Antithrombin III activity is associated with prognosis, infection, and inflammation in patients with hepatitis B virus-related acute-on-chronic liver failure

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Objective Patients with hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF) are characterized by severe liver function impairment, coagulation disorder, and multiple organ function impairment. The aim of this study was to explore the predictive value of antithrombin III activity to the prognosis of HBV-ACLF patients.

Methods A total of 186 HBV-ACLF patients were included in the analysis, and the baseline clinical data of patients were recorded to analyze the risk factors affecting the 30-day survival outcome of patients. Bacterial infection, sepsis, and hepatic encephalopathy were observed in ACLF patients. Antithrombin III activity and serum cytokine levels were determined.

Results The antithrombin III activity of ACLF patients in the death group was significantly lower than that in the survival group, and antithrombin III activity was independent factors affecting the 30-day outcome. The areas under the receiver operation characteristic (ROC) curve of antithrombin III activity to predict the 30-day mortality of ACLF was 0.799. Survival analysis showed that the mortality of patients with antithrombin III activity less than 13% was significantly increased. Patients with bacterial infection and sepsis had lower antithrombin III activity than those without infection. Antithrombin III activity was positively correlated with platelet count, fibrinogen, interferon (IFN)-γ, interleukin (IL)-13, IL-1β, IL-4, IL-6, tumor necrosis factor-α, IL-23, IL-27, and IFN-α, but negatively correlated with C-reactive protein, D dimer, total bilirubin, and creatinine levels.

Conclusion As a natural anticoagulant, antithrombin III can be regarded as a marker of inflammation and infection in patients with HBV-ACLF, and as a predictor of survival outcome in patients with ACLF. Eur J Gastroenterol Hepatol 35: 914–920

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Introduction

Hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF) is the most common type of severe liver disease, which results in a high short-term mortality and is very difficult to treat. ACLF has a high mortality rate despite advances in critical care and liver transplantation (50–90%) [1].

Coagulopathy is a typical clinical feature of ACLF. Vitamin K1-dependent coagulation factors (II, VII, IX, and X) are synthesized in the liver, of which coagulation factor VII is an important factor involved in exogenous coagulation pathways, so prothrombin time or international normalized ratio (INR) can reflect blooding risk. But they may not accurately reflect bleeding risk because they only measure clotting factors. The dysfunction of synthesis and the impairment of immune response caused by liver failure lead to the disorder of the procoagulant, anticoagulant, and fibrinolytic systems, leading to the concept of coagulation rebalancing.

Since the protein synthesis of anticoagulants (protein C, protein S, and antithrombin) is also present in the liver, liver failure may even manifest as a hypercoagulable state in addition to prolonged bleeding. In addition to the rebalanced clotting system, there are changes in platelet production due to decreased liver thrombopoietin production, increased von Willeblood factor due to low-level endothelial cell activation, and hyperfibrinolysis and fibrinogen abnormalities due to changes in synthetic liver dysfunction [2]. In conclusion, the coagulation disorder of liver failure is caused by multiple factors. Antithrombin III is a small molecule of anticoagulant blood glucose protein produced by the liver. It inactivates several enzymes in the clotting pathway [3]. It is made up of 432 amino acids. It contains three disulfide bonds and a total of four possible glycosylation sites. The main form of antithrombin is α-antithrombin. It has one oligosaccharide occupying each glycosylation site [4].

Antithrombin III activity was found to be significantly lower in decompensated cirrhosis and acute liver failure, and

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it can predict the risk of liver failure early in liver surgery. Added antithrombin can reduce inflammatory factor [IL-6, IL-1β, tumor necrosis factor (TNF)-α] levels in extracorporeal circulation treatment [5], and antithrombin III can also predict the severity of the sepsis and the occurrence of liver damage [6]. It is suggested that AT is not only a key coagulation factor in the coagulation system, but also plays an important role in inhibiting systemic inflammatory response. Up to now, there have been few studies on antithrombin III activity in ACLF patients. In this study, the application value of antithrombin III activity in ACLF patients was discussed by analyzing the relationship between antithrombin III activity and the survival period, biochemical indexes, and inflammatory factors of HBV-ACLF patients.

