The Role of Prophylactic Antibiotics In Hepatitis B Virus-Related Acute-On-Chronic Liver Failure Patients: A Retrospective Study

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Abstract

Background: Acute-on-chronic liver failure (ACLF) is characterized by an excessive systemic inflammatory response and organ failure and has high mortality. Bacterial infections (BIs) worsen the clinical course of ACLF and carry a poor prognosis in ACLF patients. The efficacy of third-generation cephalosporins has been challenged in recent years. The aim of this study was to characterize the difference between ACLF patients with and without BIs and to provide a reference for medical intervention.

Methods: A total of 147 patients with hepatitis B virus-related ACLF (HBV-ACLF) hospitalized at the Department of Infectious Diseases, Huashan Hospital, Fudan University (Shanghai, China) between May 2013 and January 2020 were enrolled. Mann-Whitney U test was used to compare the baseline characteristics of HBV-ACLF patients with and without BIs. Univariate and multivariate analyses were performed to find predictors of BIs. The characteristics of BIs and the role of prophylactic antibiotics were profiled.

Results: A total of 104 episodes of BIs occurred in HBV-ACLF patients either at admission or during hospitalization. Patients with and without BIs differed in clinical characteristics. The incidence of BIs showed a positive correlation with the ACLF grade ($P < 0.001$) and the clinical course ($P < 0.001$). The 90-day transplant-free survival of patients with BIs was lower than those without BIs ($P < 0.0001$). Patients administered prophylactic antibiotics showed a lower incidence of BIs and had a higher transplant-free survival probability than those patients there were not administered prophylactic antibiotics ($P = 0.038$). No statistical differences in antibiotic efficacy between third-generation and other antibiotics were observed ($P = 0.108$).

Conclusions: BIs affected the clinical course and prognosis of patients with HBV-ACLF. Prophylactic antibiotics were of potential clinical importance in the prevention of BIs and improving the clinical course and prognosis in HBV-ACLF patients. Third-generation cephalosporins were qualified for use in antibiotic prophylaxis.

1. Introduction

Acute-on-chronic liver failure (ACLF) is a severe clinical syndrome of chronic liver disease and is accompanied by an increased risk for short-term mortality (1, 2). Chronic hepatitis B infection (CHB) is one of the important etiological factors for HBV-associated acute-on-chronic liver failure (HBV-ACLF) in developing countries. Moreover, HBV-ACLF accounts for 87–91% of overall ACLF cases in China (3, 4). HBV-ACLF has emerged as a serious healthcare and financial problem in developing countries (5).

Bacterial infections (BI) are both a precipitating factor and a common complication of ACLF (6, 7). Previous studies have reported that 45.9–75.5% of ACLF patients who did not acquire BIs at disease onset developed BIs during follow-up due to immunoparesis (6, 8–10). Furthermore, the occurrence of BIs exacerbated the inflammatory response and aggravated the ischemia-reperfusion injury of organs, such as the liver, kidneys, and lungs, which subsequently resulted in organ failure and an unfavorable

prognosis (8, 11). BIs were an independent predictor of death in patients with ACLF-1 and ACLF-2 (8), and thus, preventing BIs is of great significance for ACLF patients (7, 12). Prophylaxis for BIs applies to the following situations: 1) after an episode of spontaneous bacterial peritonitis (SBP); 2) patients with variceal bleeding; and 3) patients at high risk of developing bacterial infections (7). In patients with cirrhosis, prophylactic antibiotics is a vital strategy in preventing not only additional BIs, but also hepatorenal syndrome, recurrent variceal hemorrhage, and even death (7, 12, 13). However, few studies focused on the role of prophylactic antibiotics in hepatitis B virus-related acute-on-chronic liver failure patients. On the other hand, due to the rise of antibiotic-resistant bacteria, especially multidrug-resistant (MDR) bacteria, the efficacy of third-generation cephalosporins was challenged (7, 13, 14), whereas report about the efficacy of third-generation cephalosporins in HBV-ACLF patients was rare. This study aimed to profile the prevalence of BIs in patients with HBV-ACLF, demonstrate the clinical benefits of prophylactic antibiotics, and provide new medical evidence for specific therapeutic strategies.

2. Methods

2.1 Study subjects

In this study, HBV-ACLF patients admitted to the Department of Infectious Diseases, Huashan Hospital, Fudan University (Shanghai, China) from May 2013 to January 2020 were recruited. The inclusion criteria were as follows: (1) serum hepatitis B surface antigen-positive and/or HBV-DNA-positive for at least six months; (2) progressive jaundice with total bilirubin (TB) 10-fold higher than the upper limit of normality or a daily increase of ≥ 17.1 mmol/L; and (3) prothrombin activity (PTA) ≤ 40% or an international normalized ratio (INR) ≥ 1.50. The exclusion criteria included: (1) patients aged < 18 years; (2) patients with serious underlying diseases of the brain, heart, kidneys, lungs, and other organs; (3) patients with malignant tumors; (4) pregnant women; (5) patients with incomplete clinical data; and (6) patients that received a liver transplant.

