Long-Term Prognosis of Patients with Hepatitis B Virus-Related Acute-on-Chronic Liver Failure: A Retrospective Study

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Abstract

Introduction and Objectives: The long-term prognosis of patients with hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF) is not well characterized. We sought to assess the short-term and long-term outcomes and the associated risk factors of HBV-ACLF patients in south China.

Patients and Methods: We retrospectively analyzed clinical data, adverse events, and clinical endpoint events of HBV-ACLF patients treated at our department between January 2014 and December 2018.

Results: A total of 1177 HBV-ACLF patients were included in the study, including 616 (52.3%) cirrhotic patients and 561 (47.7%) non-cirrhotic patients. 973 (83%) patients were associated only with HBV, and 204 (17%) patients had two or more etiologies. The leading cause of simple HBV-ACLF patients was lack of antiviral treatment and the proportion of patients receiving antiviral treatment for HBV was low (20%). Further analyses indicated non-cirrhotic patients had a significantly lower 90-day transplantation-free mortality and greater 5-year survival rate than cirrhotic patients (59.5% vs. 27.6%, 62% vs. 36%, P 0.05). Age, hepatic encephalopathy, liver cirrhosis, nucleoside (acid) analogues (NAs) withdrawal, total bilirubin, and prothrombin time were independent risk factors for 90-day mortality in HBV-ACLF patients. Cirrhosis at admission (AOR=3.675, 95% CI: 2.408–6.594) was a strong independent risk factor for long-term prognosis.

Conclusion: The proportion of HBV-ACLF patients receiving antiviral treatment was extremely low in south China. HBV combined with acute hepatitis E, or DILI had no significant effect on the short-term mortality rate in HBV-ACLF patients. Remarkably, the effect of withdrawal of NAs and cirrhosis on short-term outcomes cannot be ignored. No significant improvement in the short-term prognosis of HBV-ACLF patients was observed compared with previous studies.

Trial Registration: The trial is registered at ClinicalTrials.gov (CT.gov identifier: NCT04231565). Registered 13 May 2020

https://register.clinicaltrials.gov/prs/app/action/SelectProtocol?sid=S0009OZY&selectaction=Edit&uid=U00036P1&ts=2&cx=27seqt

1. Introduction

Acute-on-chronic liver failure (ACLF) is a systemic multi-organ dysfunction caused by acute hepatic insult in the backdrop of previously diagnosed or undiagnosed chronic liver disease or cirrhosis. It is characterized by rapid disease progression and is associated with a short-term mortality rate of up to 40–90% [1–4]. Hepatitis B virus (HBV) infection is the main cause of ACLF, accounting for 90% of all ACLF cases [5]. Studies have found that HBV activation and withdrawal of antiviral drugs are the most common causes of HBV-related acute-on-chronic liver failure (HBV-ACLF) [6]. Currently, several prognostic models are used to evaluate the short-term outcomes of HBV-ACLF patients. However, the intrahepatic etiology is not factored in the currently used prognostic models.

With the popularization of antiviral drug treatment and artificial liver support systems (ALSS), some patients experience alleviation of symptoms after active medical treatment. However, studies have found that some HBV-ACLF patients who survive acute injury develop post-necrotic cirrhosis and hepatocellular carcinoma (HCC) after several years. The long-term prognosis of patients with HBV-ACLF and the associated risk factors are not well characterized. A previous study investigated approximately 200 patients with HBV-ACLF in southern China, who were followed-up between 2009 and 2016 [7–8]. In contrast, the present study had a larger sample size and focused on the long-term prognosis of HBV-ACLF patients in south China over the past five years. Furthermore, the risk factors for disease progression were explored to provide a basis for further diagnosis and treatment.

2. Patients And Methods

2.1 Study participants

We retrospectively reviewed 1697 patients who were diagnosed with HBV-ACLF at the Department of Infectious Diseases, Third Affiliated Hospital of Sun Yat-Sen University between January 2014 and December 2018. The inclusion criteria were: 1) patients with chronic hepatitis B who were diagnosed as ACLF based on the definition by the Asian Pacific Association for the Study of Liver (APASL) in 2014; 2) availability of complete inpatient clinical data. The exclusion criteria were: 1) age > 65 years or < 18 years; 2) concomitant presence of liver cancer or other tumors, autoimmune liver disease, or genetic metabolic liver disease; 3) other serious comorbid conditions that can significantly affect patient survival, such as diabetes with severe complications, renal failure, and severe coronary heart disease with cardiac function level 3; and 4) lack of timely follow-up. Finally, 1177 patients were included in this study, and their clinical and follow-up data were analyzed.

2.2 Diagnostic criteria

The diagnosis of chronic hepatitis B was based on the guidelines for the prevention and treatment of chronic hepatitis B in China (2015) [9–10]. ACLF was diagnosed based on the definition by the APASL in 2014 [11]. The diagnosis of liver cirrhosis was based on the following: 1) confirmation by liver biopsy; 2) clinical evidence of decompensation events or varices; 3) supportive imaging evidence, such as liver nodule formation. If the patient's Child-Turcotte-Pugh (CTP) score was > 7 or there were complications related to portal hypertension, the diagnosis was decompensated cirrhosis [12].

The diagnosis of HCC was based on clinical manifestations and multi-slice spiral computed tomography (CT), magnetic resonance imaging (MRI), or other imaging examinations [13].

