REVIEW ARTICLE

Characterization of the Clinical Features in HBV-Related Acute-on-Chronic Liver Failure

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ABSTRACT

Objective • Acute-on-chronic liver failure (ACLF) is a type of liver failure commonly found in China, and currently the mechanism of the disease remains unknown. This study aimed to investigate the epidemiology, clinical features and prognostic factors in ACLF.

Methods • This study retrospectively included 170 patients with ACLF admitted to Beijing Friendship Hospital in Beijing, China from November 2017 to May 2019. Patients were divided into 2 groups: the improved group and the deteriorated group, according to the severity of their disease. Patients' demographic data; clinical manifestations; complications; laboratory indicators including platelets (PLT), alanine aminotransferase (ALT), aspartate amino transferase (AST), total bilirubin (TBIL), prothrombin time (PT), activated partial thromboplastin time (APTT), prothrombin activity (PTA), international normalized ratio (INR), and alkaline phosphatase (ALP) were collected. The relationship between these factors and the patients' prognosis were analyzed by logistic multivariate regression analysis.

Results • The highest morbidity rate was in the age group 40 to 49 years (29.41%). The age group with the second highest morbidity was between 50 and 59 years (25.29%), followed by >60 (21.18%), 30 to 39 (20.59%), 20 to 29 (2.94%) and <20 years (0.59%). A total of 53 patients (31.18%) had a family history of hepatitis B virus infection. The patients' main clinical manifestations were ascites (77.65%) and weakness (68.23%). The most common complications were hypoalbuminemia (80%), infection (67.65%) and electrolyte imbalance (44.12%). In addition, the PTA ($P = .009$), hepatorenal syndrome ($P = .005$) and hepatic encephalopathy (level IV) ($P = .005$) were independently related to the prognosis of ACLF. There is a significant relationship between complications and prognosis ($\chi^2 = 8.502$; $P = .004$).

Conclusion • This study showed that prothrombin activity, hepatorenal syndrome and hepatic encephalopathy were independently related to the prognosis of ACLF. This outcome provided more options for reducing patient mortality in clinic. (*Altern Ther Health Med.* 2022;28(2):65-69).

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INTRODUCTION

Acute-on-chronic liver failure (ACLF) is acute hepatic failure based on chronic liver disease, with severe clinical symptoms, which can lead to a clinical syndrome of jaundice, coagulation dysfunction, ascites and hepatic encephalopathy.[1,2] The most common ACLF disease in China is mainly viral hepatitis. The disease has an acute onset, short course, high mortality rate and no specific drugs for treatment, which mainly depends on comprehensive internal medicine treatment and liver transplantation.[3-5] Early prevention and timely targeted treatment can effectively reduce mortality in ACLF.

ACLF is the most common type of liver failure in China, and chronic infection is the most important cause of ACLF. Clinically, it is generally manifested as sudden weakness and loss of appetite in the prior 4 weeks, progressive increased bilirubin (BIL) levels and coagulopathy, no or hepatic

encephalopathy and at least 1 organ or system failure (liver, kidney, brain, coagulation, circulatory or lung).[6]

The mechanism of ACLF is not clear. The pathogenesis of ACLF is closely related to the initial severe inflammatory reaction or immune dysfunction caused by immune hyperactivity, immune paralysis and sepsis.[7] When the body is fighting infection and non-infectious threats, the immune and excessive immune responses play a central role in the occurrence of ACLF.[8]

Acute kidney injury is also one of the major complications of ACLF. Studies have shown that acute kidney injury progresses faster in patients with ACLF compared with patients with acute kidney injury due to decompensated cirrhosis. The mortality rate is also higher, but the possibility of recovery from acute kidney ACLF injury is greater as the patient's condition improves.[9] Liver-kidney syndrome is a functional form of acute kidney injury that often occurs in patients with advanced cirrhosis. Hepatic encephalopathy (HE) is the most common complication in various acute, chronic and end-stage liver diseases. The mechanism of hepatic encephalopathy may be related to bacterial infection and inflammatory reaction, and the substance produced by intestinal bacterial amino acid metabolites damages astrocyte function and affects neurotransmitter transmission.[10,11] Our study aims to identify factors that have an impact on outcomes in patients with epidemiological factors, complications and various laboratory indicators.

MATERIALS AND METHODS

Study Design

A total of 170 patients with ACLF diagnosed in Beijing Friendship Hospital in China from November 2017 to May 2019 were retrospectively analyzed, including 128 males and 42 females. Their ages ranged from 17 to 80 years, and the average age was 48.8 years.