The diagnosis of HBV-ACLF was based on the criteria formalized by the 2019 ACLF consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL) (15). The severity of ACLF was assessed by the Chinese Group on the Study of Severe Hepatitis B (COSSH) ACLF score, which was calculated using the formula 0.741 × INR + 0.523 × HBV - Sequential Organ Failure Assessment (SOFA) + 0.026 × age (yr) + 0.003 × TBil (μmol/L) (16). Finally, a total of 147 patients satisfied the inclusion criteria and 143 patients were excluded (Fig. 1).

BI episodes were recorded either at admission or during hospitalization in HBV-ACLF patients. Bacterial peritonitis was diagnosed as a polymorphonuclear cell count greater than 250/mm^3 in ascites, with or without a positive ascites culture (17). Pneumonia was diagnosed by the presence of radiological evidence of consolidation plus at least two of the following criteria: fever higher than 38 °C or hypothermia less than 36 °C, cough, pleuritic chest pain, purulent sputum, dyspnea, or signs of

consolidation upon medical examination (18). Bloodstream infection was diagnosed by the growth of a non-common skin contaminant from ≥ 1 blood culture (BC) and of a common skin contaminant from ≥ 2 BCs drawn at separate sites with signs of infection (19). Biliary tract infection was diagnosed by a detailed examination, including consultation and physical examination, after which blood tests and diagnostic imaging were performed (20). Unproven BIs were diagnosed by the presence of fever and leukocytosis, which required antibiotic therapy without any identifiable source (21). Multi-site infection referred to a situation where two or more infections mentioned above occurred simultaneously. Other infections referred to a perianal abscess case in this study. Prophylactic antibiotics administered intravenously were initiated within two days of hospital admission. Prophylactic antibiotics, including third-generation cephalosporins, piperacillin-tazobactam, cefoperazone and sulbactam, carbapenem, and combination therapy with enzyme inhibitors, were prescribed according to the clinical experience of the physicians. All of the patients were treated with oral antiviral drugs (entecavir or tenofovir).

2.2 Data collection and follow-up

Demographic data, medical history, clinical parameters, including vital signs and radiology, laboratory, microbiology, and treatment data, were collected upon admission and during the entire hospitalization stay. The lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), disseminated intravascular coagulation (DIC) score, transplant-free survival probability, and cumulative incidence of BIs were then calculated. The patients were followed 90 days after their first admission to our hospital. A 90-day transplant-free survival was considered the primary endpoint. Information on prognosis was confirmed through medical records and telephone contact.

2.3 Statistical analyses

For all analyses, $P < 0.05$ was considered significant, and all tests were two-tailed. Student's *t* test was used to assess the average of a normally distributed continuous variable. A Mann-Whitney U test was used to assess the continuous variables when assumptions of normality were not met. Kaplan-Meier curves were plotted to display the survival of patients in terms of BIs and prophylactic antibiotics. Multivariate logistic regression was fitted with a forward stepwise selection method using clinically and statistically baseline factors that had been screened in univariate analysis to assess the clinical factors associated with the BIs in HBV-ACLF patients.

3. Results

3.1 Baseline characteristics of the patients

HBV-ACLF patients with and without BIs showed systemically different clinical characteristics. Among the 104 HBV-ACLF patients with BIs, the median age was 45 (interquartile range, 37–56) years. Males (n = 91, 87.5%) were the predominant population. In eight (7.7%) cases of HBV-ACLF, BIs acted as a precipitating event for the development of ACLF. The frequency of complications, including ascites and gastrointestinal hemorrhage, was substantially different between patients with and without BIs (76.9% vs

48.8%, $P = 0.001$; 10.6% vs 0%, $P = 0.034$, respectively). Prophylactic antibiotics were administered in 22 (21.2%) HBV-ACLF patients with BIs as compared with those without BIs 29 (67.4%)—this difference was significant ($P < 0.001$). The laboratory data showed that HBV-ACLF patients with BIs experienced a worse clinical course, with a higher total bilirubin level ($P = 0.002$) and lower levels of alanine aminotransferase ($P = 0.006$) and sodium ($P = 0.002$). Additionally, patients with BIs suffered more serious coagulation defects with a lower platelet count ($P = 0.014$) and a higher INR level ($P = 0.05$) and DIC score ($P = 0.006$). Moreover, HBV-ACLF patients with BIs were more prone to suffer organ failures, especially liver ($P = 0.017$), coagulation ($P = 0.005$), cerebral ($P = 0.041$), and circulation ($P = 0.018$). Finally, HBV-ACLF patients with BIs had a poorer outcome with a 28-day transplant-free survival of 54.7% and a 90-day transplant-free survival of 42.9% as compared with HBV-ACLF patients without BIs (86% and 83.1%, respectively, $P < 0.001$) (Table 1).

Table 1
Comparison of clinical features and laboratory results between HBV-ACLF patients with and without bacterial infections.

