Bacterial infection is a risk factor for progression to acute-on-chronic liver failure in patients with severe hepatitis flare of HBV-related compensated liver cirrhosis

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Research Article

Keywords: compensated liver cirrhosis, hepatitis flare, bacterial infection, hepatic decompensation, acute-on-chronic liver failure, hepatitis B

Posted Date: May 18th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1654575/v1

Abstract

Aims

The aims of this study were to investigate the risk factors for bacterial infection (BI) and the association of BI with progression to acute-on-chronic liver failure (ACLF) in patients with severe hepatitis flare of hepatitis B virus (HBV)-related compensated liver cirrhosis.

Methods

237 patients with HBV-related compensated liver cirrhosis and severe hepatitis flare were retrospectively reviewed. Baseline demographics characteristics, biochemical were compared between patients with and without occurring of BIs and progression to ACLF. Univariate and multivariate logistic regression were used to identify independent risk factors associated with development of BI and ACLF.

Results

48 (20.3%) patients progressed to ACLF after admission. 101 (42.6%) patients progressed to hepatic decompensation (HD) and 52 (20.3%) patients had BIs before development of ACLF. Patients with BIs had significantly higher incidence of HD (73.1%) and ACLF (46.2%) than those without BIs (34.1% and 13.0%, respectively, $P < 0.01$). Total bilirubin (TBil, OR = 1.003, 95% CI: 1.000-1.006) and Child-turcotte-pugh (CTP) score (OR = 1.745, 95% CI: 1.345–2.265) were identified as independent risk factors associated with BI. BI (OR = 7.113, 95% CI: 2.714–18.644), gamma-glutamyl transpeptidase (OR = 0.094, 95% CI: 0.988–0.999), TBil (OR = 1.004, 95% CI: 1.001–1.007), international normalized ratio (OR = 114.05, 95% CI:17.4-746.3) and platelet (OR = 0.984, 95% CI: 0.972–0.996) were independent risk factors associated with progression to ACLF.

Conclusion

High level of TBil and CTP score are risk factors associated with occurring of BI and BI is a risk factor related with progression to ACLF in patients with HBV-related compensated liver cirrhosis and severe hepatitis flare.

Introduction

During the long course of chronic hepatitis B virus (HBV) infection, patients will experience hepatitis flares with various degrees of liver injury [1, 2]. Hepatitis flare may occurs spontaneously or triggered by other factors such as co-infection with other hepatitis virus, treatment and withdrawal of chemotherapy, nucleot(s)ide analogues, interferon, etc. Spontaneous hepatitis flare occurs frequently in patients with

chronic HBV infection in clinical practice[2]. Repeated or sustained hepatitis flares will result in liver fibrosis or even liver cirrhosis. The patients with severe hepatitis flare are at high risk to further progress to hepatic decompensation (HD) and acute-on-chronic liver failure (ACLF)[3, 4]. In China and other high HBV epidemic countries, severe spontaneous hepatitis flare in patients with or without HBV-related liver cirrhosis is one of the most common precipitating events of ACLF[5].

Patients with chronic HBV infection often have different degrees of liver fibrosis, with compensated liver cirrhosis as a significant stage in this process. When patients with compensated liver cirrhosis progress to HD and ACLF, the complications of liver cirrhosis and extrahepatic organ failures have marked impacts on prognosis[6]. Therefore, the pathogenesis involved in the disease progression before and after ACLF development are different[7]. Most previous studies focus on the prognosis prediction in patients with ACLF[8], the clinical, biochemical and viral characteristics before progression to ACLF have not been well elucidated[9].

ACLF can developed from patients with different underlying liver diseases[4, 6], World Gastroenterology Organization working party suggested ACLF be classified into three types according to the underlying chronic liver disease, type A from non-cirrhotic liver disease, type B from compensated cirrhosis and type C from decompensated cirrhosis[10]. Recently a few studies found patients with ACLF developed from different underlying diseases had different prognosis[11, 12], it is therefore clinically important to understand the clinical characteristics of patients with ACLF developed from different underlying liver diseases.