Liver transplantation (LT) criteria: Model for End-Stage Liver Disease (MELD) score is the main reference index for evaluating the indication for liver transplantation. MELD score of 15–40 is the optimal indication for liver transplantation [14]; liver transplantation is recommended within 28 days for patients

with grade 2 or 3 (CLIF-C score < 64) after active comprehensive medical therapy and artificial liver therapy [15].

2.3 Follow-up and data collection

In this study, most patients were followed-up via telephone and during outpatient visits to record disease progress and survival after discharge, including the occurrence of adverse clinical events, such as decompensated liver cirrhosis, HCC, liver failure recurrence, death, and liver transplantation. The last follow-up was on May 1, 2020. Taking the time of diagnosis of HBV-ACLF as the baseline, we retrospectively analyzed the following data: age, sex, comorbidities, complications, HBV-DNA, total bilirubin (TBIL), albumin (ALB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), cholinesterase (CHE), prothrombin time (PT), international normalized ratio (INR), fibrinogen (Fib), alpha-fetoprotein (AFP), white blood cell (WBC) count, platelet (PLT) count, fasting blood glucose (FBG), blood creatinine (Cr), blood urea nitrogen (BUN), estimate glomerular filtration rate (eGFR), Child-Turcotte-Pugh (CTP), MELD score, MELD-Na score, the Chinese Group on the Study of Severe Hepatitis B (COSSH)-ACLF II score and abdominal ultrasound or CT results.

2.4 Statistical analysis

SPSS 25.0 statistical software was used for data processing and analyses. Continuous variables are presented as mean ± standard deviation and median value. Categorical variables are presented as frequency (percentage). The *t* test and Mann-Whitney U test were used for the comparisons of continuous variables, and the Chi-squared test was used for the comparison of categorical variables. The survival rate was estimated using the Kaplan-Meier method, and between-group differences in survival outcomes were assessed using the log-rank test. Univariate logistic regression analysis and multivariate analysis were used to identify risk factors for 90-day death and disease progression. The forward method was used to construct the multivariate logistic regression model. Receiver operating characteristic (ROC) curve analysis was performed to obtain the optimal cut-off value of independent risk factors for 90-day mortality. Diagnostic accuracy was obtained by the area under the curve (AUC). To compare the AUC of prognostic models, the *z* test was applied. *P* values < 0.05 were considered indicative of statistical significance.

3. Results

3.1 Patient characteristics

A total of 1697 ACLF patients met the enrollment criteria and were followed-up by telephone or during outpatient visits. Of these, detailed clinical data of 361 patients were not available because of telephonic follow-up and 159 patients were lost to follow-up. Finally, 1177 patients with HBV-ACLF for whom complete follow-up data were available were included in this study (Figure 1). These included 616

(52.3%) patients with liver cirrhosis (cirrhosis group) and 561 (47.7%) patients without cirrhosis (non-cirrhosis group). Patients in the cirrhosis group were older than those in the non-cirrhosis group. Of note, the proportion of patients receiving antiviral treatment for HBV in our cohort was extremely low (20%). The proportions of patients in whom antiviral treatment and treatment with NAs was withdrawn were higher in the cirrhosis group compared with the non-cirrhosis group (P<0.001). Compared with other antiviral drugs, entecavir was more widely taken in the overall subjects. However, the proportion of patients on entecavir in the non-cirrhosis group was significantly higher than that in the cirrhosis group. The levels of AST, ALT, CHE, Fib, eGFR, FBG, serum Na, PLT, AFP, and HBV-DNA were significantly lower in the cirrhosis group compared with the non-cirrhosis group (P<0.001). Furthermore, patients in the cirrhosis group had higher liver prognostic scores than patients in the non-cirrhosis group, such as MELD score, MELD-Na, and CTP score (P<0.05) (Table 1).

Table 1
Baseline characteristics of study patients

Parameter	Total	Cirrhosis	Non-cirrhosis	*P*
	(n=1177)	(n=616)	(n=561)	
Age (years)	45.06 ±10.57	47.38 ±10.28	42.52 ±10.30	<0.001
Sex, male (%)	124 (10.5)	72 (11.7)	52 (9.3)	0.209
Antiviral therapy (%)	239 (20.3)	172 (27.9)	67 (12.0)	<0.001
NAs withdrawal (%)	171 (14.6)	115 (18.7)	56 (10.0)	<0.001
Drug resistance (%)	21 (1.8)	8 (1.3)	13 (2.3)	0.187
TBIL (μmol/L)	355.57 ±163.47	359.72 ±168.67	351.00 ±157.60	0.361
AST (U/L)	215.50 (107.75, 598.50)	158.50 (92.00, 360.75)	316.00 (136.00, 817.00)	<0.001
ALT (U/L)	304.50 (88.00, 854.75)	142.00 (65.00, 482.25)	580.00 (177.50, 1316.00)	<0.001
ALB (g/L)	34.46 ±17.49	34.65 ±23.75	34.27 ±4.80	0.709
PA (mg/L)	38.05 ±25.42	38.02 ±24.42	38.07 ±26.50	0.977
CHE (U/L)	4035.22 ±1885.37	3697.90 ±1882.33	4406.34 ±1819.41	<0.001
PT (sec)	28.03 ±11.92	28.21 ±9.10	27.82 ±14.41	0.572
INR	2.67 ±2.09	2.68 ±1.75	2.65 ±2.41	0.832
Fib (g/L)	1.56 (1.26, 1.96)	1.51 (1.19, 1.83)	1.65 (1.32, 2.09)	<0.001
BUN (mmol/L)	3.81 (2.74, 5.38)	4.15 (3.00, 6.02)	3.39 (2.48, 4.68)	<0.001
Cr (μmol/L)	83.11 ±61.82	87.23 ±54.99	78.57 ±68.30	0.016
eGFR	103.69 ±39.05	98.36 ±32.18	109.56 ±44.73	<0.001
FBG (mmol/L)	4.91 ±2.88	4.81 ±3.56	4.15 ±1.83	<0.001
Na (mmol/L)	136.13 ±5.87	135.55 ±5.24	136.77 ±6.43	<0.001
WBC (109/L)	7.09 (5.38, 9.39)	6.72 (4.94, 9.02)	7.31 (5.93, 9.90)	<0.001