Materials and methods

Patient data

The clinical data of 186 ACLF patients admitted to ICU of Infection Department of Wuxi Fifth People's Hospital from January 2013 to June 2020 were retrospectively analyzed, including 144 males and 42 females. The diagnostic criteria of HBV-ACLF were determined referring to the Asian-Pacific Association for the Study of the Liver ACLF consensus of 2019 [7]. Exclusion criteria: (a) the patients with active bleeding or disseminated intravascular coagulation; (b) the patients with severe allergy to blood products or drugs such as plasma, heparin, and protamine used in the treatment process; (c) the patients with unstable infarctions caused by cardiovascular and cerebrovascular accidents; and (d) the patients with extravascular hemolysis. This study was approved by the ethics committee of Wuxi Fifth People's Hospital (Wuxi Fifth Academy Papers Lun Zi 2020-003-1).

Comprehensive treatment

The HBV-ACLF patients received comprehensive treatment, including general supportive treatment, antiviral treatment, supplementation of energy and vitamins, supplementation of blood products such as albumin and plasma, and treatment of potential complications, and all these patients were not treated with glucocorticoids. The family members signed an informed consent form before the patients underwent artificial liver treatment. Artificial liver treatment includes plasma exchange and continuous hemofiltration.

Observation indicators

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBil), INR, antithrombin III activity, white blood cell (WBC) count, platelet count, creatinine and model for end-stage liver disease (MELD) score were recorded at admission. In addition, the peripheral blood samples were taken for cytokine detection at baseline. The 30-day survival rate of the patients was recorded.

Laboratory instruments and reagents

INR and antithrombin III activity were detected by using the STA-R Automatic Coagulation Analyzer (STAGO, France), whose original reagent kits were used. The biochemical indicators were detected by using the full-automatic biochemical analyzer ADVIA2400 (Siemens Medical, Germany). The blood routine examination was performed by using XN-10 Automatic Blood Cell Analyzer (SYSMEX, Japan). The ELISA was performed to detect the serum levels of cytokines by using ThermoFisher Multiskan FC Microplate Reader (ThermoFisher, USA).

Statistical methods

SPSS 19.0 statistical software (IBM Inc., Armonk, New York, USA) was used for data processing. The continuous variables of normal distribution were expressed as $\bar{x} \pm s$, and *t*-test was used for comparison between groups. The measurement data of non-normal distribution were expressed as *M* (*QR*), and the rank sum test was performed for comparison between groups. The counting data were expressed as percentage and analyzed by chi square test. Cox regression analysis was used to analyze the risk factors for death and Kaplan–Meier method was used for the survival analysis; $P < 0.05$ indicated that the difference was statistically significant. GraphPad Prism 9.0 software (GraphPad Software Inc., San Diego, California, USA) was used for creating statistical charts. X-tile software (http://tissuearray.org/) was used to identify the optimal cutoff value.

Results

Comparison of clinical data between death group and survival group

Among the 186 HBV-ACLF patients, 63 died and 123 survived. The TBil, urea nitrogen, urea nitrogen/creatinine ratio, lactic acid, WBC, prothrombin time, INR, and MELD in the death group were significantly higher than those in the survival group. The antithrombin III activity was significantly lower in the death group, and the incidence of hepatic encephalopathy, bacterial infection, and sepsis was higher than that in the survival group (Table 1).

Antithrombin III activity might be a significant marker between survival and death groups.

Cox regression analysis revealed that hepatic encephalopathy, antithrombin III activity at baseline, urea nitrogen, TBil, and MELD score were independent factors affecting the 30-day survival outcome of patients(Table 2). To compare the predictive value of antithrombin III activity and MELD score in estimating the prognosis of patients with HBV-ACLF, we examined the ROC curve of these parameters (Fig. 1); the area under curve (AUC) of antithrombin III activity and MELD score was 0.799 and 0.681, respectively, whereas the AUC of antithrombin III activity combined with MELD score was 0.806. The cutoff value for antithrombin III activity was 13%. The sensitivity was 82.54%, and the specificity was 65.85% (Table 3). Thus, similar to MELD score, antithrombin III activity might have been a significant marker in the survival and death groups.