Inclusion criteria. Patients with chronic liver disease, the clinical syndrome of acute or subacute short-term liver function decompensation (<4 weeks) including patients with: (1) extreme fatigue, obvious gastrointestinal symptoms; (2) rapid increase of jaundice, serum total BIL 10 times >the upper limit of normal or a daily increase ≥17.0 μmol/l; (3) bleeding tendency, prothrombin activity (PTA) ≤40% (or international normalized ratio (INR) ≥1.5) and exclusion of other causes; (4) decompensated ascites and (5) with or without hepatic encephalopathy.

Exclusion criteria. Patients with (1) serious heart, brain, kidney, lung, blood system and other significant organ diseases; (2) have diffuse intravascular coagulation, pregnancy; (3) require long-term anticoagulant drugs due to other diseases; (4) with chronic or metabolic diseases such as hyperthyroidism, tuberculosis and tumors; (5) with liver transplantation.

The criteria for clinical healing included patients in whom: (1) clinical symptoms such as fatigue, anorexia, abdominal distension, oliguria, bleeding tendency and hepatic encephalopathy disappeared; (2) jaundice subsided and the liver returned to normal size; (3) liver function indicators returned to normal and (4) PTA/INR returned to normal.

The criteria for clinical improvement included patients in whom: (1) clinical symptoms such as fatigue, anorexia, abdominal distension and bleeding tendency improved significantly, and hepatic encephalopathy disappeared; (2) signs of jaundice and ascites improved significantly and (3) liver function indicators improved significantly (total BIL [TBIL] decreased to >5 × normal, PTA >40% or INR <1.6).

Patient Categorization

The patients were categorized as either leaving the hospital or having died in the hospital and were divided into 2 groups: the improved group and the deteriorated group (including exacerbation and death). The description "improved" was used to define patients who were able to be discharged from hospital because their clinical symptoms improved and liver function was recovered. The description of "deteriorated" was defined as patients who died or deteriorated when they were voluntarily discharged from the hospital, except for those patients who died or further deteriorated because of other diseases or accidents. The grouping criteria were: (1) clinical healing - symptoms or signs basically disappeared or were significantly improved, liver function was normal or just slightly abnormal (ALT ≤ 60 IU/L or TBIL ≤ 25mol/L) and (2) clinical basic healing - symptoms and signs basically disappeared, or were significantly improved, liver function was normal or slightly abnormal (ALT fluctuations about 1 time the upper limit of normal or TBIL ≤34.2 mol/L); (3) clinical improvement, symptoms and signs improved, and liver function improved significantly (ALT and TBIL decreased by more than 50% compared with the baseline) and there were no significant fluctuations; (4) remaining was considered invalid for ACLF. Based on these criteria, patients were divided into an improved group (meeting the criteria of clinical healing, clinical basic healing and clinical improvement) and the deterioration group (meeting the criteria of invalid).

Analytical Indicators

Demographic information was collected for each patient, including gender, age, occupation, ethnicity, family history, clinical manifestations, complications and other infections. Laboratory monitoring indicators included platelets (PLTs), alanine aminotransferase (ALT), aspartate amino transferase (AST), total bilirubin (TBIL), prothrombin time (PT), activated partial thromboplastin time (APTT), prothrombin activity (PTA), international normalized ratio (INR) and alkaline phosphatase (ALP).

Statistical Analysis

IBM® SPSS 16.0 statistical software was used for analysis. Data were shown as means ± standard deviation (SD). The continuous variables were analyzed by *t* test, the classification data were compared by χ^2 test. Potential factors that may have influenced the prognosis were examined by logistic analysis. $P < .05$ indicated statistical significance.

RESULTS

Epidemiology of Patients with ACLF

Among the 170 patients with ACLF, there were 128 men (75.29%) and 42 women (24.70%), with a man-to-women ratio of 3.04:1. The mean patient age was 48.80 ± 12.38 years (range, 17 to 80 years). The highest morbidity (29.41%) was in the age group 40 to 49 years. The age group with the second highest morbidity was between 50 and 59 years (25.29%), followed by >60 years (21.18%), 30 to 39 years (20.59%), 20 to 29 years (2.94%) and <20 years (0.59%).

With regard to the occupation of the patients with hepatitis B virus (HBV)-related ACLF, farmers comprised the highest percentage, followed by retired people, workers, drivers, unemployed individuals, staff members and students.

The ethnic composition of the patients included 152 Han, (89.41%), 8 Man (4.71%), 6 Tibetans (3.53%) and 4 Mongolians (2.35%).

A total of 53 patients (31.18%) had a family history of HPV infection. Of the 170 patients, 106 (62.35%) had no ascertainable cause of disease, 16 (9.41%) had disease caused by alcohol abuse, followed by fatigue (5.88%) and cold (4.71%) (see Table 1).