Total bilirubin, TBIL; albumin, ALB; aspartate aminotransferase, AST; alanine aminotransferase, ALT; cholinesterase, CHE; prothrombin time, PT; alpha-fetoprotein, AFP; white blood cell, WBC; international normalized ratio, INR; fibrinogen, Fib; platelets, PLT; creatinine, Cr; blood urea nitrogen, BUN; estimated glomerular filtration rate, eGFR; fasting blood glucose, FBG; Child-Turcotte-Pugh, CTP; Model for End-Stage Liver Disease, MELD; 95% CI, 95% confidence interval; OR, odds ratio.

Parameter	Total	Cirrhosis	Non-cirrhosis	*P*
	(n=1177)	(n=616)	(n=561)	
NEU (%)	0.72±0.46	0.71 ±0.38	0.73±0.54	0.467
PLT (109/L)	117.77 ±74.32	96.61 ±54.73	140.97 ±85.29	<0.001
AFP (ng/mL)	34.85 (10.07, 96.85)	29.90 (10.21, 96.90)	35.50 (9.44, 102.90)	<0.001
lgHBVDNA	5.07 (3.51, 6.53)	4.52 (3.04, 6.12)	5.53 (4.20, 7.04)	<0.001
CTP score	10.89 ± 1.63	11.31 ± 1.48	10.42 ± 1.67	<0.001
MELD score	25.76 ± 6.67	26.48 ±6.69	24.97 ±6.56	<0.001
MELD-Na score	23.95 ± 12.41	25.55 ±11.94	22.18 ±12.69	<0.001

Total bilirubin, TBIL; albumin, ALB; aspartate aminotransferase, AST; alanine aminotransferase, ALT; cholinesterase, CHE; prothrombin time, PT; alpha-fetoprotein, AFP; white blood cell, WBC; international normalized ratio, INR; fibrinogen, Fib; platelets, PLT; creatinine, Cr; blood urea nitrogen, BUN; estimated glomerular filtration rate, eGFR; fasting blood glucose, FBG; Child-Turcotte-Pugh, CTP; Model for End-Stage Liver Disease, MELD; 95% CI, 95% confidence interval; OR, odds ratio.

3.2 Etiology of HBV-ACLF

Of the 1177 patients with HBV-ACLF in this study, 973 (83%) were associated only with HBV, and the remaining 204 (17%) had two or more etiologies. The top three causes were as follows: 68 cases (6%) with concomitant acute hepatitis E, 57 cases (5%) with alcoholic liver disease (ALD), and 41 cases (3%) with drug-induced liver injury (DILI) (Figure 2A). On further analysis of the precipitating events in patients with simple HBV-ACLF, the main cause was lack of antiviral treatment (734; 75%), followed by withdrawal of nucleoside (acid) analogues (NAs) (171; 18%), antiviral drug resistance (21; 2%), and non-viral factors (47; 5%) (Figure 2B).

3.3 90-day transplantation-free mortality of HBV-ACLF patients

Out of 1177 HBV-ACLF patients in the study, 130 cirrhotic patients and 47 non-cirrhotic patients received liver transplantation within 90 days. A total of 431 (43.1%) patients died within 90 days, including 289 in the cirrhosis group and 142 in the non-cirrhosis group. The 90-day transplantation-free mortality rate and liver transplantation rate in the cirrhosis group was significantly higher than that in the non-cirrhosis group (59.5% vs. 27.6% and 21.1% vs. 8.4%, $P<0.001$) (Figure 3).

3.4 Occurrence of clinical adverse events

New decompensated liver cirrhosis, HCC, and ACLF reoccurrence in patients who survived more than 90 days were identified as clinical adverse events. The cirrhosis group had significantly higher incidence of new decompensated liver cirrhosis and HCC than the non-cirrhosis group (*P*=0.005, *P*=0.022). However, there was no significant between-group difference with respect to the incidence of ACLF reoccurrence (*P*=0.057) (Table 2).

