagnosis and Treatment of Liver Failure (2018 edition) [17]; ② Patients

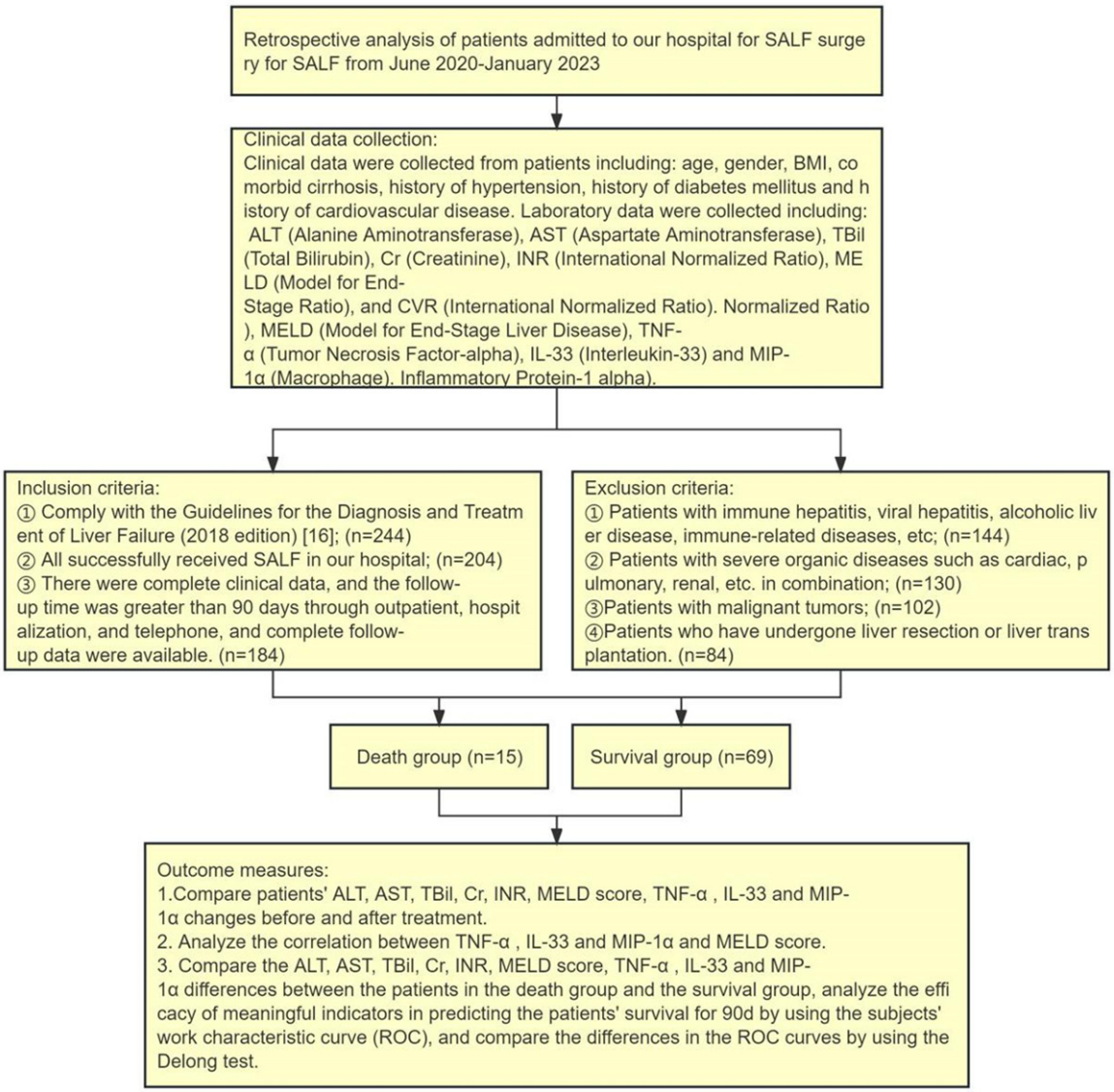

Figure 1. Study procedures.

who successfully received ACLF in the No. 2 People's Hospital of Lanzhou; ③ Patients with complete clinical data; and ④ Patients who were followed up lasted for more than 90 days through outpatient, inpatient, and telephone.