	Patients without bacterial infection (n = 43)	Patients with bacterial infection (n = 104)	*P*-value
Clinical data			
Age (yr)	49 (37–56)	45 (37–56)	0.784
Male sex, % (no.)	100 (43)	87.5 (91)	**0.011**
Underlying disease, % (no.)			0.985
Chronic hepatitis B	46.5 (20)	48.1(50)	-
Compensated cirrhosis	32.6 (14)	31.7 (33)	-
Decompensated cirrhosis	20.9 (9)	20.2 (21)	-
Precipitating events			
HBV reactivation, % (no.)	53.5 (23)	42.3 (44)	0.216
Bacterial infection, % (no.)	0 (0)	7.7 (8)	0.053
Complications, % (no.)			
Ascites	48.8 (21)	76.9 (80)	**0.001**
GI hemorrhage	0 (0)	10.6 (11)	**0.034**
Prophylactic antibiotics	67.4 (29)	21.2 (22)	**0.000**
Laboratory data			
Alanine aminotransferase (U/L)	235.5 (99–653)	126 (62–289)	**0.006**
Albumin (g/L)	32 (29–36)	32 (29–37)	0.825
Total bilirubin (μmol/L)	256.2 (173.9–347.3)	336.8 (248.2–458.3)	**0.002**
Creatinine (μmol/L)	69 (58–79)	71 (58–100)	0.251
Sodium (mmol/L)	137.5 (133–140)	135 (131–138)	**0.044**
White blood cell count (10^9/L)	5.91 (4.64–9.68)	7.92 (5.56–10.57)	**0.014**
Neutrophil count (10^9/L)	3.98 (2.95–7.06)	6.02 (3.93–7.85)	**0.012**

Abbreviations: ACLF, acute-on-chronic liver failure; HBV, hepatitis B virus; GI, gastrointestinal; INR, international normalized ratio; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; DIC, disseminated intravascular coagulation. Data are expressed as the median (interquartile range) or percent (number). Bold numbers represent significant difference ($P < 0.05$).

	Patients without bacterial infection (n = 43)	Patients with bacterial infection (n = 104)	*P* value
Hemoglobin (g/L)	130 (115–140)	116 (95–128)	**0.000**
Platelet count (10^9/L)	98 (76–133)	84 (58–113)	**0.014**
INR	1.98 (1.76–2.38)	2.18 (1.83–2.77)	**0.050**
LMR	2.05 (1.32–2.75)	1.39 (1–1.93)	0.358
NLR	3.77 (2.47–6.20)	5.2 (3.46–9.07)	**0.020**
DIC score	4 (3–5)	5 (4–6)	**0.006**
Organ failure, % (no.)			
Liver	69.8 (30)	86.5 (90)	**0.017**
Coagulation	18.6 (8)	43.3 (45)	**0.005**
Kidney	14.0 (6)	16.3 (17)	0.716
Cerebral	9.3 (4)	24.0 (25)	**0.041**
Lung	4.7 (2)	11.5 (12)	0.235
Circulation	4.7 (2)	20.2 (21)	**0.018**
Transplant-free survival probability (%)			
28-day	86.0	54.7	**0.000**
90-day	83.1	42.9	**0.000**

Abbreviations: ACLF, acute-on-chronic liver failure; HBV, hepatitis B virus; GI, gastrointestinal; INR, international normalized ratio; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; DIC, disseminated intravascular coagulation. Data are expressed as the median (interquartile range) or percent (number). Bold numbers represent significant difference ($P < 0.05$).

3.2 The characteristics of BIs in HBV-ACLF patients

HBV-ACLF patients with and without BIs were significantly different in regards to overall transplant-free survival in the study population (42.9% vs 83.1%, $P < 0.0001$). The difference was obvious to observe in grade 0, grade 1, and grade 2 HBV-ACLF patients with and without BIs. As for grade 3 HBV-ACLF patients, the transplant-free survival showed no difference.

The incidence of BIs increased with the severity of HBV-ACLF. For grades 2 and 3 HBV-ACLF patients, the incidence of BIs increased to 89.2% and 90%, respectively. There were statistical differences between grade 0 and grade 2 ($P = 0.001$) and grade 1 and grade 2 ($P = 0.008$). Additionally, HBV-ACLF patients with BIs experienced a worse clinical course than those without BIs and were prone to a poorer hospital

outcome. Among all 147 HBV-ACLF patients, the cumulative incidence of infection progressed fastest within the first 28-day course and then slowly evolved along with the clinical course.

In this study, bacterial peritonitis (33.65%) was the most prevalent infection site, followed by pneumonia (25.96%), multi-site infection (23.08%), unproven infection (10.58%), bloodstream infection (2.88%), biliary tract infection (2.88%), and other infection (0.96%), which referred to one perianal abscess case (Fig. 2).