Table 2
Occurrence of clinical adverse events

	Total (n=630)	**CIR (n=256)**	**Non-CIR (n=374)**	*P*
Decompensated cirrhosis	42(3.6)	31(5.0)	11(2.0)	0.005
ACLF	10(1.6)	7(2.7)	3(0.8)	0.057
HCC	9(1.4)	7(2.7)	2(0.5)	0.022

3.5 Cumulative survival rate of HBV-ACLF patients

Kaplan-Meier survival analysis was performed to compare survival rates between the cirrhosis group and the non-cirrhosis group. The cumulative survival rates of overall patients at 12, 36, and 60 months were 63%, 61% and 50%, respectively. The corresponding cumulative survival rates at 12, 36, and 60 months in the cirrhosis group were lower than these in the non-cirrhosis group (55%, 45%, and 36% vs.72%, 69%, and 62%). The between-group difference in the cumulative survival rate was statistically significant (log-rank test, *P*<0.001) (Figure 4).

3.6 Risk factors for 90-day mortality in HBV-ACLF patients

We assessed the correlation between clinical parameters and 90-day mortality in HBV-ACLF patients (Table 3). Univariate logistic regression analysis revealed significant between-group differences with respect to age, liver cirrhosis at admission, hepatic encephalopathy (HE), NAs withdrawal, AST level, CHE level, TBIL level, PT level, Cr level, PLT level, FBG level, MELD score, and ALSS therapy (P<0.05). These variables were then subjected to multivariate regression. In the multivariate logistic regression analysis, age, HE, liver cirrhosis at admission, NAs withdrawal, TBIL level, and PT level were identified as independent predictors of 90-day mortality in HBV-ACLF patients (P<0.05).

Table 3
Risk factors for 90-day mortality in HBV-ACLF patients

	Univariate analysis	P value	Multivariate analysis	P value
	COR (95%CI)		AOR (95%CI)	
Age	1.060 (1.047, 1.074)	<0.001	1.049 (1.035, 1.063)	<0.001
Cirrhosis	2.190 (1.694, 2.839)	<0.001	1.906 (1.448, 2.509)	<0.001
HE	5.061 (3.718, 6.934)	<0.001	3.545 (2.520, 4.986)	<0.001
NAs withdrawal	1.665 (1.165, 2.374)	0.005	1.845 (1.267, 2.686)	0.002
HBV+ ALD	0.484 (0.245, 0.956)	0.037		
AST	1.000 (1.000, 1.000)	0.002		
CHE	1.076 (1.059, 1.094)	<0.001		
TBIL	1.003 (1.003, 1.004)	0.001	1.003 (1.002, 1.004)	<0.001
PT	1.486 (1.317, 1.684)	<0.001	1.054 (1.037, 1.072)	<0.001
Cr	0.978 (0.973, 0.982)	<0.001		
FBG	0.924 (0.898, 0.950)	<0.001		
PLT	0.998 (0.997, 0.998)	<0.001		
lgHBV DNA	1.186 (1.155, 1.220)	<0.001		
MELD score	1.155 (1.127, 1.183)	<0.001		
ALSS	0.868 (0.766, 0.977)	0.022		

HE; nucleoside (acid) analogues, NAs; alcoholic liver disease, ALD; aspartate aminotransferase, AST, CHE; Total bilirubin, TBIL; prothrombin time, PT; creatinine, Cr; platelets, PLT; fasting blood glucose, FBG; Model for End-Stage Liver Disease, MELD; artificial liver support system, ALSS; adjusted odds ratio, AOR; crude odds ratio, COR.

3.7 Risk factors for long-term prognosis of HBV-ACLF patients

New decompensated liver cirrhosis, HCC, ACLF reoccurrence, and mortality of patients who survived more than 90 days were identified as signs of disease progression. The baseline clinical data of patients were analyzed in the logistic regression model. The results showed that age, liver cirrhosis at admission and HE were independent risk factors for disease progression, which were consistent with the risk factors for 90-day mortality. Remarkably, liver cirrhosis at admission (3.675, 95% CI: 2.408–6.594) was a strong risk factor for long-term outcomes in the HBV-ACLF patients. Moreover, unlike risk factors for 90-day mortality,

PT level, TBIL level, and MELD score showed no significant correlation with long-term prognosis of HBV-ACLF patients (Table 4).

Table 4
Risk factors for long-term prognosis in HBV-ACLF patients

	Univariate analysis	P value	Multivariate analysis	P value
	COR (95%CI)		AOR (95%CI)	
Age	1.055 (1.034, 1.077)	<0.001	1.043 (1.018, 1.068)	0.001
Cirrhosis	3.973 (2.553, 6.352)	<0.001	3.675 (2.408, 6.594)	<0.001
AST	0.999 (0.999, 1.000)	0.006		
CHE	1.000 (1.000, 1.000)	<0.001		
TBIL	1.001 (1.000, 1.002)	0.210		
PT	1.004 (0.985, 1.019)	0.603		
Cr	1.002 (0.999, 1.005)	0.197		
PLT	0.992 (0.988, 0.996)	<0.001	0.994 (0.989, 0.999)	0.020
lgHBV DNA	0.865 (0.776, 0.963)	0.009		
MELD score	1.075 (1.031, 1.120)	0.001		
ALSS	0.542 (0.283, 0.963)	0.049		

4. Discussion

ACLF is an acute hepatic injury syndrome occurring in the backdrop of chronic hepatitis or cirrhosis. Because of the different definitions of ACLF used in Eastern and Western countries, there are no standardized diagnostic criteria and prognostic models for these patients. This study focused on the 90-day transplantation-free mortality, five-year survival rate, and risk factors for adverse outcomes in patients with HBV-ACLF in south China.

