The impact of hepatotoxic drugs on the outcome of patients with acute deterioration of hepatitis B virus-related chronic disease

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Background and aims Hepatotoxic drugs can worsen outcomes in patients with chronic liver disease (CLD), whereas this negative effect in acute deterioration of hepatitis B virus (HBV)-related CLD (HBV-CLD) is rarely reported. We aimed to assess the impact of hepatotoxic drugs on the outcome of patients with acute deterioration of HBV-CLD.
Methods This retrospective study included consecutive patients admitted to three medical centers in eastern China from 2015 to 2020 for HBV-related severe liver injury (HBV-SLI) or acute decompensation of cirrhosis (HBV-AD). The prevalence of hepatotoxic drugs and their impact on organ failure, the development of acute-on-chronic liver failure (ACLF), and 90-day survival were evaluated.
Results: A total of 335 patients with HBV flare (median age, 44 years; 85.7% male; 38.2% HBV-SLI and 61.8% HBV-AD) were included. Of them, 72 (21.5%) received hepatotoxic drugs, with herbs (44.4%) being the most common form. Patients in the drugs group had a significantly higher prevalence of all types of organ failure except respiratory failure. The multivariate logistic model showed that hepatotoxic drugs raised the risk of developing ACLF by 7.66-fold. ACLF occurrence was the strongest risk factor for 90-day mortality with a hazard ratio of 5.54 in the Cox regression analysis. In contrast, the hepatitis B envelope antigen status and HBV DNA levels had weak associations with the development of organ failure and ACLF.
Conclusions: Hepatotoxic drugs are closely associated with the development of organ failure and ACLF, and contribute to reduced 90-day survival rates among patients with acute deterioration of HBV-CLD. Eur J Gastroenterol Hepatol 34: 782–790

Introduction

Chronic hepatitis B virus (HBV) infection remains a global health problem and affects more than 250 million affected individuals worldwide [1]. Although patients with chronic HBV infection can be asymptomatic for years or decades, a significant proportion (around 15–40%) of them may develop liver cirrhosis, hepatocellular carcinoma, and even liver failure, which are the common causes of over 780 000 HBV-related deaths annually [2]. Acute-on-chronic liver failure (ACLF) is a complex syndrome associated with the presence of organ failure and a high rate of short-term mortality [3,4]. HBV-related ACLF (HBV-ACLF), which progresses from HBV-related severe liver injury (HBV-SLI) or acute decompensation of cirrhosis (HBV-AD), predominates in the ACLF population in the Asia-Pacific region, especially in China [5–7]. Although HBV flare is considered the main precipitant event in the development of HBV-ACLF, the triggers remain unclear in more than 15% of HBV-ACLF cases [8]. Additionally, numerous studies have suggested that other types of acute insults such as drinking alcohol, bacterial infection (BI), and upper gastrointestinal bleeding (UGIB), contribute to more cases of organ failure and poorer outcomes among patients with HBV-ACLF [6–9].

Some medications (e.g. anti-tuberculosis drugs, immunosuppressive drugs, and antiretroviral drugs) [10–12] are associated with hepatotoxicity and can cause varying degrees of liver injury ranging from slightly elevated liver enzymes to acute liver failure, particularly in individuals with chronic liver disease (CLD) [13–15]. Moreover, a significant proportion of herbs are linked to hepatotoxicity despite their constituents being varied [16,17]. Recent research from the Asian Pacific Association for the Study of the Liver ACLF Research Consortium has indicated that drug-induced ACLF accounted for 10.5% of 3132 Asian cases of ACLF, with complementary treatment and herbs constituting more than 50% of relevant hepatotoxic drugs [18].

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The Asia-Pacific region has high burdens of chronic HBV infection and other forms of CLD, contributing more than 60% of global deaths due to liver diseases [19]. However, the impact of hepatotoxic drugs on the development of HBV-ACLF is poorly studied. Therefore, we designed this multicenter study to assess the impact of hepatotoxic drugs on the outcomes of patients with HBV-SLI or HBV-AD. We hypothesized that in these patients, the combined effects of hepatotoxic drugs and HBV flare would accelerate the development of organ failure and consequent ACLF, leading to a higher short-term mortality rate compared to HBV flare alone.