3.3 Predictors of the incidence of BIs in HBV-ACLF patients

Univariate and multivariate analysis of risk factors for BIs were performed in HBV-ACLF patients. Although univariate analysis showed that sodium (odds ratio [OR], 0.934 [95% confidence interval{CI}, 0.874–0.999], $P = 0.046$), hemoglobin (OR, 0.970 [95% CI, 0.954–0.986], $P = 0.000$), INR (OR, 1.697 [95% CI, 1.002–2.873], $P = 0.049$), ascites grade (OR, 1.627 [95% CI, 1.173–2.256], $P = 0.004$), hepatic encephalopathy grade (OR, 1.700 [95% CI, 1.069–2.704], $P = 0.025$), and DIC score (OR, 1.339 [95% CI, 1.082–1.657], $P = 0.007$) were relevant to the incidence of BIs, these indexes were not predictors in multivariate analysis. Total bilirubin (OR, 1.004 [95% CI, 1.001–1.006], $P = 0.004$) and white blood cell count (OR, 1.096 [95% CI, 1.001–1.198], $P = 0.047$) were demonstrated to be relevant to the incidence of BIs, while there was no statistic difference in multivariate analysis. Multivariate analysis confirmed that platelet count (OR, 0.991 [95% CI, 0.983–0.999], $P = 0.038$) and prophylactic antibiotics (OR, 0.367 [95% CI, 0.170–0.790], $P = 0.010$) at admission were identified as independent predictors of in-hospital BIs in patients with HBV-ACLF. Prophylactic antibiotics was an independent negative prognostic factor in this study (Table 2).

Table 2
Predictors of BI in the univariate and multivariate analyses in patients with HBV-ACLF.

Predictors	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* value
Age (yr)	-	0.818	-	-
Underlying liver disease	-	0.981	-	-
Prior decompensation	-	0.851		
Precipitating events	-	0.320	-	-
Total bilirubin (μmol/L)	**1.004 (1.001–1.006)**	**0.004**	**1.003 (1.000–1.005)**	**0.058**
Creatinine (μmol/L)	1.001 (0.997–1.005)	0.206	-	-
Sodium (mmol/L)	0.934 (0.874–0.999)	0.046	-	-
White blood cell count (10^9/L)	**1.096 (1.001–1.198)**	**0.047**	**1.092 (0.982–1.214)**	**0.103**
Neutrophil count (10^9/L)	1.189 (1.057–1.337)	0.851	-	-
Hemoglobin (g/L)	0.970 (0.954–0.986)	0.000	-	-
Platelet count (10^9/L)	**0.990 (0.983–0.997)**	**0.007**	**0.991 (0.983–0.999)**	**0.038**
INR	1.697 (1.002–2.873)	0.049	-	-
Ascites grade	1.627 (1.173–2.256)	0.004	-	-
Hepatic encephalopathy grade	1.700 (1.069–2.704)	0.025	-	-
LMR	-	0.719	-	-
NLR	-	0.686	-	-
DIC score	1.339 (1.082–1.657)	0.007	-	-
Prophylactic antibiotics	**0.328 (0.162–0.664)**	**0.002**	**0.367 (0.170–0.790)**	**0.010**

Abbreviations: HBV-ACLF, hepatitis B virus-related acute-on-chronic liver failure; INR, international normalized ratio; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; DIC, disseminated intravascular coagulation; OR, odds ratio; CI, confidence interval. Bold-face font represents factors that are significant predictors of infection in multivariate analyses. The multivariate logistic regression model was fitted with a forward stepwise selection method using clinically and statistically baseline factors that were screened in the univariate analysis.

3.4 The role of prophylactic antibiotics in HBV-ACLF patients.

In this study, 96 patients received conventional therapy and 51 patients received prophylactic antibiotics in addition to conventional therapy. Third-generation cephalosporins, as a first-line treatment, were

administered to 25 patients. MDR-covering agents were also administered to patients, including piperacillin-tazobactam, which was administered to 6 patients, cefoperazone and sulbactam, which was administered to 6 patients, carbapenem, which was administered to 11 patients, and a combination therapy, which included enzyme inhibitors and carbapenem, was administered to 3 patients. Among the 147 HBV-ACLF patients, those that received prophylactic antibiotics exhibited a lower probability of infection than those without prophylactic antibiotic treatment irrespective of the HBV-ACLF grade level. Moreover, patients who received prophylactic antibiotics showed a higher 28-day and 90-day transplant-free survival than those who did not receive prophylactic antibiotics. As for the efficacy of the antibiotic regimen, there was no statistical difference between third-generation cephalosporins and MDR-covering agents (50% vs. 28%, $P = 0.108$) (Fig. 3). No patients showed side effects of antibiotic treatment in this study.

4. Discussion

ACLF is an acute deterioration of chronic liver disease characterized by multiple organ failure and high short-term mortality, with 3-month and 1-year mortality rates being 53.7% and 67.4%, respectively (22). ACLF patients are highly susceptible to BIs because these patients display sepsis-like immune paralysis (23–25).

BIs play a critical role in the development and progression of ACLF because they exacerbate the inflammatory reaction via pathogen-associated molecular patterns (PAMPs) in the body. BIs also trigger the occurrence of ACLF in patients with cirrhosis (2, 8). The systemic inflammatory response induced by BIs leads to multiple extra-hepatic organ failures and further increases mortality in patients with ACLF (26). A worse clinical course and a lower 90-day probability of survival (49%) or a higher short-term mortality by 2- to 4- fold was reported in ACLF patients with concurrent BIs (either at diagnosis or during follow-up) than ACLF patients without BIs (8, 27). Our results also showed that irrespective of the grade level, once BIs occurred, ACLF patients were prone to a lower transplant-free survival than those without BIs. At the same time, our study confirmed that the frequency of BIs increased with higher ACLF grades, varying from 47.6–90%. The clinical course was quite different between HBV-ACLF patients with and without BIs. Patients without BIs showed a 2-fold higher improvement proportion relative to patients with BIs. On the other hand, patients with BIs showed a 2-fold higher worsening proportion relative to patients without BIs. Thus, in this study, we demonstrated that the occurrence of BIs exerted a negative impact on the severity level, clinical course, and mortality in HBV-ACLF patients, which was consistent with previous studies (6, 8).