It is well established that bacteria infection (BI) is a common trigger for HD and ACLF in patients with decompensated liver cirrhosis[13], but the role of BI in patients with compensated liver cirrhosis has been less understood. A recent study found that in patients with compensated liver cirrhosis and clinically significant portal hypertension[14], BI was associated with high prevalence of HD and poor prognosis during a 36 months of follow-up. However, most patients in that study were hepatitis C virus-related liver cirrhosis without hepatitis flare, moreover, whether BI impaired the prognosis of patients via increasing the development of ACLF has not been studied in that study. In another study, no increased risk of HD was observed in patients with BI and HBV related compensated cirrhosis undergoing antiviral therapy[15]. These studies indicated that the impacts of BI on the poor outcomes of patients with compensated liver cirrhosis are limited to these with advanced acute and chronic liver injury, whether BI confers risk of ACLF in patients with compensated liver cirrhosis during severe hepatitis flare remains unknown. In this study we retrospectively studied the risk factors of BI and the association of BI with progression to ACLF in patients with HBV-related compensated liver cirrhosis and severe hepatitis flare.

Patients And Methods

Study population

The flow chart of the study group selection process is presented in Figure 1. The inclusion criteria were patients with severe hepatitis flare of HBV-related compensated liver cirrhosis and did not fulfilled the diagnostic criteria of ACLF on admission. 364 hospitalized patients at the Affiliated Hospital of Zunyi Medical University from January 2011 to March 2020 were included. 127 patients were excluded by the exclusion criteria, which included coinfection with hepatitis A, C, D, or E viruses; coexistence with other liver diseases including alcoholic liver disease, hepatocellular carcinoma, drug-induced hepatitis, autoimmune hepatitis, Wilson disease, or serious diseases involving other organ systems; pregnancy; patients who had been treated with chemotherapy or had nucleot(s)ide analogues withdrawal within 1 year. The patients with using of proton pump inhibitors before occurring of BI were excluded [16]. A total of 237 patients were finally included in this study.

Diagnostic criteria of severe hepatitis flare, ACLF, liver cirrhosis and BI

Severe hepatitis flare was defined as alanine aminotransferase (ALT) >5× the upper limit of normal (ULN, 200 IU/L) and total bilirubin (TBil) ≥5×ULN (85 μmol/L) or prothrombin activity (PTA) 40%-60% in patients with HBV-related compensated liver cirrhosis.

ACLF was diagnosed as the criteria proposed by Asian Pacific Association for the Study of the Liver (APASL), which includes the recent development of jaundice (TBil ≥5×ULN) and coagulopathy (PTA<40% or international normalized ratio [INR] ≥1.5), complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease [17].

The diagnosis of cirrhosis was based on previous liver biopsy findings or a composite of clinical signs and findings provided by laboratory tests, endoscopy, radiologic imaging, and fibroscanning. HD was defined as development of ascites, bleeding due to portal hypertensive sources, or overt hepatic encephalopathy[18]. Patients with no previous decompensation were included in this study as compensated liver cirrhosis.

BIs were diagnosed as per the following criteria [19]: (1) spontaneous bacterial peritonitis (SBP): ascitic fluid polymorphonuclear cells >250/mL or positive ascitic fluid cultures; (2) bacteremia: positive blood cultures without a source of infection; (3) pneumonia: new pulmonary infiltrate with fever (>38°C) with any respiratory symptoms (e.g., cough, sputum, dyspnea) or any findings on auscultation (rales or crepitation), or white blood cell (WBC) counts >10×10^9/L or <4×10^9/L; (4) urinary tract infection (UTI): more than 10 leucocytes per high power field in urine and positive urine cultures or significant leucocyte count per field without positive cultures; and (5) other bacterial infections, including skin infections, intra-abdominal infections, and infections of unknown origin. In patients with suspected respiratory infections and infections with unknown origin, the IgM antibody to Influenza virus A and B, Parainfluenza virus, Adenovirus, Mycoplasma and Chlamydia and DNA of Epstein-Barr virus and Cytomegalovirus were detected to exclude the infections induced by these pathogens. In addition, the diagnosis of BI was made by two independent investigators. If there was any discrepancy between the two investigators, a senior investigator was requested to make decision.

Candidate predictor variables and treatment schedule

The demographics, clinical and laboratory variables, and imaging findings of patients were retrospectively collected. In addition, liver disease severity was assessed using the Model for End-Stage Liver Disease (MELD) -Na score, Child-turcotte-pugh (CTP) score and chronic liver failure-sequentail organ failure assessment (CLIF-SOFA) score [6]. Standard medical care including antiviral therapy with lamivudine, entecavir, or telbivudine was administered to all patients according to HBV replication levels and patient willingness. Patients with BI were treated with antibiotic therapy following current recommendations was initiated[20].