Exclusion criteria: ① Patients with immune hepatitis, viral hepatitis, alcoholic liver disease, immune-related diseases; ② Patients with severe organic disorders such as cardiac, pulmonary, or renal; ③ Those with malignant tumors; ④ Those who have ever undergone hepatic resection or liver transplantation.

Sample screening

In this study, we collected 184 eligible samples according to the inclusion criteria and obtained 86 suitable samples according to the exclusion criteria. According to the 90 d-death, we categorized the patients into a death group (n=15) and a survival group (n=69), and we drew a sample screening flow chart (**Figure 1**).

Outcome measurement

Primary outcome measures: We assessed the biochemical markers, such as liver function indices (ALT, AST, TBil), renal function (Cr), coagulation profile (INR), and the Model for End-Stage Liver Disease (MELD) score before and after the treatment in patients, and performed correlation analysis of key inflammatory markers (TNF-α, IL-33, MIP-1α) and the MELD score to determine their relationship with liver disease severity.

Table 1. Patient baseline data

Index	n=86
Age	
≥50 years	56
<50 years	30
Gender	
Male	52
Women	34
BMI	
≥25 kg/m^2	22
<25 kg/m^2	65
Combined cirrhosis	
Yes	17
No	69
History of hypertension	
Yes	13
No	73
History of diabetes	
Yes	11
No	75
History of cardiovascular disease	
Yes	8
No	78

Note: BMI, body mass index.

Secondary outcome measures: We compared patients in the death group and the survival group regarding the changes in ALT, AST, TBil, Cr, INR, MELD score, TNF-α, IL-33, and MIP-1α, aiming to identify significant biomarkers that could predict 90-day survival in these patients. Receiver operating characteristic (ROC) curve analysis: The effectiveness of these significant indicators in predicting patient survival was further analyzed using ROC curves. The Delong test was employed to compare the differences in ROC curves, providing a statistical measure of the predictive power of these biomarkers.

Statistical analysis

SPSS 26.0 software was used for data analysis. The counted data were expressed as rate (%) and compared using the chi-square test. Statistics were also performed on the measured data, and Kolmogorov-Smirnov was used to examine the data distribution. Data conforming to a normal distribution were expressed as mean ± standard deviation (Mean ± SD), and an independent samples t-test was used. Data that did not meet the normal distribution were described as P50 using quartiles (P25, P75). The correlation between inflammatory factors and MELD scores was analyzed using the Pearson test. In-depth statistical analyses were performed using the R language (4.2.2), and the "rocr" package was used to produce ROC curves. The results were consideredsignificant if the *P*-value was less than 0.05.

Results

Baseline information

Our study encompassed 86 patients, and their clinical data were meticulously compiled and analyzed (**Table 1**).

Changes in liver function indexes before and after treatment

A comparative analysis of ALT, AST, and TBil levels was conducted to assess the efficacy of the treatment. Remarkably, post-treatment levels of ALT, AST, and TBil were significantly reduced compared to pre-treatment levels ($P<0.05$, **Table 2**), indicating a positive response to the treatment regimen and improvement in liver function.

Changes in Cr, INR, and MELD scores before and after the treatment

Changes in Cr, INR, and MELD scores before and after the treatment were compared. It was found that the Cr, INR, and MELD score of the patients were significantly reduced after treatment compared to those before treatment ($P<0.05$, **Table 3**).