The survival analysis showed a negative correlation between antithrombin III activity and survival rate for patients with hepatitis B virus-related acute-on-chronic liver failure

Furthermore, we calculated the cutoff value, sensitivity, specificity, positive predictive value, and negative predictive value of antithrombin III activity for evaluating prognosis in patients with HBV-ACLF by X-tile software. Taking

Table 1 Comparison of the patient baseline data between the survival group and death group

	Survival group (*N* = 123)	Death group (*N* = 63)	Test value	*P* value
HBV DNA (log_{10}IU/ml)	4.2 ± 2.6	3.9 ± 2.8	$t = 0.408$	0.685
Gender (female/male)	25/98	17/46	$X^2 = 1.057$	0.304
Age (years)	49.4 ± 14.4	53.3 ± 12.7	$t = -1.819$	0.070
ALT (U/l)	673 (1235.5)	398 (624.5)	$Z = -2.603$	**0.009**
AST (U/l)	305 (617.15)	277.5 (311)	$Z = -0.613$	0.540
TBil (μmol/l)	277.9 ± 123.9	335.2 ± 127.3	$t = -2.956$	**0.004**
GGT (U/l)	99.5 (73)	102.5 (115)	$Z = -0.27$	0.787
ALP (U/l)	136 (63)	141.5 (58)	$Z = -0.878$	0.380
Albumin (g/l)	29.7 (6.9)	27.8 (7.4)	$Z = -1.287$	0.198
Creatinine (μmol/l)	63 (19)	64 (48.5)	$Z = -1.09$	0.276
Urea nitrogen (mmol/l)	4.1 (2.25)	6 (5.6)	$Z = -2.717$	**0.007**
Urea nitrogen/creatinine	18.1 ± 8.6	26.2 ± 14.9	$t = -3.267$	**0.002**
Cholinesterase (U/l)	3142 (2793)	2665 (2350)	$Z = -1.626$	0.104
Glucose (mmol/l)	5.5 ± 2.9	6.5 ± 3.4	$t = -1.465$	0.147
Lactic acid (mg/l)	1.7 ± 1.6	3.0 ± 2.3	$t = -3.234$	**0.002**
WBC (10^9/l)	6.4 ± 2.6	8.8 ± 5.8	$t = -3.09$	**0.003**
PLT (10^9/l)	99.4 ± 54.3	93.7 ± 53.3	$t = 0.497$	0.620
C reactive protein (mg/l)	7.75 (13.5)	10.9 (25.4)	$Z = -1.489$	0.136
Ammonia (μmol/l)	52.1 ± 10.5	53.6 ± 9.4	$t = -0.172$	0.864
PT (s)	23.6 ± 7.1	34.0 ± 25.9	$t = -2.422$	**0.020**
INR	2.3 ± 1.5	2.9 ± 1.7	$t = -2.6$	**0.010**
Antithrombin III activity (%)	32.1 ± 13.5	18.3 ± 11.4	$t = 6.907$	**<0.001**
Fibrinogen (g/l)	1.7 ± 0.7	1.4 ± 0.7	$t = 1.513$	0.134
D-dimer (μg/ml)	2.9 ± 3.3	4.2 ± 3.8	$t = -1.793$	0.076
MELDs	21.4 ± 5.7	26.1 ± 7.9	$t = -4.202$	**<0.001**
Hepatic encephalopathy (cases)	6	21	$X^2 = 19.988$	**<0.001**
Bacterial infection (cases)	17	18	$X^2 = 1.99$	0.158
Sepsis (cases)	4	14	$X^2 = 11.66$	**0.001**
Artificial liver (cases)	92	46	$X^2 = 0.069$	0.793

The bold P-value indicates that the two groups of data are statistically different.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; HBV, hepatitis B virus; INR, international normalized ratio; MELD, model for end-stage liver disease; PLT, platelet; PT, prothrombin time; TBil, total bilirubin; WBC, white blood cell.

Table 2 Risk factors associated with 30-day mortality, as analyzed by Cox proportional hazards analysis

	Hazard ratio[a]	95% CI	*P*
ALT	1.421	0.552–3.656	0.467
Hepatic encephalopathy	0.205	0.086–0.489	**<0.001**
Sepsis	1.599	0.364–7.016	0.534
Antithrombin III activity	0.326	0.124–0.856	**0.023**
Urea nitrogen	0.294	0.12–0.718	**0.007**
INR	0.876	0.092–8.31	0.908
C reactive protein	0.513	0.136–1.933	0.324
Lactic acid	0.355	0.114–1.102	0.073
MELD	1.624	1.628–4.201	**0.037**
PT	0.514	0.054–4.877	0.562
TBil	0.327	0.149–0.718	**0.005**
WBC	1.542	0.696–3.417	0.286
Urea nitrogen/creatinine	0.718	0.295–1.745	0.464

The bold P-value indicates that the two groups of data are statistically different.
ALT, alanine aminotransferase; INR, international normalized ratio; MELD, model for end-stage liver disease; PT, prothrombin time; TBil, total bilirubin; WBC, white blood cell.
[a]Hazard ratio is derived from multiple cox regression calculations.