Relationship Between Complications and Prognosis

The patients' main clinical manifestations were ascites (77.65%) and weakness (68.23%) (see Table 2). The most common complications were hypoalbuminemia (80%), infection (67.65%) and electrolyte imbalance (44.12%) (see Table 3). In the improved group there were 57 males and 21 females, and there were 72 males and 20 females in the deteriorating group; the average age of patients in the improved group and the deteriorating group was 46.48 ± 11.56 years and (50.91 ± 14.77) years, respectively. The average age of the groups was statistically significant ($P < .05$) (see Table 4).

Our study showed that PT, APTT, PTA, INR and TBIL were statistically different in the two groups (see Table 5). According to the patient's clinical statistics, the factors were analyzed by logistic single factor regression analysis. The prognosis of patients in both groups was analyzed by statistical analysis. The results showed that the patients' prognoses were related to PT, APTT, PTA, INR, TBIL, hepatic encephalopathy[3,4] and liver and kidney syndrome. Logistic multivariate regression analysis was performed by multivariate analysis of factors influencing prognosis selected by univariate analysis. The results showed that PTA ($P = .009$), hepatorenal syndrome ($P = .005$) and hepatic encephalopathy (level IV) ($P = .005$) were independently related to the ACLF prognosis.

There is a significant relationship between complications and prognosis in the two groups (51/68 vs 90/92, respectively; $\chi^2 = 8.502$; $P = .004$). Hepatic encephalopathy (level IV) and hepatorenal syndrome are closely related to the prognosis (see Table 6).

Table 1. Precipitating Factors for ACLF.

Inducement	n	Percentage
Self-stop/reduce medication	7	4.12
Drinking alcohol	16	9.41
Fatigue	10	5.88
Cold	8	4.71
Fever	4	2.35
Post-surgery	5	2.94
High-fat diet	5	2.94
Health examination	3	1.76
Take medicine	6	3.53
No obvious cause	106	62.35

Table 2. Clinical Manifestations in Patients with Acute-on-Chronic Liver Failure

Clinical manifestations	n	Percentage (%)
Symptoms		
Weakness	116	68.23
Anorexia	95	55.88
Ventosity	63	37.06
Nausea	43	25.29
Emesis	43	25.29
Diarrhea	12	7.06
Sign		
Ascites	132	77.65
Liver palms	77	45.29
Spider nevus	28	16.47
Splenomegaly	36	21.18
Hepatomegaly	10	5.88
Liver area pain	16	9.41

Table 3. Complications of Acute-on-Chronic Liver Failure

Complications	n	Percentage
Hepatic encephalopathy	56	32.94
level I	18	10.58
level II	10	5.88
level III	10	5.88
level IV	18	10.58
Hemorrhage of digestive tract	18	10.58
Hepatorenal syndrome	38	22.35
Spontaneous peritonitis	4	2.35
Infection	115	67.65
Electrolyte imbalance	75	44.12
Hypoalbuminemia	136	80.00

Table 4. Relationship Between Gender, Age and Groups

Factor	Promotion group	Deterioration group	*F*	*P* value
Male patients	57	72	-	-
Female patients	21	20	-	-
Age (years)	46.48 ± 11.56	50.91 ± 14.77	1.029	.046

Table 5. Comparison of Laboratory Indicators

Item	Promotion Group	Deterioration Group	*P* value
PLT	97.51 ± 68.57	92.35 ± 40.36	.668
PT	27.17 ± 6.15	34.65 ± 13.15	.001
APTT	45.77 ± 11.65	53.22 ± 13.02	.007
PTA (%)	31.38 ± 7.59	26.43 ± 11.87	.026
INR	2.40 ± 0.56	3.08 ± 1.18	.001
ALT	321.79 ± 437.40	382.33 ± 619.90	.607
AST	303.91 ± 413.86	392.63 ± 702.92	.225
TBIL	400.23 ± 207.21	266.76 ± 173.44	.002
ALP	36.89 ± 33.44	41.61 ± 79.94	.729

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate amino transferase; APTT, activated partial thromboplastin time; INR, international normalized ratio; PLT, platelets; PT, prothrombin time; PTA, prothrombin activity; TBIL, total bilirubin.

Table 6. Statistical Analysis of Complications in Patients with Acute-on-Chronic Liver Failure

Complication	χ^2	*P* value
Hepatic encephalopathy		
level I	2.793	.094
level II	0.001	.673
level III	0.945	.316
level IV	6.078	.011
Hemorrhage of digestive tract	0.056	.542
Hepatorenal syndrome	6.47	.009
Spontaneous peritonitis	0.071	.653
Infection	0.035	.538
Electrolyte imbalance	0.484	.320
Hypoalbuminemia	0.2006	.685

DISCUSSION

The causes of ACLF include (1) infectious factors, including HBV activity or mutation and other non-viral factors; (2) non-infectious factors, including gastrointestinal (GI) bleeding, drug factors, alcohol factors, diarrhea, fatigue, liver cancer, autoimmunity sexual diseases, pregnancy, etc. HBV is an important factor in the initiation and development of HBV-ACLF.