HBV reactivation is the main etiology of acute injury in HBV-ACLF patients in Asia. Conversely, infection is the leading etiology in America and European countries [16–17]. In addition to HBV infection, 204 cases (17%) of HBV-ACLF patients had more than one etiologies, such as overlapping acute hepatitis E (68 cases; 6%), ALD (57 cases; 5%), and DILI (41 cases; 3%). Compared with the previous studies [18], the proportion of HBV-ACLF patients combined with ALD in this study was lower (5% vs 15.1%), and the incidence of DILI was slightly higher (3% vs 2.8%). Furthermore, our results suggested that HBV-ACLF combined with acute hepatitis E, or DILI had no significant effect on the 90-day transplantation-free

mortality rate in univariate and multivariate logistic analyses. Significantly, the proportion of patients receiving antiviral treatment for HBV in our cohort was extremely low (20%), which is comparable with the national figures for China (10.8%) [19]. Moreover, the proportion of patients in the non-cirrhosis group who received antiviral therapy was higher than that in the cirrhosis group. However, the proportion of patients who self-discontinued antiviral therapy was also higher in the cirrhosis group, indicating that patients with cirrhosis show poor medication compliance and lack regular follow-up. Given the current status of antiviral therapy of HBV patients in China, it is crucial to implement a strategy for screening and dissemination of antiviral drugs across the country, which will help reduce the incidence of HBV-ACLF.

In this study, cirrhotic patients had a significantly higher 90-day transplantation-free mortality than non-cirrhotic patients (27.6% vs. 59.5%). Compared with a European multicenter study in 2011, the 90-day transplantation-free mortality of cirrhotic patients was slightly higher in our study (59.5% vs 51.2%) [20]. However, the aforementioned result was inconsistent with that from a large study in China [21]. In the Chinese Group on the Study of Severe Hepatitis B (COSSH) study, which was conducted between 2013 and 2016, the 90-day transplantation-free mortality of HBV-ACLF patients with cirrhosis was higher than that of patients in the current study (69.7% vs. 59.5%). Collectively, despite the development of antiviral drugs and ALSS therapy in recent years, the short-term outcome of ACLF have not improved significantly compared with these reported by previous studies. Moreover, we found that the 5-year cumulative mortality rate in whole patients was quite close to the 90-day transplantation-free mortality (50.0% vs. 43.1%), which indicated that HBV-ACLF patients who survived more than 90 days had a favorable prognosis in the late stage. Compared with another cohort study in China [7], the long-term survival rate in this study was significantly lower (62% vs. 97.2%), which may be attributed to the exclusion of patients who died within 3 months from the previous study. At present, there are no reports of 5-year cumulative survival rate in patients with HBV-ACLF in China. Therefore, this study will fill the gap in China.

Most notably, the results showed that liver cirrhosis at admission, older age, and HE were independent risk factors for both short-term and long-term outcomes. Several studies have found a correlation between cirrhosis and poor prognosis in patients with HBV-ACLF [22–24]. We also found that cirrhotic ACLF patients had significantly higher incidence of new decompensated liver cirrhosis and HCC than the non-cirrhotic patients in the long-term outcomes ($P<0.05$). Of note, withdrawal of NAs was an important acute injury event [25]. Compared with other acute intrahepatic etiologies, patients who discontinued NAs were shown to have a worse short-term prognosis [26]. In a study by Shi et al. [27], withdrawal of NAs was a strong independent risk factor for 90-day mortality in HBV-ACLF patients, which was consistent with our study. However, there is no prognostic model for HBV-ACLF patients that includes the intrahepatic precipitating factor. Our study suggests that, in addition to liver function indices, factors such as cirrhosis and hepatic precipitating events should be included in the prognostic models of HBV-ACLF patients. In all, early active intervention and long-term surveillance are essential for cirrhotic patients who discontinued antivirals and have HE at onset.

This was a single-center retrospective study with certain limitations. First, ACLF patients were assessed using the APASL diagnostic criteria and not those of EASL-CLIF, which may limit the generalizability of our results. Second, the rate of loss to follow-up was high. Besides, most patients were followed up via telephone; thus the results may have been influenced by recall bias. These limitations need to be addressed in a multicenter prospective study.

In summary, the proportion of HBV-ACLF patients receiving antiviral treatment was extremely low in south China. HBV combined with acute hepatitis E, or DILI had no significant effect on the short-term mortality rate in HBV-ACLF patients. Remarkably, the effect of withdrawal of NAs and cirrhosis on short-term outcomes cannot be ignored. No significant improvement in the short-term prognosis of HBV-ACLF patients was observed compared with previous studies. Wider access to antiviral treatment and long-term surveillance of HBV patients are key imperatives to reduce the incidence of HBV-ACLF.

Abbreviations

Hepatitis B virus, HBV; chronic hepatitis B, CHB; Acute-on-chronic liver failure, ACLF; artificial liver support system, ALSS; hepatocellular carcinoma, HCC; liver transplantation, LT; hepatic encephalopathy, HE; hepatorenal syndrome, HRS; alcoholic liver disease, ALD; drug-induced liver injury, DILI; nucleoside (acid) analogues, NAs; total bilirubin, TBIL; albumin, ALB; aspartate aminotransferase, AST; alanine aminotransferase, ALT; cholinesterase, CHE; prothrombin time, PT; alpha-fetoprotein, AFP; white blood cells, WBC; international normalized ratio, INR; fibrinogen, Fib; platelets, PLT; creatinine, Cr; blood urea nitrogen, BUN; estimated glomerular filtration rate, eGFR; fasting blood glucose, FBG; Child-Turcotte-Pugh, CTP; Model for End-Stage Liver Disease, MELD; the Chinese Group on the Study of Severe Hepatitis B, COSSH; 95% CI, 95% confidence interval; OR, odds ratio; adjusted odds ratio, AOR; crude odds ratio, COR.