The end point of study was the development of ACLF within 28 days after admission. The BIs and HD occurring before the development of ACLF were recorded. The protocol conformed to the provisions of the Declaration of Helsinki and was approved by the Human Ethical Committee of the Affiliated Hospital of Zunyi Medical University.

Statistical analysis

Statistical analyses were performed using SPSS version 19.0 (IBM Corp., Armonk, NY, USA). Patient characteristics were compared between patients with and without progression to ACLF and BIs using c^2 tests for categorical variables, t tests for variables with normal distribution, and Mann-Whitney U tests for variables with an abnormal distribution. Continuous variables are summarized as mean ± standard deviation (SD) or median (interquartile range, IQR), respectively. Categorical variables are displayed as counts or percentages (%). Logistic regression analysis was used for univariate and multivariate analyses to identify the risk factors associated with progression to BI and ACLF. $P < 0.05$ was considered statistically significant.

Results

1. Patient characteristics

237 patients with compensated liver cirrhosis and severe hepatitis flare were included in this study. They were mostly male (209, 88.2%), with average age of 43 years old. 48 (20.3%) patients progressed to ACLF within 28 days after admission. 101 (42.6%) patients progressed to HD before progression to ACLF. The mean number of days between hospital admission and development of ACLF was 6.1 days (range, 1 ~ 14 days).

Before development of ACLF, 52 (21.9%) patients had 57 episodes of BI, including 33 patients with digestive infections (20 patients with SBP); 9 patients with respiratory infections (7 patients with pneumonia); 4 patients with SBP and pneumonia; 3 patients with UTIs; 1 patient with phlegmon; 1 patient with pneumonia and acute suppurative otitis media; and 1 patient with Brucellosis infection. 41 patients had community-acquired infection and 11 had nosocomial infection. 2 patients had culture-positive

infections, 1 patient with Klebsiella pneumoniae isolated from phlegm fluid, another with Brucellosis isolated from blood.

2. The risk factors associated with bacteria infection in patients with HBV-related compensated liver cirrhosis during severe hepatitis flare

As showed in Table 1, the patients with BIs had significantly higher levels of alkaline phosphatase (ALP), TBil, urea nitrogen, prothrombin time (PT), INR, white blood cell (WBC), neutrophil (NEUT), neutrophil-to-lymphocyte ratio (NLR), CTP score, CLIF-SOFA score and MELD-Na score, significantly lower levels of albumin (ALB), sodium (Na^+) and PLT than those without BIs.

Table 1
Clinical and biochemical characteristics of patients with and without bacteria infections in patients with HBV-related compensated liver cirrhosis during severe hepatitis flare

	Total (n = 237)	With BIs (n = 52)	Without BIs (n = 185)	*P*
Age (years)	43.0 ± 11.8	45.37 ± 11.71	42.35 ± 11.82	0.105
Males	209 (88.2)	49 (94.2)	160 (86.5)	0.094
ALT (U/L)	586.0 (296.0, 974.5)	413.0 (222.5, 837.3)	598.0 (332.0,1032.0)	0.018
AST (U/L)	542.0 (287.0, 875.0)	381.0 (231.3, 873.0)	597.0 (309.5, 875.0)	0.105
GGT (U/L)	145.0 (94.0, 231.5)	144.5 (87.3, 226.0)	151.0 (97.0, 239.5)	0.365
ALP (U/L)	190.68 ± 75.59	209.54 ± 65.307	185.38 ± 77.57	0.042
TBil (μmol/L)	163.9 (89.8, 280.2)	284.8 (125.1, 371.9)	153.8 (83.2, 231.5)	0.000
ALB (g/L)	33.64 ± 5.08	31.36 ± 5.36	34.28 ± 4.82	0.000
Na^+ (mmol/L)	136.96 ± 3.12	136.00 ± 3.05	137.23 ± 3.09	0.011
BUN (mmol/)	4.2 (3.3, 4.9)	4.4 (3.6, 6.9)	4.1(3.2, 4.8)	0.011
Cr (μmol/L)	74.0 (66.0, 82.0)	76.0 (69.0, 88.0)	73.0 (66.0, 82.0)	0.160
PT (s)	16.14 ± 2.77	16.99 ± 2.85	15.90 ± 2.71	0.012
INR	1.36 ± 0.26	1.44 ± 0.28	1.34 ± 0.24	0.009
PTA	58.7(50.4, 76.5)	58.7 (47.4, 75.1)	58.7 (50.6, 77.0)	0.592
WBC (10^9/L)	5.0 (3.9, 6.6)	7.1 (5.4, 8.3)	3.7 (4.8, 5.8)	0.000
NEUT (10^9/L)	3.41 ± 1.78	4.93 ± 2.01	2.98 ± 1.45	0.000
LYM (10^9/L)	1.3 (0.9, 1.7)	1.3 (0.8, 1.6)	1.3 (1.0, 1.7)	0.307
NLR	2.85 ± 2.14	4.62 ± 3.06	2.35 ± 1.47	0.000
PLT (10^9/L)	113.3 ± 52.3	128.7 ± 58.1	108.9 ± 49.8	0.016