HBV induces a series of destructive immune responses by directly acting on the body's cells. The protein expressed by the HBV virus can increase the sensitivity of hepatocytes to inflammatory mediators, accelerate hepatocyte necrosis and apoptosis, trigger inflammatory reactions and promote the transcription of a large number of inflammatory factors,[12-14] which becomes severe hepatitis and aggravates the development of acute liver failure.[15,16] If chronic liver disease patients drink alcohol, they can easily develop liver failure. In combination with obesity or type 2 diabetes can increase the disease severity. Alcohol-induced hepatotoxicity, increased apoptosis, acquired immune activation, impaired liver regeneration and other liver damage can also cause intestinal micro-ecological disorders and increased intestinal permeability, leading to increased intestinal toxin release. Alcohol metabolism increases oxygen free radicals (ROS) and hepatocyte apoptosis induced by mitochondria and endoplasmic reticulum stress[17,18]

Whether ACLF can be reversed depends on the severity of the attack, the nature of the cause and the severity of the chronic primary disease. Therefore, it is important to provide reasonable antiviral therapy early, and it is necessary to specifically disseminate knowledge about HBV, strengthen patient compliance and not stop antiviral drugs at will. During antiviral treatment, liver function and HBV DNA quantification should be reviewed regularly. Once the HBV mutation occurs, the appropriate antiviral drugs should be replaced as soon as possible. In order to control HBV activities, patients with HBV should pay attention to daily habits, stop drinking, avoid drug abuse, fatigue, infection, etc., to try to reduce or avoid predisposing factors and reduce the incidence of liver failure.

Patients with cirrhosis have decreased liver drug metabolism and clearance, hypoalbuminemia leads to higher levels of free drug in the blood circulation and drug-induced liver damage is more likely to occur, which is more difficult to recover from.[19,20] Patients with acute venous varices and sepsis are prone to bacterial translocation and increased bacterial infection, leading to liver failure.[21-23] Patients with cirrhosis have immune system dysfunction and sustained activation of immune cells, and susceptibility to bacterial infections is also significantly increased.[23] Patients with bacterial infections have a significantly increased mortality rate.[24] Studies have shown that extrahepatic organ failure is the most important determinant of death in patients with ACLF associated with bacterial infection.[25]

This study shows that there are significantly more males than females in the affected population. The percentage of young and middle-aged people affected is high, and the percentage of farmers is the highest. It may be related to the living environment, lifestyle, medical conditions, cognitive level and lack of timely medical treatment. The percentage of the Han population affected is relatively high. In this study, 70% of patients have a family history of HBV infection, and China is a high-risk area for HBV. This study found that the common predisposing factors in ACLF include overwork and self-discontinuation. Therefore, patients with HBV infection should be under the care and guidance of a physician, take medication and avoid heavy physical activity. At the same time, the study found that there is no obvious incentive for the majority of patients with ACLF, which may be related to life, work environment, mental stress and mood. The clinical symptoms were mostly fatigue, loss of appetite and signs such as ascites and liver palms.

A total of 32.55% of patients were admitted to the hospital with hepatic encephalopathy, and grade IV hepatic encephalopathy was significantly associated with prognosis; 22.09% of patients were accompanied with hepatorenal syndrome, 80.23% of patients had hypoalbuminemia, and 67.44% of patients had other infections.

BIL is metabolized in the liver, and the liver produces most of the clotting factors in the body. Liver failure leads directly to massive necrosis of hepatocytes, BIL metabolism disorder, clotting factor synthesis disorder and prolonged clotting times. This study found that patient prognosis is related to PTA, hepatorenal syndrome and hepatic encephalopathy, and changes in the these indicators contribute to the assessment of outcomes in patients with ACLF. Patients with liver failure are prone to complications such as hemorrhage, infection, hepatic encephalopathy, and hepatorenal syndrome. This study shows that hepatic encephalopathy and hepatorenal syndrome are important indicators for determining patient outcomes.

Study Limitations

However, there were some limitations in this study. The outcome was based on a retrospective single-center study, and the findings remain to be proven by a prospective multi-center study. Besides, we did not analyze the correlation between HBV-related clinical information, including HBV genotype, HBV DNA titer and HBsAg titer, and ACLF. A more comprehensive analysis needs to be performed.

CONCLUSION

At the present time, there is a lack of specific medicine and methods for the treatment of ACLF. Early assessment of prognosis requires certain interventions to actively prevent and treat complications that can dynamically monitor important clinical indicators, inform patients in order to strengthen self-protection, eliminate bad habits, and thus improve the probability of patient survival.

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