Declarations

Ethics approval and consent to participate

The study protocol conforms to the ethical principles of the 1975 Declaration of Helsinki (6th revision, 2008), and was approved by the Medical Ethics Committee of the Third Affiliated Hospital of Sun Yat-Sen University (approval number: [2020]02-009-01). All patients provided written informed consent and informed consent was obtained from legal guardians of dead patients for this retrospective study.

Consent for publication□Not applicable□

Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon request.

Competing interest

We certify that none of the authors have any conflicts of interest with regards to this research.

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Author Contributions

All authors contributed to the concept and design, patient recruitment, and follow-up of this study. Wenxiong Xu and Lu Wang had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Xuejun Li, Dabiao Chen, Yeqiong Zhang, Yuanli Chen, Juan Wang and Qiumin Luo were responsible for the acquisition, analysis, and interpretation of data. Lu Wang drafted the manuscript. Liang Peng and Chan Xie obtained the funding, and took responsibility for the supervision.

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Figures

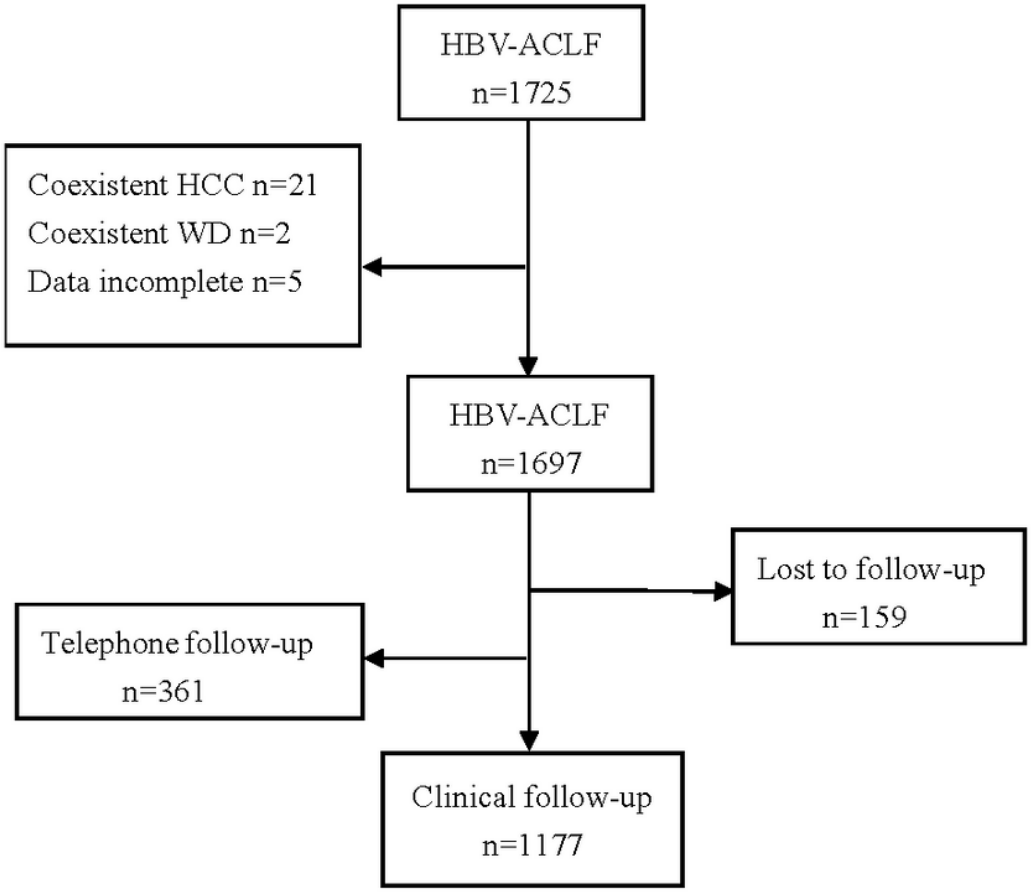
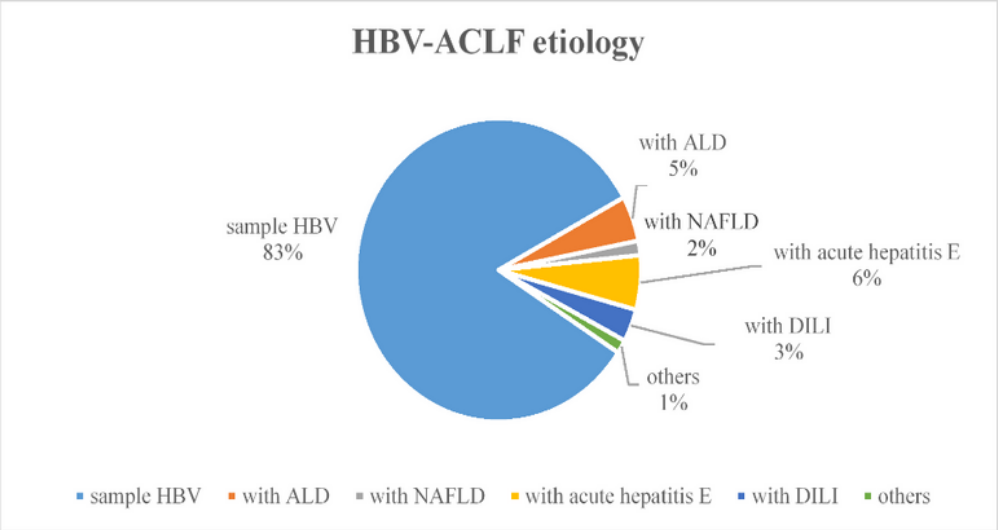