Changes in inflammatory factors before and after the treatment

The study further examined the effects of treatment on inflammatory markers, including TNF-α, IL-33, and MIP-1α. Post-treatment levels indicated a significant reduction in these inflammatory markers compared to their pre-treatment levels ($P<0.05$, **Table 4**), suggesting that the treatment effectively mitigated inflammatory responses in patients.

Correlation analysis of inflammatory factors and MELD score before and after treatment

The correlation between inflammatory factors and MELD scores of patients before and after

Table 2. Changes in liver function indexes before and after the treatment

Index	Pre-treatment	Post-treatment	t-value	*P*-value
ALT (U/L)	288.84±36.44	149.97±14.48	32.840	<0.001
AST (U/L)	227.92±41.33	101.68±11.72	27.252	<0.001
TBIL (μmol/L)	364.09±56.34	169.07±26.23	29.101	<0.001

Note: ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; TBil, Total Bilirubin.

Table 3. Changes in liver function before and after the treatment

Index	Pre-treatment	Post-treatment	t-value	*P*-value
Cr (μmol/L)	67.20±5.36	56.96±6.75	11.023	<0.001
INR	2.30±0.35	1.87±0.28	8.798	<0.001
MELD score	78.12±2.05	71.29±2.21	20.977	<0.001

Note: Cr, Creatinine; INR, International Normalized Ratio; MELD, Model for End-Stage Liver Disease.

Table 4. Changes in inflammatory factors before and after the treatment

Index	Pre-treatment	Post-treatment	t-value	*P*-value
TNF-α (pg/mL)	21.32±4.07	18.69±3.53	<0.001	21.32
IL-33 (pg/mL)	26.28±3.47	22.60±2.94	<0.001	26.28
MIP-1α (pg/mL)	19.75±2.96	16.81±3.20	<0.001	19.75

Note: TNF-α, Tumor Necrosis Factor-α; IL-33, Interleukin-33; MIP-1α, Macrophage Inflammatory Protein-1α.

treatment was analyzed. The correlation analysis between inflammatory factors and MELD scores before treatment showed that TNF-α (r=0.389), IL-33 (r=0.313), and MIP-1α (r=0.380) all showed significant positive correlations with MELD scores (P<0.01, **Figure 2**). After treatment, the relationship between the corresponding inflammatory factors and MELD score was maintained as a positive correlation, and the association remained significant (P<0.01, **Figure 2**).

Predictive value of indicators for patient prognosis

We followed the patients' survival for 90 days. The patients were divided into a death group (n=15) and a survival group (n=69) according to their survival. Subsequently, we compared the indexes of the patients in the survival and death groups. The results showed that MELD, TNF-α, IL-33, and MIP-1α were significantly higher in the patients in the death group than those in the patients of the survival group (all P<0.01, **Table 5**). Subsequently, we plotted ROC curves and found that MELD, TNF-α, and IL-33 AUC were all greater than 0.8, while MIP-1α AUC also reached 0.799 (**Figure 3**; **Table 6**). Finally, we found that there was no difference in the AUC between MELD and TNF-α by Delong test comparison, but both were greater than IL-33 and MIP-1α, and the trend was MELD=TNF-α>IL-33=MIP-1α (P<0.05, **Table 7**).

Discussion

Currently, ALF and liver transplantation are considered effective treatments for acute liver failure [18]. However, due to limited availability of liver sources and great number of contraindications to liver transplantation, the ACLF method has become the preferred treatment for most patients. Nevertheless, despite being an acute treatment approach, this therapy may not always yield the anticipated results in certain patients, as it fails to fully accomplish the functions of detoxification, synthesis, secretion, and conversion of biologically active substances, ultimately leading to a poor prognosis [19].

In our study, the management of ACLF exhibited remarkable efficacy, particularly in ameliorating liver function indices. Comparative analyses before and after the treatment revealed significant reductions in crucial liver function markers such as ALT, AST, and TBIL. This finding underscores the effectiveness of ACLF management strategies in mitigating liver injury, highlighting their role in rapidly improving patients' physiological conditions. Notably, the enhancement in these biochemical indices was closely linked to the alleviation of clinical symptoms, further affirming the pivotal role of ACLF management.