Note: Data are presented as mean ± SD, n (%), or median (interquartile range). *P*: BIs vs. Non-BIs. ACLF, acute-on-chronic liver failure; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BI, bacteria infection; BUN, urea nitrogen; CLIF-SOFA, chronic liver failure-sequentail organ failure assessment; CTP, child-turcotte-pugh; Cr, creatinine; GGT, glutamine transpeptidase; HD, hepatic decompensation; INR, international standardization ratio; LYM, lymphocyte; MELD-Na, model for end-stage liver disease-Na score; Na+, sodium; NEUT, neutrophil; NLR, neutrophil-to-lymphocyte ratio; PLT, platelet; PT, prothrombin time; PTA, prothrombin activity, TBil, total bilirubin; WBC, white blood cell.

	Total (n = 237)	With BIs (n = 52)	Without BIs (n = 185)	*P*
lgHBV DNA (copies/ml)	3.96 ± 2.60	6.05 ± 1.77	6.09 ± 1.51	0.867
CTP score	10.02 ± 1.42	10.96 ± 1.47	9.75 ± 1.29	0.000
MELD-Na score	16.93 ± 5.38	19.66 ± 6.08	16.16 ± 4.92	0.000
CLIF-SOFA score	4.85 ± 1.52	5.63 ± 1.68	4.63 ± 1.40	0.000
HD	101 (42.6)	38 (73.1)	63 (34.1)	0.000
ACLF	48 (20.3)	24 (46.2)	24 (13.0)	0.000

Note: Data are presented as mean ± SD, n (%), or median (interquartile range). *P*: BIs vs. Non-BIs. ACLF, acute-on-chronic liver failure; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BI, bacteria infection; BUN, urea nitrogen; CLIF-SOFA, chronic liver failure-sequentail organ failure assessment; CTP, child-turcotte-pugh; Cr, creatinine; GGT, glutamine transpeptidase; HD, hepatic decompensation; INR, international standardization ratio; LYM, lymphocyte; MELD-Na, model for end-stage liver disease-Na score; Na+, sodium; NEUT, neutrophil; NLR, neutrophil-to-lymphocyte ratio; PLT, platelet; PT, prothrombin time; PTA, prothrombin activity, TBil, total bilirubin; WBC, white blood cell.

In univariate logistic regression analysis we did not included WBC, NEUT and NLR because significant elevation of these index were the results of BI. Univariate logistic regression analysis revealed that ALB, TBil, Na^+, PT, INR, PLT, CTP, CLIF-SOFA and MELD-Na score were risk factors associated with BI. Multivariate logistic regression analysis showed that TBil (OR = 1.003, 95% CI: 1.000-1.007) and CTP score (OR = 1.745, 95% CI: 1.345–2.265) were independent risk factors associated with BI in patients with HBV-related compensated liver cirrhosis during severe hepatitis flare (Table 2).

Table 2
Univariate and multivariate analysis of the risk factors associated with bacteria infections in patients with HBV-related compensated liver cirrhosis during severe hepatitis flare

Variables	Univariate analysis				Multivariate analysis			
	β	OR	95% CI	*P*	*β*	OR	95% CI	*P*
ALB	-0.120	0.087	0.831–0.947	0.000				
TBil	0.004	1.004	1.002–1.006	0.000	0.003	1.003	1.001–1.006	0.037
Na^+	-0.124	0.884	0.800-0.975	0.014				
PT	0.132	1.142	1.020–1.278	0.022				
INR	1.585	4.878	1.455–16.35	0.010				
PLT	0.007	1.007	1.001–1.012	0.018				
CTP score	0.685	1.985	1.525–2.582	0.000	1.745	1.692	1.345–2.265	0.000
MELD-Na score	0.122	1.130	1.062–1.202	0.000				
CLIF-SOFA score	0.453	1.572	1.257–1.957	0.000				

Note: ALB, albumin; CI, confidence interval; CLIF-SOFA, chronic liver failure-sequentail organ failure assessment; CTP, child-turcotte-pugh; INR, international standardization ratio; MELD-Na, model for end-stage liver disease-Na score; Na+, sodium; OR, odds ratio; PLT, platelet; PT, prothrombin time; TBil, total bilirubin.