Figure 1

Patient screening flowchart

(A)



(B)

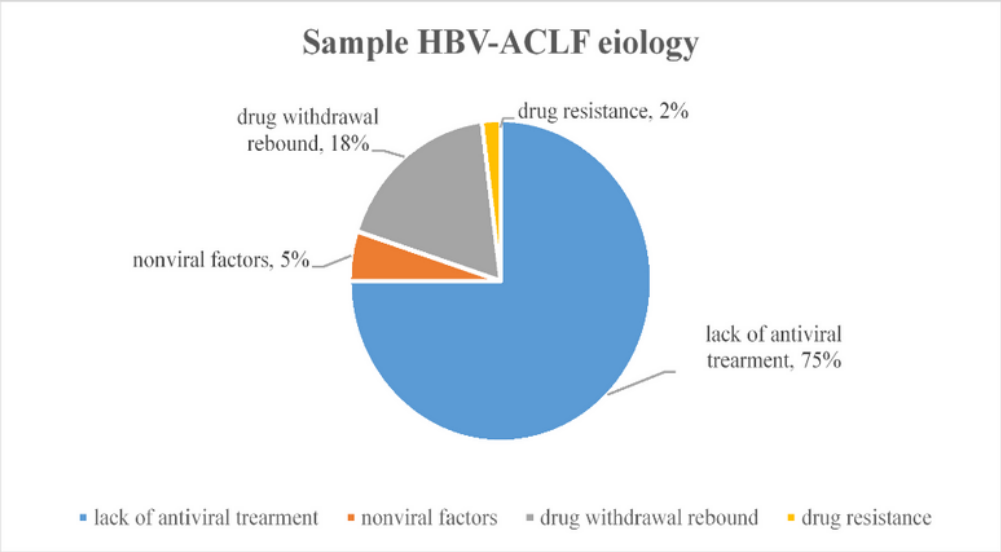


Figure 2

(A) HBV-ACLF etiology; (B) Simple HBV-ACLF etiology

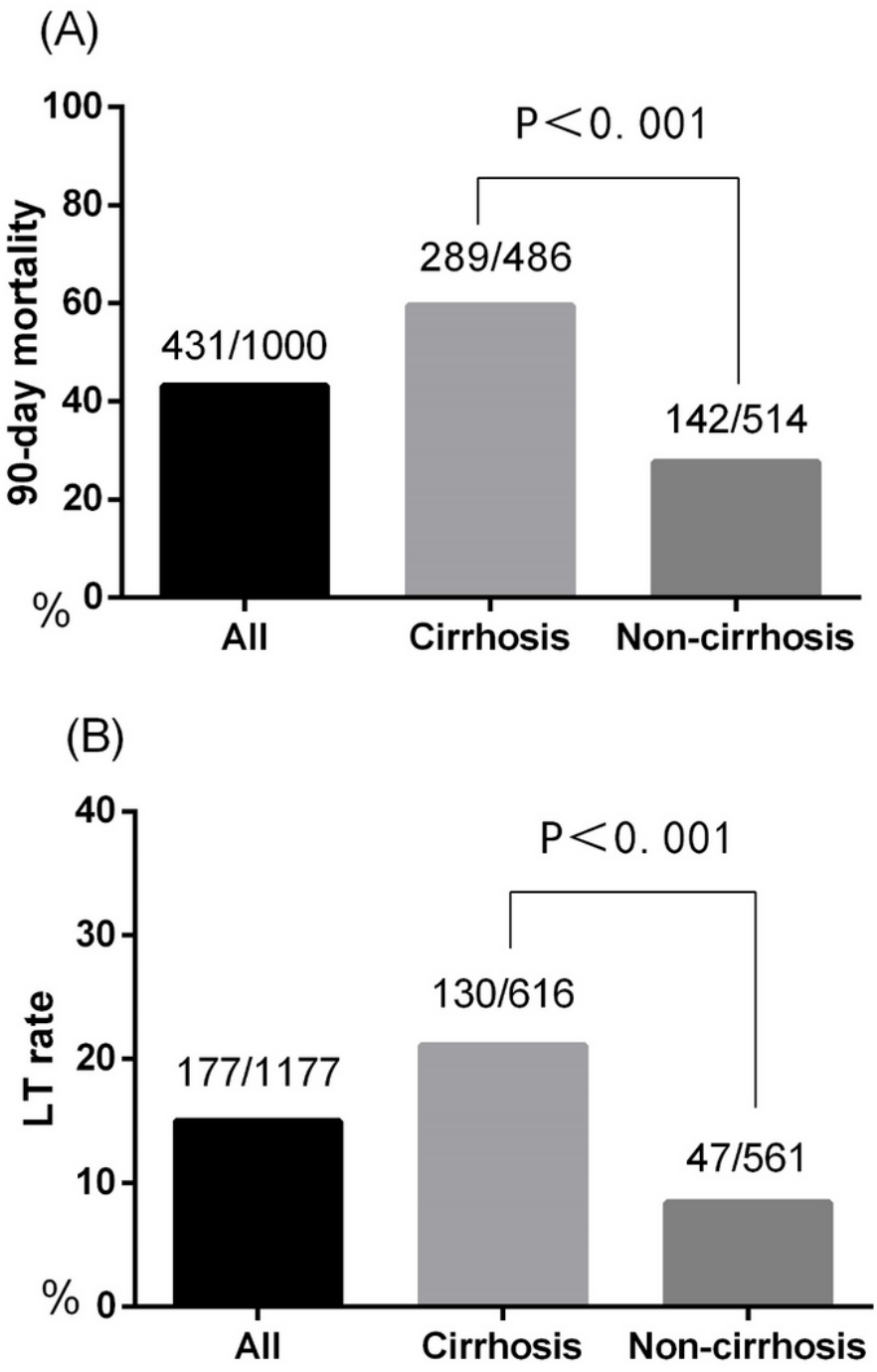


Figure 3