82.54% sensitivity and 65.85% specificity as optimal conditions, a baseline value of antithrombin III activity ≤13% was selected as a negative cutoff value and ≥29% as a positive cutoff value. A Kaplan–Meier survival curve showed the percentage survival in the three groups with different cutoff values of antithrombin III activity (≤13%, 13–29%, and ≥29%) (Fig. 2). Seventy-one of 78 patients (91.0%) with baseline antithrombin III activity ≥29% survived at the end of 30 days. By contrast, only 10 of 35 patients with antithrombin III activity ≤13% (28.6%) survived. The patients with baseline antithrombin III activity of 13–29% exhibited a survival rate of 57.5% (42 of 73 patients). Log-rank survival analysis revealed a significant difference in the survival rates among the three groups ($P < 0.001$). Therefore, antithrombin III activity might be an independent predictor of survival for short-term prognosis of patients with HBV-ACLF.

Correlation between antithrombin III activity and acute-on-chronic liver failure bacterial infection and inflammation

The antithrombin III activity in HBV-ACLF patients with bacterial infection, sepsis, and non-infected patients was compared. It was found that the antithrombin III activity in patients with bacterial infection and sepsis was lower than that in non-infected patients, and the antithrombin III activity in sepsis patients was significantly lower than that in non-infected patients and bacterial infection patients. There was no significant difference in antithrombin III activity between bacterial infected patients and non-infected patients (Fig. 3).

Pearson correlation coefficient analysis showed a negative correlation between antithrombin III and C-reactive protein (CRP), fibrinogen, D-dimer, TBil, and creatinine, and positively correlated with platelet. In addition, levels of inflammation-related cytokines in peripheral blood of HBV-ACLF patients were measured. The analysis showed a negative correlation between antithrombin III and IFN-γ, IL-13, IL-1β, IL-4, IL-6, TNF-α, IL-23, IL-27, and IFN-α. Therefore, antithrombin III activity might be an important marker of infection and inflammation in ACLF (Tables 4 and 5).

Comparison of antithrombin III and C-reactive protein in acute-on-chronic liver failure patients with bleeding/thrombotic

After 90 days of observation, 16 (8.6%) of the 186 patients had positive fecal occult blood, and 11 (5.9%)

had femoral vein thrombosis by ultrasonography of lower extremity vessels. The antithrombin III activity in patients with positive occult blood and femoral vein thrombosis was lower than that in patients with negative fecal occult blood and no thrombus, and the difference was statistically significant. The CRP in patients with positive occult blood and femoral vein thrombosis is higher than that in patients with negative fecal occult blood and patients without thrombosis, and the differences are statistically significant (Table 6).

Discussion

HBV-ACLF patients often present with multiple organ dysfunction, with a mortality rate of more than 40% [1]. These patients are characterized by hyperbilirubinemia, elevated transaminase, and hypoproteinemia; coagulation dysfunction is another important clinical feature. Patients with ACLF have progressive changes in their hemostatic system, and are at particular risk for bleeding and thrombotic complications, which may be related to the decreased synthesis of antithrombin synthesized by the liver. Antithrombin III is a 65-kDa glycoprotein belonging to a group of inhibitory factors known as serpins. It plays a critical role in the inhibition of coagulation and inflammation processes within the environment of the vascular endothelium [8]. Antithrombin III binds thrombin (coagulation factor II) and forms the thrombin–antithrombin complex, which inactivates thrombin, and heparin can accelerate this reaction [9]. Antithrombin III is the most important factor in the anticoagulation system, which is involved in the regulation of blood coagulation and fibrinolysis. The activity of antithrombin III is decreased in patients with disseminated intravascular coagulation, severe liver disease, and kidney disease, which may lead to inadequate anticoagulation effect of heparin [10].