For about 7.7% of patients, BIs were recorded as a precipitating factor of ACLF in this study. On the other hand, as ACLF developed or progressed, the incidence of BIs increased. To be specific, the incidence of BIs was 25.2% in patients admitted to our hospital, while 45.2% of patients developed BIs after HBV-ACLF diagnosis, which was consistent with previous studies (8, 9). In this study, bacterial peritonitis (33.65%) was the most prevalent infection site, followed by pneumonia (25.96%). Bacterial peritonitis is one of the most common infections in ACLF patients varying from 21.1–34.5% and is associated with a high risk of developing irreversible renal failure and hepatorenal syndrome (6, 8, 28). Pneumonia (25.96%) was the

second most common infection site in this study, and the frequency of pneumonia varied from 7.7–45.0% in previous studies (2, 6, 8). Bloodstream infection (2.88%) was less common in this study relative to other studies (28). In our study, the mortality according to different BI sites was 19.23% in bacterial peritonitis, 14.42% in multi-site infection, 13.46% in pneumonia, 7.69% in unproven infection, 1.92% in bloodstream infection, 0% in biliary tract infection, and 0% in other infection.

The increased intestinal permeability was the main cause of bacterial translocation in patients with cirrhosis, and *Escherichia coli* was the major translocating bacteria (29). There were 20 cases of bacteria isolated from 14 patients in this study, including 14 (70% of the culture-positive episodes) cases of gram-negative bacteria and 6 (30% of isolates) cases of gram-positive bacteria. Bacteria were isolated from the ascitic fluid in 8 (40% of isolates) cases, blood in 7 (30% of isolates) cases, urine in 3 (15% of isolates) cases, and sputum in 3 (15% of isolates) cases. Only one (5% of isolates) bacteria obtained from the urine of a patient without prophylactic antibiotic treatment was confirmed to be MDR *E. coli*. The MDR rate in our study was lower than other studies (2, 6, 8, 30). Fungi were isolated from three BIs cases, but fungal infections were not evaluated in this study.

In this study, the univariate and multivariate analyses confirmed that platelet count and prophylactic antibiotics were both independent negative prognostic factors of BIs. A lower platelet count usually existed in patients with cirrhosis, which also indicated the correlation between the severity level of HBV-ACLF and the prevalence of BIs. Notably, prophylactic antibiotics were an independent negative prognostic factor in this study, which suggested that prophylactic antibiotics protected HBV-ACLF patients from BIs. The positive influence of prophylactic antibiotics was also demonstrated by the improvement in the transplant-free survival probability in this study. Although the severity level of ACLF was closely related to the incidence of BIs, our study further analyzed and found that prophylactic antibiotics played an apparent protective role against BIs, irrespective of the severity of HBV-ACLF as compared with patients without prophylactic antibiotics. This makes sense because the application of prophylactic antibiotics was an important method to limit potential damage and prevent recurrence of infection (11). However, delayed initiation of antibiotics can lead to the loss of crucial time and worse outcomes in HBV-ACLF patients. Additionally, cirrhosis patients were at high risk of nosocomial infections. Thus, the early administration of prophylactic antibiotics could improve the patient's prognosis (31).

Several factors, including epidemiological, local microbiological, and risk factors for MDR, need to be considered when it comes to initiating antibiotics (32). MDR bacterial infections were the main concern for the use of prophylactic antibiotics or inappropriate antibiotics and were usually isolated in the intensive care unit and nosocomial episodes. It has been reported that the prevalence of MDR bacterial infections in patients with decompensated cirrhosis and with ACLF increased from 29–38% in culture-positive infections from 2011 to 2017–2018 in Europe (33). MDR bacterial infections is a serious event related to lower resolution rates and higher short-term mortality (8, 34). Recent studies have also reported increasing prevalence of gram-positive bacteria (33, 35, 36). However, the most frequently isolated

bacteria in this study were gram-negative bacteria, which was consistent with other studies (2, 12). Additionally, the frequency of the MDR in this study was lower than in previous studies (2).