Moreover, our research delved into the interplay between cytokines (e.g., TNF-α, IL-33, MIP-1α) and the severity of liver failure. Fluctuations in these cytokines' levels pre- and post-treatment suggest their integral involvement in the

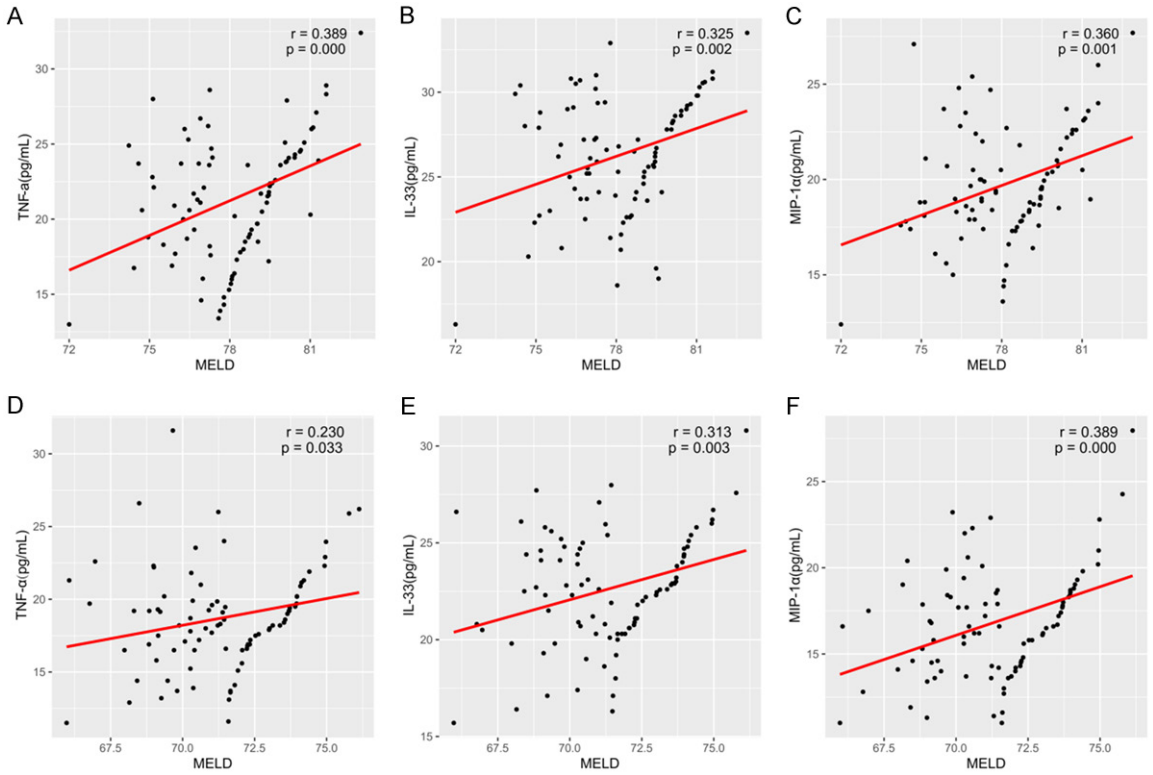

Figure 2. Correlation analysis of TNF-α, IL-33, and MIP-1α with MELD score before and after treatment. A. Correlation analysis of TNF-α and MELD score before treatment; B. Correlation analysis between IL-33 and MELD score before treatment; C. Correlation analysis between pre-treatment MIP-1α and MELD score; D. Correlation analysis between TNF-α and MELD score after treatment; E. Correlation analysis between IL-33 and MELD score after treatment; F. Correlation analysis between MIP-1α and MELD score after treatment. Note: MELD, Model for End-Stage Liver Disease; TNF-α, Tumor Necrosis Factor-α; IL-33, Interleukin-33; MIP-1α, Macrophage Inflammatory Protein-1α.