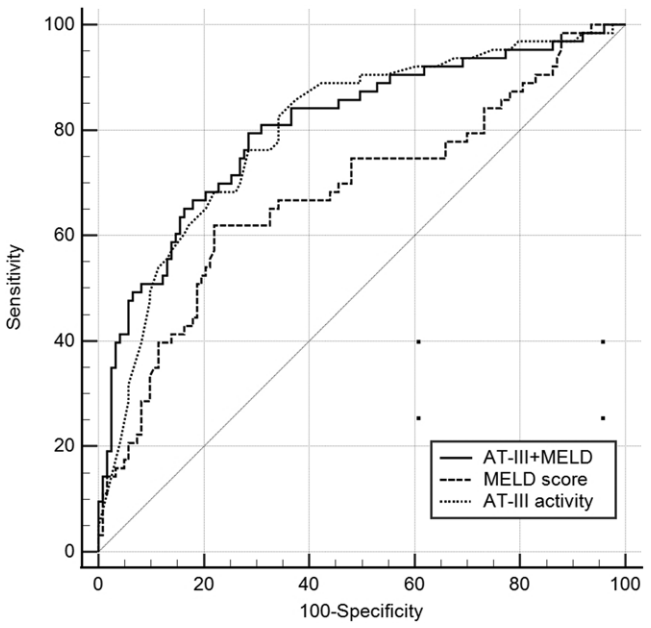

Fig. 1 Receiver operating characteristic curve indicating relative efficiencies for prediction of 30-day mortality by antithrombin III (AT-III) activity, MELD score, and their combination at admission. MELD, model for end-stage liver disease.

Coagulopathy in liver failure are complex, and although an INR value >1.5 is considered evidence of coagulopathy, it may not accurately reflect bleeding risk because it only measures procoagulant factors. As the liver participates in the protein synthesis of coagulants (factors II, V, IX, XI, and fibrinogen) and anticoagulants (protein C, protein S, and antithrombin), liver failure may even change into a hypercoagulable state in addition to prolonged bleeding time [2]. It was found that the antithrombin III activity in patients with decompensated cirrhosis was lower than that in patients with chronic hepatitis and compensated cirrhosis, and there was a significant negative correlation between ALT, AST, prothrombin time, PTT, and INR [11]. In acute liver failure without prior known liver disease, antithrombin III, prekallikrein, plasminogen, and alpha 2-antiplasmin were significantly lower in the alcoholic cirrhosis and nonalcoholic cirrhosis [12]. HBV-ACLF patients are characterized by systemic inflammatory response syndrome in the early stage of the onset of the disease. For example, the peripheral blood levels of proinflammatory cytokines and chemokines are significantly increased in the ACLF stage [13]. In liver failure the intense inflammatory response contributes to the procoagulant state, particularly by reducing the synthesis of liver synthetic protein C and antithrombin III. Severe systemic inflammatory response can lead to microcirculation disturbance, vascular endothelial injury, fibrin deposition, and microthrombi [14]. Antithrombin III plays a role in protecting liver cells and alleviating inflammation during ischemia reperfusion injury, while enhancing the anticoagulant activity of heparin [15,16]. Antithrombin III may attenuate posthepatectomy liver failure in hepatocellular carcinoma, possibly by suppressing coagulopathy [17]. It should be possible to use antithrombin III as an additional indicator for liver function and substitute for indocyanine green retention rate15 in the future [18]. Prothrombin time can be affected by a variety of factors, such as argatroban and rivaroxaban, vitamin K1 deficiency, clotting factor deficiency, and liver dysfunction. Antithrombin III is only affected by gene mutation, increased consumption, and abnormal liver function [19–24].

ACLF and liver cirrhosis patients are often complicated with infection and acute kidney injury (AKI) in the advanced stage of the disease. Bacterial infection can induce severe endotoxemia leading to increased coagulation disorders

Table 3 Area under curve for antithrombin III activity, MELD score, and their combination were calculated

	AUC	*P* value	95% CI	Cutoff value	Sensitivity	Specificity
Antithrombin III activity	0.799	0.001	0.734–0.854	13.0	82.54	65.85
MELDs	0.681	0.001	0.608–0.747	23.82	61.9	78.05
Antithrombin III activity + MELDs	0.806	0.001	0.741–0.860	0.31	79.3	71.54