3. Bacteria infections were associated with progression to hepatic decompensation and acute-on-chronic liver failure

As showed in Fig. 2, among 52 patients with BIs, 24 (46.2%) patients progressed to ACLF within 28 days after admission, which were significantly higher those in patients without BIs (13.0%, $P < 0.01$). Before progression to ACLF, 38 (73.1%) patients with BIs had HD, which was also significant higher than those in patients without BIs (34.1%, $P < 0.01$) .

4. Bacteria infection was one of the risk factors associated with progression to acute-on-chronic liver failure

As showed in Table 3, the patients with progression to ACLF after admission had significantly higher levels of ALP, TBil, WBC, INR, CTP score, CLIF-SOFA score and MELD-Na score, significantly lower levels of glutamine transpeptidase (GGT), ALB, Na^+, PTA and PLT than those without progression to ACLF.

Table 3
Clinical and biochemical characteristics of patients with and without progression to acute-on-chronic liver failure in patients with HBV-related compensated liver cirrhosis during severe hepatitis flare

Variables	Total (n = 237)	Non-ACLF (n = 189)	ACLF (n = 48)	*P*
Age (years)	43.0 ± 11.8	43.3 ± 11.9	42.0 ± 11.9	0.484
Males	209 (88.2)	165 (87.3)	44 (91.7)	0.403
ALT (U/L)	586.0 (296.0, 974.5)	609.0 (314.5, 989.5)	455.0 (213.5, 914.3)	0.044
AST (U/L)	542.0 (287.0, 875.0)	577.0 (289.5, 875.0)	415.0 (213.3, 880.0)	0.380
GGT (U/L)	145.0 (94.0, 231.5)	160.0 (110.5, 246.0)	100.0 (57.8,145.0)	0.001
ALP (U/L)	190.6 ± 75.6	184.1 ± 68.2	216.6 ± 96.2	0.031
TBil (umol/L)	163.9 (89.8, 280.2)	153.8 (88.0, 234.1)	287.6 (127.2, 425.5)	0.001
ALB (g/L)	33.64 ± 5.08	34.17 ± 4.86	31.54 ± 5.45	0.001
Na^+ (mmol/L)	136.96 ± 3.12	137.2 ± 3.1	135.9 ± 3.2	0.008
Cr (umol/L)	77.8 ± 37.8	78.3 ± 41.9	75.9 ± 12.9	0.697
INR	1.36 ± 0.26	1.30 ± 0.22	1.61 ± 0.23	0.001
PTA	58.7 (50.4, 76.5)	61.0 (51.8, 79.0)	48.5 (44.1, 58.6)	0.001
WBC (10^9/L)	5.0 (3.9, 6.6)	4.9 (3.8, 6.2)	5.5 (4.3, 7.5)	0.016
PLT (10^9/L)	113.3 ± 52.3	116.8 ± 53.5	99.6 ± 45.1	0.041
lgHBV DNA (copies/ml)	3.96 ± 2.60	6.13 ± 1.49	5.88 ± 1.83	0.385
CTP score	10.02 ± 1.42	9.85 ± 1.34	10.65 ± 1.53	0.001
MELD-Na score	16.93 ± 5.38	15.95 ± 4.85	20.76 ± 5.71	0.001
CLIF-SOFA score	4.85 ± 1.52	4.55 ± 1.41	6.02 ± 1.37	0.001
BI	52 (21.9)	28 (14.8)	24 (50.0)	0.001

Note: Data are presented as mean ± SD, n (%), or median (interquartile range). *P*: ACLF vs. Non-ACLF. ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BI, bacteria infection; BUN, urea nitrogen; CLIF-SOFA, chronic liver failure-sequentail organ failure assessment; Cr, creatinine; CTP, child-turcotte-pugh; GGT, glutamine transpeptidase; INR, international standardization ratio; MELD-Na, model for end-stage liver disease-Na score; Na+, sodium; PLT, platelet; PT, prothrombin time PTA, prothrombin activity, TBil, total bilirubin; WBC, white blood cell.