Table 5. Univariate analysis of various factors for patient's death

Index	Death group (n=15)	Survival group (n=69)	t-value	*P*-value
ALT (U/L)	273.88±38.60	292.00±35.45	-1.675	0.110
AST (U/L)	218.00 [187.55, 234.00]	218.80 [206.70, 254.60]	444.500	0.319
TBIL (μmol/L)	351.95±58.73	366.66±55.91	-0.889	0.385
Cr (μmol/L)	66.39±6.49	67.38±5.13	-0.551	0.588
INR	2.27±0.33	2.31±0.36	-0.370	0.715
MELD	80.12±1.09	77.70±1.96	6.640	<0.001
TNF-α (pg/mL)	24.50 [23.70, 26.00]	20.50 [17.75, 23.65]	890.500	<0.001
IL-33 (pg/mL)	28.71±1.99	25.77±3.51	4.444	<0.001
MIP-1α (pg/mL)	21.00 [20.10, 22.50]	18.80 [17.70, 20.75]	794.500	0.003

Note: ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; TBil, Total Bilirubin; Cr, Creatinine; INR, International Normalized Ratio; MELD, Model for End-Stage Liver Disease; TNF-α, Tumor Necrosis Factor-α; IL-33, Interleukin-33; MIP-1α, Macrophage Inflammatory Protein-1α.

progression of liver failure. Particularly, the positive correlation between these factors and MELD score indicates their critical function in the pathophysiologic processes of liver failure. This insight is vital for unraveling the mechanisms underlying ACLF, with the possibility to offer clinicians novel biomarkers for more precise assessment of disease severity and therapeutic response. Corroborating our observations, a study [20] demonstrated that ACLF