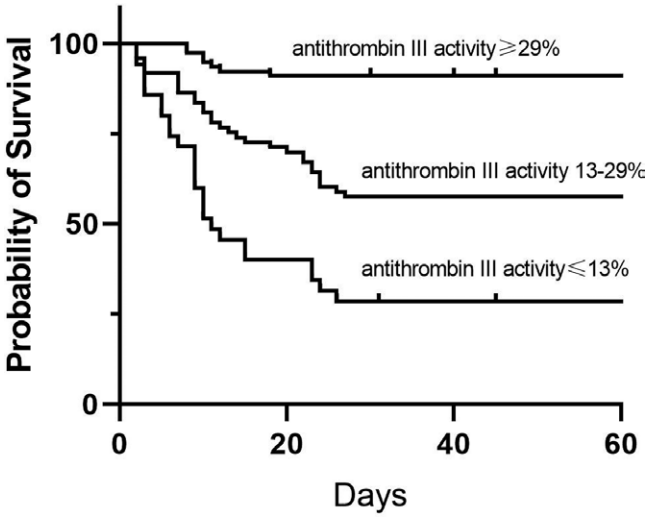

Fig. 2 Kaplan–Meier survival curve of antithrombin III activity with cut-off of 13 and 29 for the ACLF patients at admission. ACLF, acute-on-chronic liver failure.

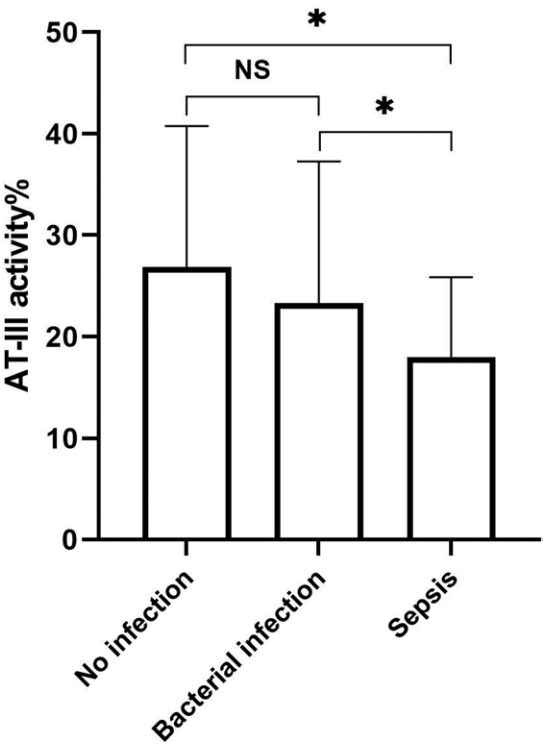

Fig. 3 Comparison of antithrombin III (AT-III) activity in ACLF patients with bacterial infection, sepsis, and no infection. ACLF, acute-on-chronic liver failure.

and multiple organ dysfunction. AKI is the most common extrahepatic organ injury. In patients with decompensated cirrhosis with AKI, antithrombin III, protein C, and protein S activities decrease and thrombin increases, leading to a hypercoagulable state. Patients with cirrhosis and AKI have low platelet aggregation and secretion, and factor XIII deficiency may also lead to increased bleeding [25]. It has been found that factor VII, platelet, fibrin degradation products, and D-dimer may be independent factors affecting the prognosis of patients with acute liver failure and sepsis [26]. It shows that sepsis is closely related to coagulation disorder. In particular, antithrombin III is most closely associated with inflammation. Decreased antithrombin III is an independent risk factor for sepsis-associated AKI and for death in sepsis patients [27,28]. Antithrombin III appears to ameliorate inflammatory response-induced kidney injury by inhibiting inflammation, oxidative stress, and apoptosis. Antithrombin III attenuates the upregulation of TNF-α, stimulated intercellular adhesion molecule-1, and monocyte chemotactic protein 1 [29]. It is suggested that coagulation disorder, infection, and kidney injury affect each other in patients with severe liver disease.

Prolonged bleeding time and fibrinolytic dysfunction in patients with liver failure may be related to platelet count and platelet function. Studies in patients with cirrhosis have found that lower platelet activation capacity being associated with low platelet count and Child-Pugh class B/C cirrhosis. Some patients with alcoholic cirrhosis have reduced platelet function, the severity of which is related to platelet count and severity of cirrhosis [30]. In patients with decompensated cirrhosis, patients with significantly increased platelet aggregation have a greater than 80% chance of further decompensation, transplantation, or

Table 4 The correlation between antithrombin III activity and patient clinical profiles using the Pearson correlation coefficient

	PLT	CRP	Fibrinogen	D-dimer	TBil	Creatinine
Antithrombin III activity						
Pearson correlation	0.382	−0.331	0.762	−0.258	−0.407	−0.267
P value	0.002	0.007	<0.001	0.038	0.001	0.032

CRP, C-reactive protein; PLT, platelet; TBil, total bilirubin.