Univariate logistic regression analysis revealed that BI, ALP, GGT, TBil, ALB, Na^+, PTA, INR, PLT CTP score, CLIF-SOFA score and MELD-Na score were risk factors associated with the progression to ACLF in patients with HBV-related compensated liver cirrhosis during severe hepatitis flare. Multivariate logistic regression analysis showed that BI (OR = 7.113, 95% CI: 2.714–18.644), GGT (OR = 0.094, 95% CI: 0.988–0.999), TBil (OR = 1.004, 95% CI: 1.001–1.007), INR (OR = 114.05, 95% CI:17.4-746.3) and PLT (OR = 0.984, 95% CI: 0.972–0.996) were independent risk factors associated with the development of ACLF (Table 4).

Table 4
Univariate and multivariate analysis of the risk factors associated with progression to ACLF in patients with HBV-related compensated liver cirrhosis during severe hepatitis flare

Variables	Univariate analysis				Multivariate analysis			
	β	OR	95% CI	*P*	*β*	OR	95% CI	*P*
BI	1.749	5.750	2.874–11.506	0.001	1.962	7.113	2.714–18.644	0.001
ALP	0.005	1.005	1.001–1.009	0.014				
GGT	-0.009	0.991	0.986–0.996	0.001	-0.06	0.094	0.988–0.999	0.026
TBil	0.005	1.005	1.003–1.008	0.001	0.004	1.004	1.001–1.007	0.010
ALB	-0.106	0.899	0.841–0.961	0.002				
Na^+	-0.132	0.876	0.792–0.970	0.011				
INR	5.768	319.8	54.8-1867.5	0.001	4.737	114.05	17.40-746.30	0.000
PTA	-0.050	0.951	0.928–0.975	0.001				
PLT	-0.007	0.993	0.986-1.000	0.043	-0.016	0.984	0.972–0.996	0.009
CTP score	0.443	1.557	1.221–1.985	0.000				
CLIF-SOFA score	0.788	2.200	1.667-2.9.4	0.000				
MELD-Na score	0.179	1.196	1.113–1.284	0.000				

Note: ACLF, acute-on-chronic liver failure; ALB, albumin; ALP, alkaline phosphatase; BI, bacteria infection; CI, confidence interval; CLIF-SOFA, chronic liver failure-sequentail organ failure assessment; CTP, child-turcotte-pugh; GGT, glutamine transpeptidase; INR, international standardization ratio; MELD-Na, model for end-stage liver disease-Na score; Na^+, sodium; OR, odds ratio; PLT, platelet; PTA, prothrombin activity; TBil, total bilirubin.

Discussion

It is well accepted that the progression and the prognosis of patients with liver cirrhosis during acute deterioration depend on both predisposing factors and precipitating factors. The predisposing factors include the severity of liver fibrosis and related portal hypertension, systemic inflammation,

immunodeficiency and gut dysbiosis, etc. The precipitating factors include spontaneous activation of HBV, hepatitis A or E virus infection, drug or alcohol induced liver injury and BI, etc[7]. Therefore, it is difficult to find the clinical and biochemical characteristics associated with disease progression in patients with different predisposing factors and precipitating factors. To overcome the these bias, in this study we only included the patients HBV-related compensated liver cirrhosis and severe spontaneous hepatitis flare to study the risk factors associated with disease progression before ACLF, the results obtained in this study were more reliable than previous studies which included patients with great diversities in degrees of liver fibrosis, in etiologies of liver cirrhosis and in precipitating factors of acute deterioration[15, 21].

One of major findings in this study was that BIs occurred in 21.9% patients, which was much higher than those reported in compensated liver cirrhosis without severe hepatitis flare (4-year cumulative incidences of 12.2% and 5 year of 12.9%) [15, 22]. A significantly higher level of TBil, PT, INR, NEUT, NLR, CTP, CLIF-SOFA and MELD-Na score and significantly lower levels of ALB, Na^+ and PLT were observed in patients with BIs than those without BIs, TBil and CTP score were found as the independent risk factors associated with BI. Patients with liver cirrhosis have increased susceptibility to BI. Liver dysfunction and its related complications such as portal-systemic shunting, bacterial translocation, liver cirrhosis-associated immune dysfunction have been implicated in the occurring of BI[23, 24]. In patients with severe acute liver inflammation, an excessive hepatic inflammatory response has been found to exhaust the function of immune cells and results in immune paralysis[12]. These studies suggested that susceptibility to BI depend on the severity of acute and chronic liver injury. The prevalence of BI in patients with compensated liver cirrhosis during severe acute hepatitis flare remains unknown. Our results suggested that severe acute liver inflammation increased the prevalence of BIs in patients with compensated liver cirrhosis.