(A) 90-day transplantation -free mortality in HBV-ACLF patients ; (B) Liver transplantation rate in HBV-ACLF patients

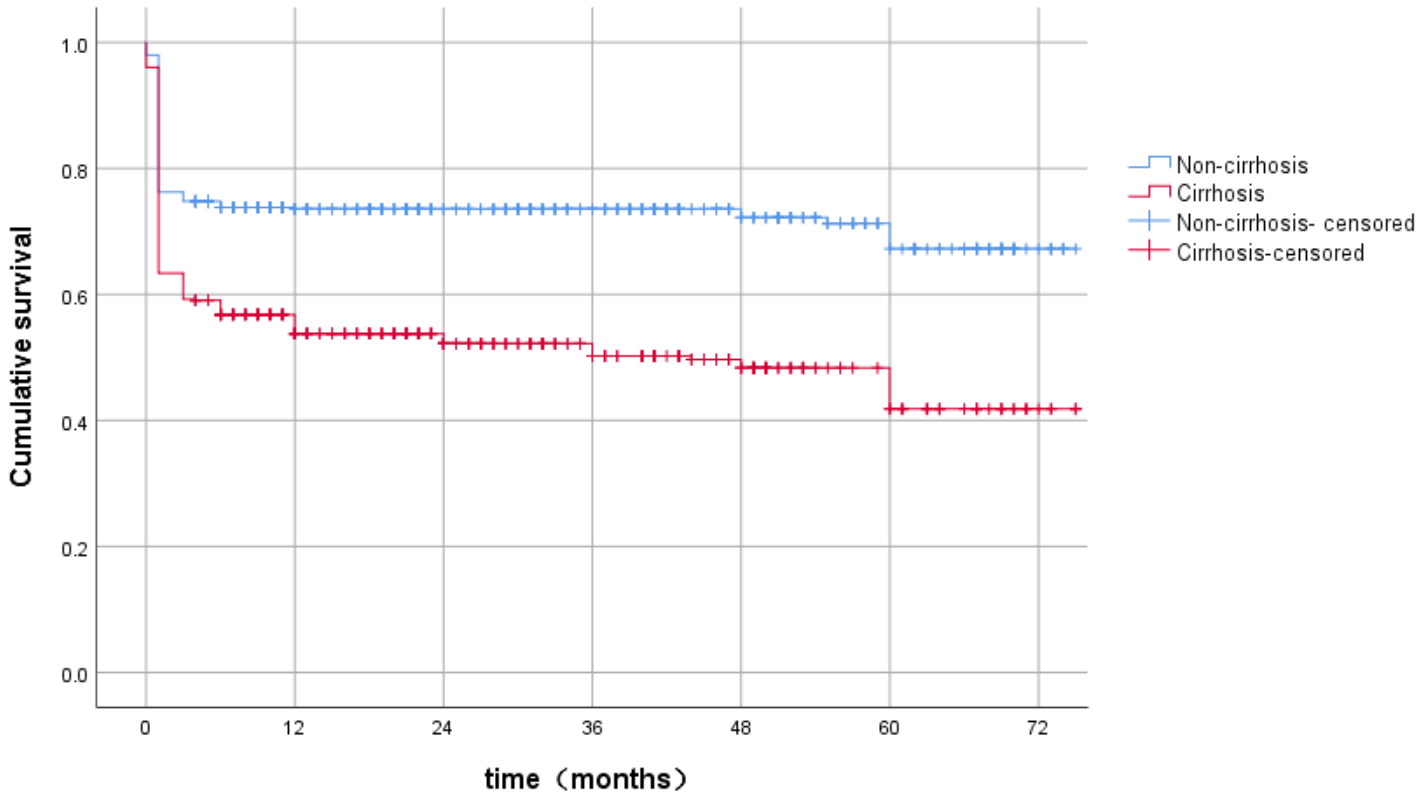


Figure 4

HBV-ACLF patient cumulative survival rates