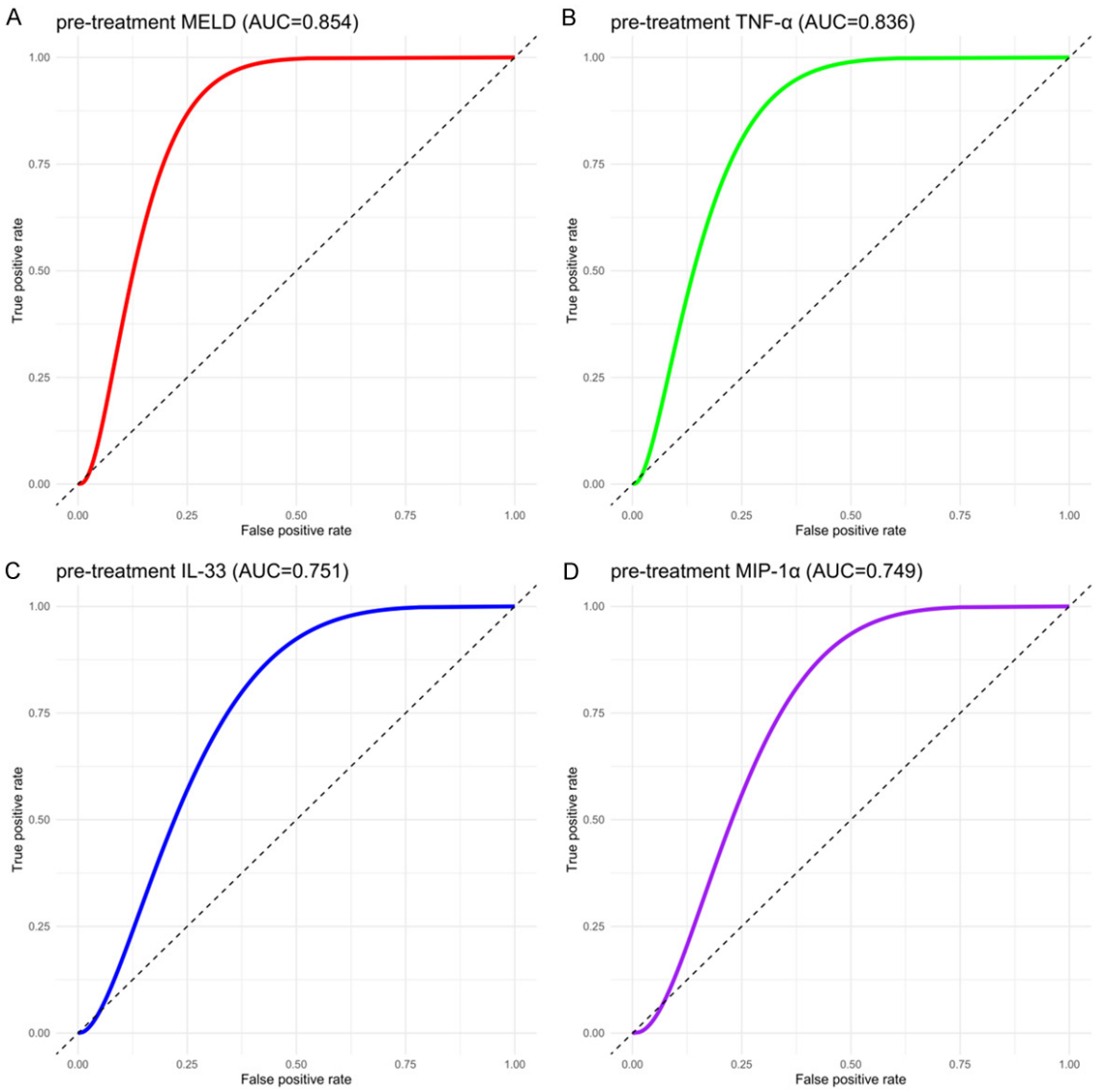

Figure 3. ROC curves of MELD, TNF-α, IL-33, and MIP-1α in predicting patient deaths. A. ROC curve of MELD score in predicting patient death; B. ROC curve of TNF-α in predicting patient mortality; C. ROC curve of IL-33 in predicting patient's death; D. ROC curve of MIP-1α in predicting patient death. Note: MELD, Model for End-Stage Liver Disease; TNF-α, Tumor Necrosis Factor-α; IL-33, Interleukin-33; MIP-1α, Macrophage Inflammatory Protein-1α.

patients receiving abiotic therapy had a significantly higher 28-day survival rate compared to untreated patients. This improvement was accompanied by notable enhancements in liver and coagulation functions and marked reductions in specific cytokines, including HBD-1, IFN-α, and IL-5. Furthermore, another study [21] explored the impact of cytosolic adsorption in ACLF patients with concurrent acute kidney injury, focusing on changes in serum bilirubin levels, inflammatory markers, liver function parameters, and patient survival. These findings validate the critical role of ACLF management, especially in modulating inflammatory responses and bolstering liver function. ACLF is characterized by its multifaceted nature and limited therapeutic options, often leading to high short-term mortality. Its pathogenesis involves systemic inflammation, acute liver injury, and the influence of occult factors contributing to disease progression [22]. Therefore, the management of ACLF is essential, requiring a comprehensive approach for this complex condition.

Table 6. Multivariate analysis of the factors affecting patient's prognosis

Index	AUC	95% CI	Specificity	Sensitivity	Youden index	Cut off
MELD score	0.857	0.778-0.857	74.65%	93.33%	67.98%	79.025
TNF-α (pg/mL)	0.836	0.753-0.836	67.61%	100.00%	67.61%	22.110
IL-33 (pg/mL)	0.749	0.643-0.749	61.97%	86.67%	48.64%	26.750
MIP-1α (pg/mL)	0.746	0.642-0.746	52.11%	100.00%	52.11%	18.835

Note: MELD, Model for End-Stage Liver Disease; TNF-α, Tumor Necrosis Factor-α; IL-33, Interleukin-33; MIP-1α, Macrophage Inflammatory Protein-1α.