Another major finding in this study was that BI was one of the risk factors associated with progression to ACLF. Previous studies showed that BI and deterioration of liver cirrhosis have a complex interplay. The outcomes of BI in patients with liver cirrhosis also depended on severity of acute and chronic liver injury and the severity of BI. BI often trigger extrahepatic organ injuries and organ failure, and was one of the most common precipitating factors for progression to ACLF and death in patients with decompensated liver cirrhosis. In patients with compensated liver cirrhosis, however, the role of BI for progression to ACLF has not been studied. A few previous studies respectively investigated risk factors for development of ACLF in patients with different degrees of liver fibrosis and inflammation found different results, however, and as we know, no study had included BI as a risk factor for ACLF progression [25–27]. Our study firstly demonstrated that BI was a risk factor associated with progression to ACLF in pre-ACLF stage in patients with HBV-related compensated liver cirrhosis during severe hepatitis flare. This finding is clinical relevant in prevention and treatment of patients with liver cirrhosis and ACLF.

Because most patients in this study had BI and HD on admission, we could not determine which one occurred first, so we could not decide whether BI was the result of HD or as the precipitating factor of HD.

However, we found a strong association between HD and BI in this study. Previous study found that in patients with compensated liver cirrhosis, BI mostly occurred before HD, suggesting BI as a trigger of HD in patients with compensated liver cirrhosis.

The robustness of this study was that we included the largest group of patients with great homogeneous in etiologies and the severity of acute and chronic liver injury to study the risk factors for ACLF development. In addition, we only studied the association of BI with ACLF development in a short-term period, which might reflect the direct impacts of BI on ACLF development. Our study also had several limitations. At first, the diagnosis of BI was mostly based on clinical data, the patients with culture-positive BI were few in this study. This can be partly explained by the fact that in most patients BI had occurred before the admission and antibiotics had been used in local hospital and we only recorded the BIs before ACLF development. However, as we diagnosed BI based on strict established criteria and we had used examination to exclude the common pathogen infections, we believed most patients with BI had been correctly captured in this study. Secondly, it was a retrospective, single-center study, the findings in this study need to be verified in a multi-entered prospective study.

Declarations

Competing Interests: The authors declare no competing interests

Acknowledgments

This work was supported by the Funds of Chinese National Natural Science Foundation Project (81860114).

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Figures

Figure 1

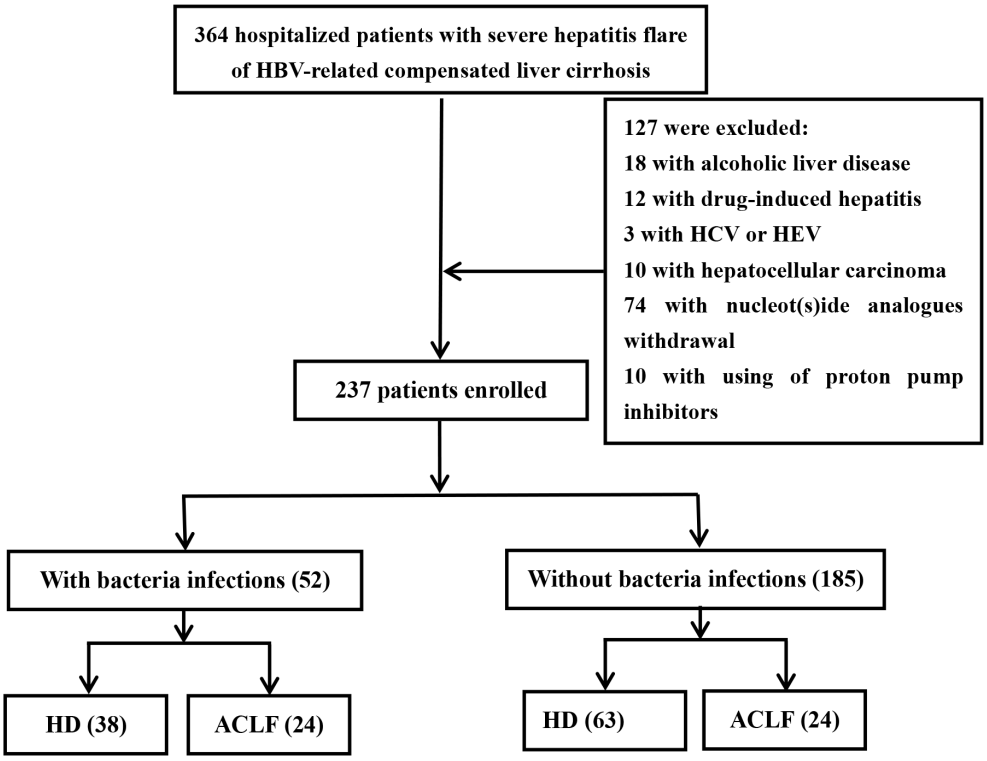

Figure 1

Outline of the screening and case selection protocol. ACLF, acute-on-chronic liver failure; HCV, hepatitis C virus; HD, hepatic decompensation; HEV, hepatitis E virus.