Previous studies have demonstrated MDR-covering strategies to be effective, as they yield a higher infection resolution rate or a higher chance of microbiological susceptibility as compared to classical antibiotics strategies, especially in nosocomial infections and severe infections (12, 33). However, in a randomized clinical trial when the infection was not complicated by sepsis, the benefit derived from the use of broad-spectrum antibiotics was blunted (12). We also need to recognize the toxicity and risk of secondary infection due to the application of broad-spectrum antibiotics. Third-generation cephalosporins have been recommended as an appropriate first-line prophylaxis in advanced cirrhosis patients because of antibiotic effectiveness and low hepatic and renal toxicity (12, 37). Emerging studies have revealed that the efficacy of third-generation cephalosporins has been reduced due to the spread of MDR bacterial infections (13, 14, 31). However, evidence has also shown that third-generation cephalosporins, as first-line antibiotics, achieved a recovery rate of approximately 75% in SBP patients and cefotaxime was the first choice in community-acquired infections (6) (38). Our results also suggested that the antibiotic efficacy of third-generation cephalosporins was higher than MDR antibiotics, indicating that third-generation cephalosporins are more appropriate prophylactic antibiotics for HBV-ACLF patients. Although there was no significant difference in the efficacy between third-generation cephalosporins and MDR-covering agents—most likely due to the limited number of patients in this study—further studies are needed to confirm this finding.

The major limitation of this study was the small number of patients enrolled, and as a result, a lack of power to demonstrate the efficacy of prophylactic antibiotics. Additionally, this was a retrospective study. Adequately powered randomized controlled trials are needed to show a high level of evidence for the efficacy of prophylactic antibiotics in HBV-ACLF patients and to confirm the efficacy of third-generation cephalosporins in prophylactic treatment. Mortality and adverse events and other clinically important outcomes should also be evaluated.

5. Conclusions

BI is a major risk factor for survival in patients with HBV-ACLF. It is imperative to minimize and prevent the risk of BI. Once ACLF is diagnosed, prophylactic antibiotics should be initiated early to minimize the damage in HBV-ACLF patients. Aside from MDR-covering agents, third-generation cephalosporins are suitable candidates for use in prophylactic strategies.

Abbreviations

ACLF, acute-on-chronic liver failure;

BIs, bacterial infections;

HBV, hepatitis B virus;

HBV-ACLF, hepatitis B virus-related ACLF;

CHB, Chronic HBV infection;

SBP, spontaneous bacterial peritonitis;

MDR, multidrug-resistant;

PTA, prothrombin activity;

INR, international normalized ratio;

APASL, Asian Pacific Association for the Study of the Liver;

COSSH, Chinese Group on the Study of Severe Hepatitis B;

SOFA, Sequential Organ Failure Assessment;

BC, blood culture;

LMR, lymphocyte-to-monocyte ratio;

NLR, neutrophil-to-lymphocyte ratio;

DIC, disseminated intravascular coagulation;

OR, odds ratio;

CI, confidence interval;

PAMPs, pathogen-associated molecular patterns.

Declarations

Ethics approval and consent to participate

The study was consistent with the Declaration of Helsinki and approved by the ethics committee of Huashan Hospital, Fudan University (Shanghai, China).

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files (Additional files 1).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XL and XZ were equal contributors in collecting the patients' data, designing the study, and writing the manuscript. YY analyzed and interpreted the patients' data. JZ and JS interpreted the patients' data. WZ, JZ, and YH revised the manuscript. All authors read and approved the final manuscript.