Table 7. Delong test

Marker 1	Marker 2	Z value	*P* value	AUC difference	95% CI
MELD before treatment	Pre-treatment TNF-α (pg/mL)	1.781	0.075	0.021	-0.002-0.043
MELD before treatment	IL-33 before treatment (pg/mL)	4.22	<0.001	0.108	0.058-0.158
MELD before treatment	MIP-1α before treatment (pg/mL)	4.753	<0.001	0.111	0.065-0.156
Pre-treatment TNF-α (pg/mL)	IL-33 before treatment (pg/mL)	4.474	<0.001	0.087	0.049-0.126
Pre-treatment TNF-α (pg/mL)	Pre-treatment MIP-1α (pg/mL)	5.084	<0.001	0.09	0.055-0.125
IL-33 before treatment (pg/mL)	Pre-treatment MIP-1α (pg/mL)	0.301	0.763	0.003	-0.016-0.021

Note: MELD, Model for End-Stage Liver Disease; TNF-α, Tumor Necrosis Factor-α; IL-33, Interleukin-33; MIP-1α, Macrophage Inflammatory Protein-1α.

Prognostic assessment is crucial in managing ACLF as it helps guide treatment decisions and predict disease progression [23, 24]. In particular, understanding the changes in biochemical indices and cytokine levels before and after treatment is essential for assessing efficacy and patient prognosis in ACLF. Therefore, our study aimed to compare the differences in biochemical markers between patients in the death and survival groups after receiving ACLF, and to evaluate the efficacy of these markers in predicting 90-day survival. By utilizing ROC curve analysis, we were able to identify critical biomarkers that are closely associated with disease severity and patient prognosis with higher accuracy. When comparing data from patients in the death group to those in the survival group, we observed significant differences in post-treatment biochemical parameters and cytokine levels. Key liver function parameters, such as ALT, AST, and TBIL, showed significant improvement in patients receiving ACLF. Furthermore, ROC curve analysis demonstrated that these indices had significant diagnostic value in predicting 90-day survival. These findings provide clinicians with essential tools to more accurately assess disease severity and patient prognosis. In a previous human study by Qi et al. [25], serum α-fetoprotein demonstrated an AUC of 0.675 (0.550-0.80) in predicting 90-day prognosis of artificial liver in hepatitis B virus-associated SALF patients. Similarly, Yan et al. [26] found that it had predictive value for prognosis in patients with non-HBV liver failure with an AUC of 0.747. These studies highlight the importance of comprehensive and meticulous biochemical monitoring of patients with ACLF, which is crucial for optimizing therapeutic strategies and improving patient survival. However, despite the significant results for improving liver function, some patients still fail to achieve the expected therapeutic effects in actual clinical practice.

The present study successfully demonstrated the effectiveness of ACLF in improving liver function indices in patients with ACLF. However, the study also identified some limitations. Specifically, the treatment did not achieve the expected results in certain patients, which could be attributed to individual patient differences, disease severity, or comorbidities. Additionally, while the study identified key biomarkers closely associated with disease severity and prognosis through ROC curve analysis, further validation and optimization of this approach may be necessary. Future research will focus on developing personalized treatment regimens, optimizing treatment timing, improving existing ALSTs, and exploring the combina-

tion of other therapeutic approaches such as pharmacological treatments or stem cell therapies. Furthermore, the study aims to expand the application of specific biochemical indicators and explore other potential biomarkers to enhance the accuracy of treatment efficacy and prognostic assessment, ultimately improving patient survival and quality of life.

In conclusion, ACLF can significantly reduce TNF-α, IL-33, and MIP-1α levels in patients with ACLF, and postoperative levels of these biomarkers have predictive value for patient prognostic outcomes.

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Disclosure of conflict of interest

None.

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