Figure 2

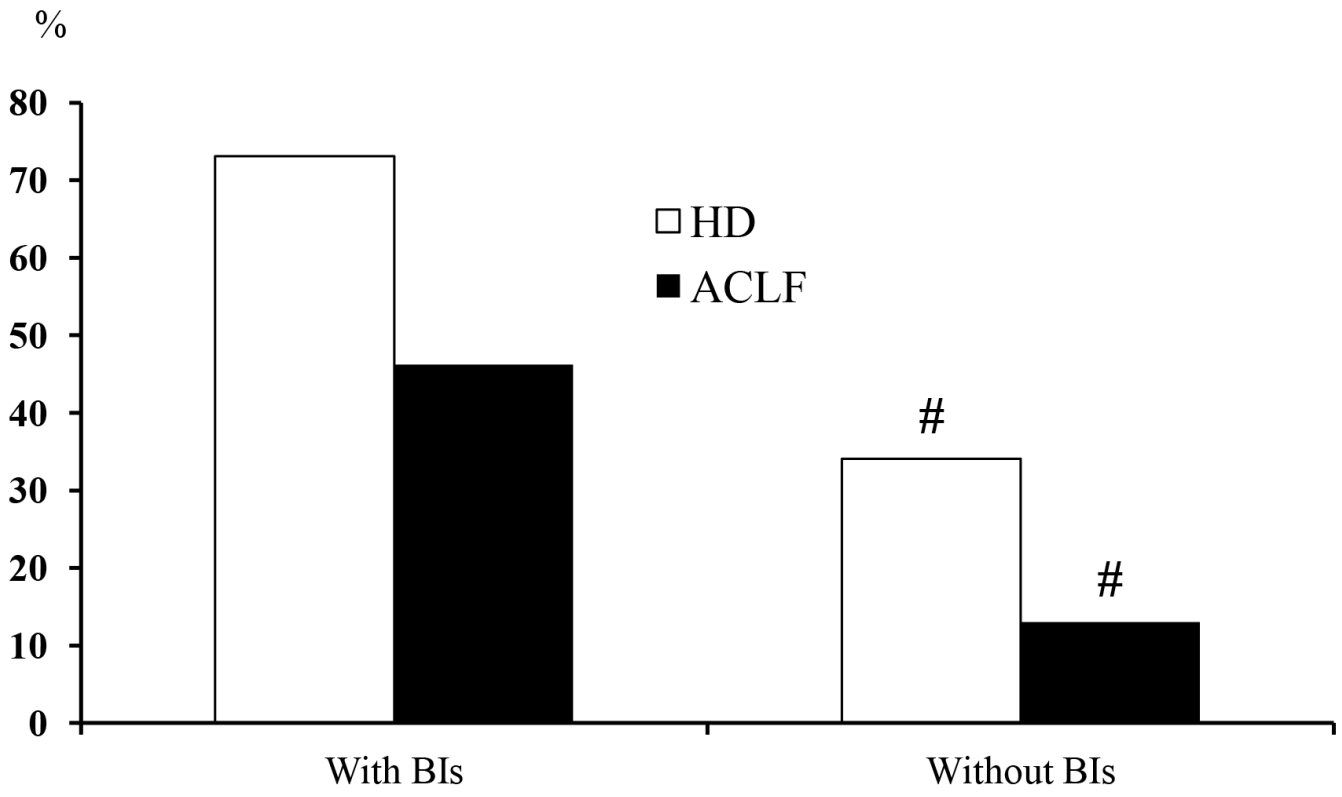

Figure 2

Bacteria infections were associated with occurring of hepatic decompensation and acute-on-chronic liver failure in patients with HBV-related compensated liver cirrhosis during severe hepatitis flare. ACLF, acute-on-chronic liver failure; BI, bacteria infection; HD, hepatic decompensation; HBV, hepatitis B virus. #: *P*<0.01, compared with those with BIs.