Table 5 The correlation between antithrombin III activity and inflammatory factors in peripheral blood of patients using the Pearson correlation coefficient

	IFN-γ	IL-13	IL-1β	IL-4	IL-6	TNF-α	IL-23	IL-27	IFN-α
Antithrombin III activity									
Pearson correlation	−0.278	−0.331	−0.280	−0.330	−0.263	−0.329	−0.255	−0.269	−0.259
P value	0.025	0.007	0.024	0.007	0.034	0.007	0.04	0.03	0.037

TNF, tumor necrosis factor.

Table 6 Comparison of antithrombin III and C reactive protein in ACLF patients with bleeding/thrombotic

	Bleeding		No bleeding	Thrombosis		No thrombosis
Antithrombin III activity	10.7 ± 6.7	$P < 0.001$	29.0 ± 13.9	10.64 ± 4.3	$P < 0.001$	28.5 ± 14.1
C reactive protein	9.2 (19.35–4.2)	$P = 0.022$	5.8 (10.1–0.5)	9.2 (19.3–4.4)	$P = 0.037$	5.75 (15.3–1.3)

ACLF, acute-on-chronic liver failure.

death [31]. These studies suggest that platelet function is closely related to the prognosis of severe liver disease.

In addition to the Model for end-stage liver disease score, decreased antithrombin III activity tends to be superior in predicting acute liver failure compared with traditionally thought predictors in patients supported with mechanical circulatory treatment [32]. This study also found that antithrombin III activity was significantly reduced in ACLF patients, and the survival rate of patients with a critical value ≤13% was only 28.6%, which was a good predictor of the prognosis of patients with liver failure. Stratified analysis, early screening of patients with low antithrombin III activity for complete medical treatment, or liver transplantation may be an effective way to improve the survival rate of patients with liver failure. Similarly, this study found a significant linear relationship between antithrombin III and platelets, CRP, D dimer, and creatinine. In addition, platelet and D dimer are both sensitive indicators of thrombosis, indicating that antithrombin III is one of the important factors in the mechanism of coagulation disorder in liver failure.

The analysis showed a negative correlation between antithrombin III and IFN-γ, IL-13, IL-1β, IL-4, IL-6, TNF-α, IL-23, IL-27, and IFN-α. Therefore, antithrombin III activity might be an important marker of infection and inflammation in ACLF. In sepsis, reduced antithrombin III activity is due to sustained clotting factor depletion, systemic inflammatory responses, capillary leakage syndrome, and impaired synthesis [6]. Exogenous antithrombin can reduce immune cell response and improve microcirculation dysfunction and tissue damage in injured animals during endotoxemia [33]. In mice with ischemia-reperfusion induced intestinal injury, antithrombin supplementation can inhibit thrombin production, fibrin degradation products and fibrin deposition, as well as inhibit the expression of inflammatory factors such as IL-6, and inhibit coagulation disorders and inflammatory reactions [34]. This suggests that antithrombin plays an important role in inhibiting inflammation.

Antithrombin III may inhibit inflammation by inhibiting thrombin, a clotting factor that interacts with endothelial cells, and direct interaction with inflammatory mediators [35,36]. For example, by interacting with heparin sulfate of endothelial cells, antithrombin III stimulates the production of prostocycline by endothelial cells and inhibits the production of cytokines and tissue factors by endothelial cells and monocytes. The activity characteristics of antithrombin III indicate the close role of anticoagulants and anti-inflammatory pathways [37].

To sum up, ACLF results in vascular endothelial injury due to severe systemic inflammatory reaction, reduced synthesis of antithrombin III and increased consumption of activated fibrinolysis system, and patients present with hypercoagulability. It showed decreased platelet and D dimer, and even microthrombus. Compared with bleeding complications, thrombus occurrence should be paid more attention. The predictive value of antithrombin III in ACLF should be emphasized because it can predict the short-term mortality of patients and is closely related to infection and inflammation. Due to the small sample size in this study, no studies have been conducted on the mechanism of coagulation and inflammation. The role of antithrombin III in ACLF still needs further research.

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Conflicts of interest

There are no conflicts of interest.

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