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Figures

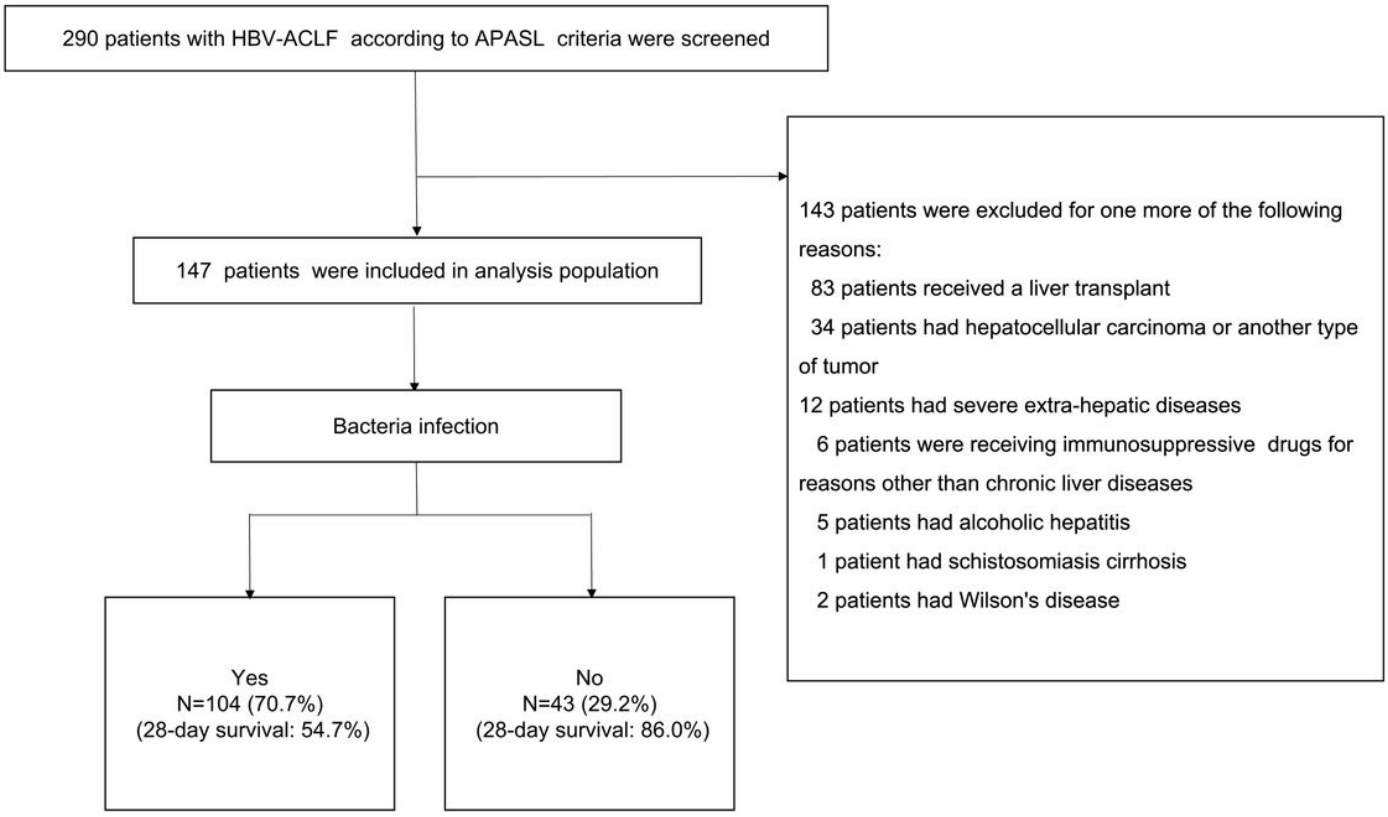

Figure 1

Flow diagram of the patient recruitment process followed in this study. Abbreviations: HBV-ACLF, hepatitis B virus-related acute-on-chronic liver failure; APASL, the Asian Pacific Association for the Study of the Liver

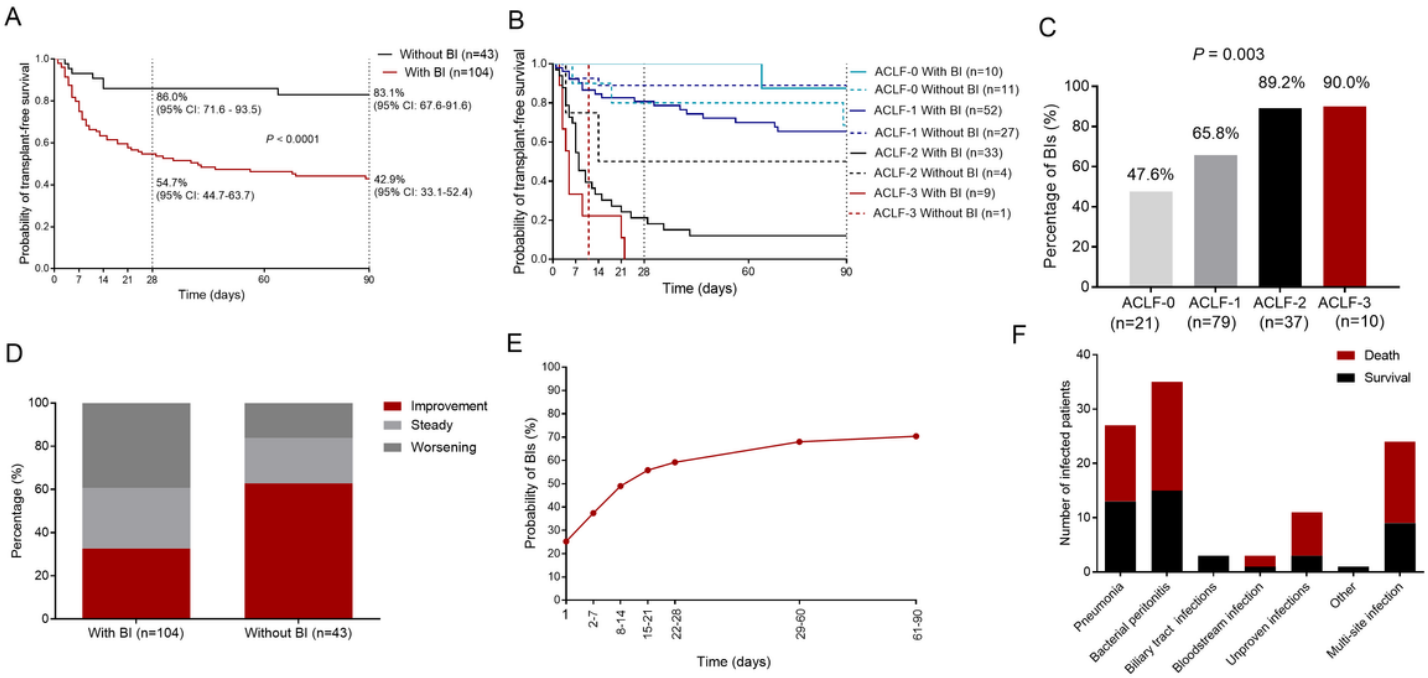

Figure 2

The characteristics of BIs in HBV-ACLF patients. The transplant free survival probability difference between HBV-ACLF patients with and without BIs. (A) in overall study population; (B) in different grades population. C. The relationship between the incidence of BIs and the severity of HBV-ACLF. D. The relationship between the occurrence of BIs and the clinical course of HBV-ACLF. E. The cumulative incidence of BIs among the 147 HBV-ACLF patients within 90-day after their diagnosis of HBV-ACLF. F. The distribution characters of BIs in HBV-ACLF patients. Abbreviations: HBV-ACLF, hepatitis B virus-related acute-on-chronic liver failure; BIs, bacterial infections; CI, confidence interval.

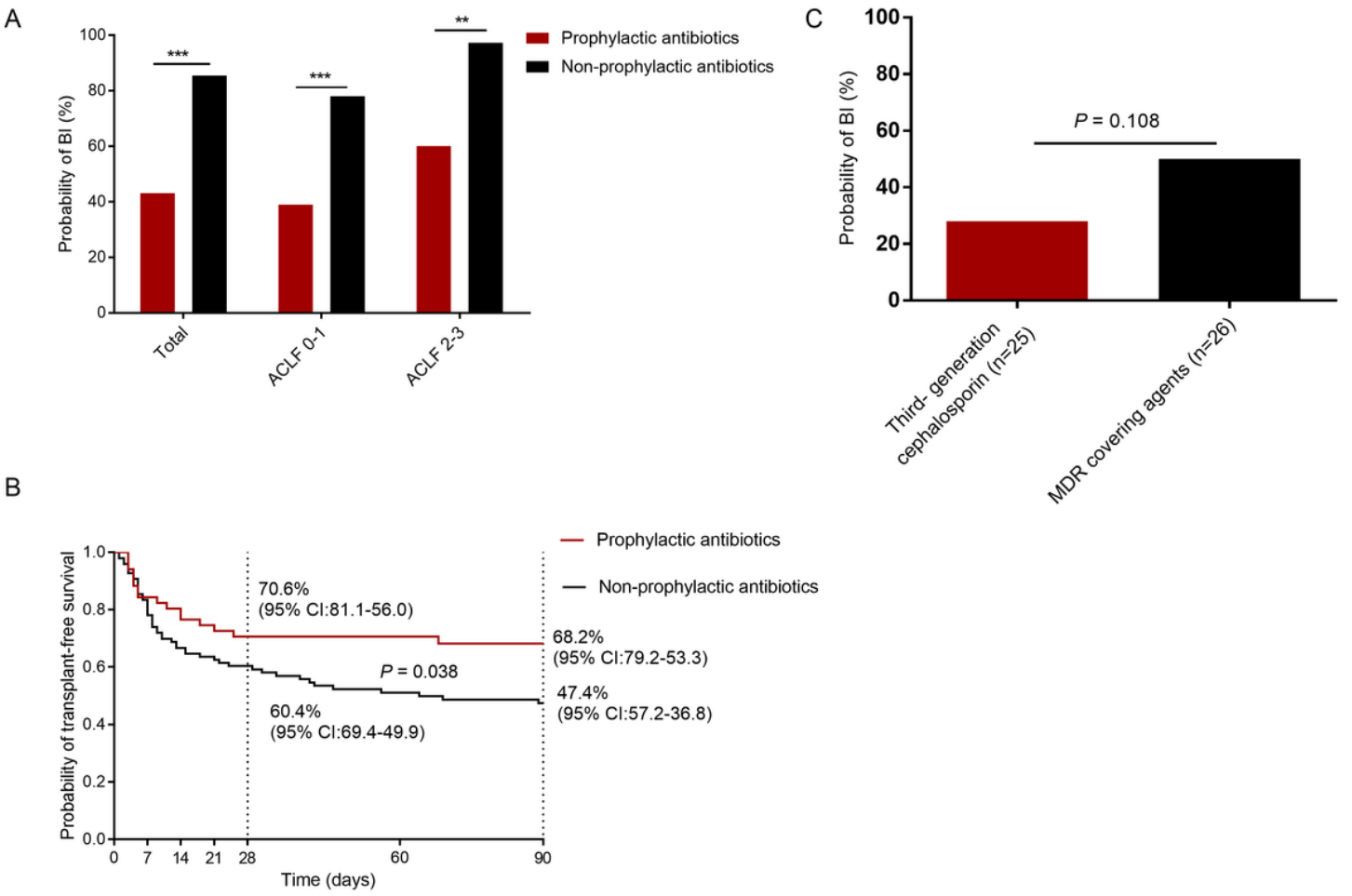

Figure 3

The significance of prophylactic antibiotics on BIs and the probability of transplant-free survival. A) Comparison of the probability of BIs between HBV-ACLF patients with and without prophylactic antibiotics. B) Comparison of the transplant-free survival probability between HBV-ACLF patients with and without prophylactic antibiotics. C) Comparison of the probability of BIs between antibiotic regimen with the third-generation cephalosporin and with MDR covering-agents in HBV-ACLF patients. Abbreviations: BIs, bacterial infections; HBV-ACLF, hepatitis B virus-related acute-on-chronic liver failure; MDR, multiple drug resistance; OR, odds ratio; CI, confidence interval.

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