Methods

Study design

In this retrospective study, we evaluated consecutive patients who were hospitalized for HBV-SLI or HBV-AD at three academic centers in eastern China (the First and the Second Affiliated Hospital of Wannan Medical College, Wuhu, and the First Hospital of Quanzhou, Fujian Medical University, Fuzhou) from January 2015 to December 2020. Two investigators at each center were responsible for reviewing the patient charts to (1) confirm the diagnosis of HBV-SLI or HBV-AD; (2) identify hepatotoxic drugs associated with disease onset or development along with other competing precipitants; (3) identify the development of organ failure and ACLF; and (4) assess patient survival. Any discrepancy between the findings of the two investigators was adjudicated by a senior physician. This study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008), and the study protocol was approved by the Institutional Ethics Review Committee at each center, who waived the need for written informed consent.

Patient selection

Consecutive patients who were hospitalized for severe liver injury [total bilirubin (TBIL) ≥5 mg/dL and international normalized ratio (INR) ≥1.5] [8] or acute decompensation of cirrhosis [ascites or hepatic encephalopathy (HE) or UGIB or jaundice] from chronic HBV infection [HBV surface antigen (HBsAg)–positive for ≥6 months] [9] were initially screened and included in this study.

Patients were excluded if any of the following criteria were met: (1) younger than 18 years or older than 80 years; (2) pregnant; (3) had superimposed infection with other hepatitis viruses (e.g. hepatitis A virus, hepatitis C virus, or hepatitis E virus); (4) had another form of CLD (e.g. alcoholic liver disease, auto-immune hepatitis, Wilson's disease, or Schistosoma liver disease); (5) had hepatocellular carcinoma or other malignancies; (6) had severe comorbidities associated with poor outcome (e.g. active tuberculosis, end-stage renal disease, or chronic obstructive pulmonary disease with respiratory failure); (7) died or was discharged within 24 hours of admission or underwent liver transplant during the 90-day follow-up after admission; (8) lacked key data for evaluating organ failure or diagnosing ACLF [e.g. mean arterial pressure (MAP), percutaneous oxygen saturation (SpO_2), and fraction of inspired oxygen (FiO_2)]; or were (9) lost to follow-up.

Patients with no evidence supporting HBV flare within 4 weeks before admission were excluded from the final analysis. Moreover, patients with competing precipitating events (including alcohol consumption and UGIB) were also excluded to minimize their negative impact on short-term survival data. The flowchart of this study is shown in Fig. 1. During hospitalization, all patients received standard medical treatment, including a high-calorie diet, nucleos(t)ide analogs, sodium restriction and diuretics for ascites, L-or-nithine aspartate for HE, renal dialysis for hepatorenal syndrome, and antibiotic therapy for BI.

Data collection and outcome assessment

We collected the following demographic and clinical data: age, sex, medical history, complications, vital signs (including MAP, SpO_2, and FiO_2), laboratory tests, events of organ failure, treatment information (including renal dialysis, mechanical ventilation, and vasopressor administration), and prognosis. For all patients, data were collected at admission and at diagnosis of ACLF. The Child–Turcotte–Pugh (CTP) [20], model of end-stage liver disease (MELD) [21], MELD-Na [22], and the Chinese Group on the Study of Severe Hepatitis B (COSSH) ACLF scores [5] were calculated at admission. In each patient included in the analysis, instances of organ failure and ACLF development were counted only once according to the first encountered decompensation episode within 4 weeks during hospitalization. The category and course of hepatotoxic drugs (taken by a patient during 7 days around disease onset or within 4 weeks before admission), as well as their adverse effects, were also recorded. All patients were followed-up with for 90 days with respect to their clinical outcome.

Definitions

Active alcohol consumption was defined as more than 14 drinks per week in women and more than 21 drinks per week in men [23]. HBV flare was defined as an upsurge of alanine aminotransferase (ALT) greater than five times the upper limit of normal or more than twice the baseline value with HBV DNA detectable within 4 weeks before admission [8]. BI was diagnosed according to the conventional criteria [9]. The diagnostic criteria for organ failure and ACLF were based on the CLIF-C criteria [23] and the COSSH criteria [5], respectively. The diagnosis of cirrhosis was mainly based on clinical presentation and biochemical and radiological evidence (e.g. shrinkage of or superficial changes in the liver, portal hypertension, ascites, or splenomegaly); some patients undertook liver biopsy, endoscopy, or FibroScan imaging (Echosens, Paris, France) before or after admission, and their results were taken into consideration as well.

Statistical analyses

Categorical variables are presented as frequency (percentage) and were compared using the Chi-square test, followed by Fisher's exact test, as appropriate. Continuous variables with a normal distribution are presented as mean ± SD values and were compared using the Student's *t*-test. Continuous variables with a skewed distribution expressed as median with interquartile range (IQR) values, were compared using the Mann–Whitney *U* test. Kaplan–Meier curves were plotted for survival analyses.

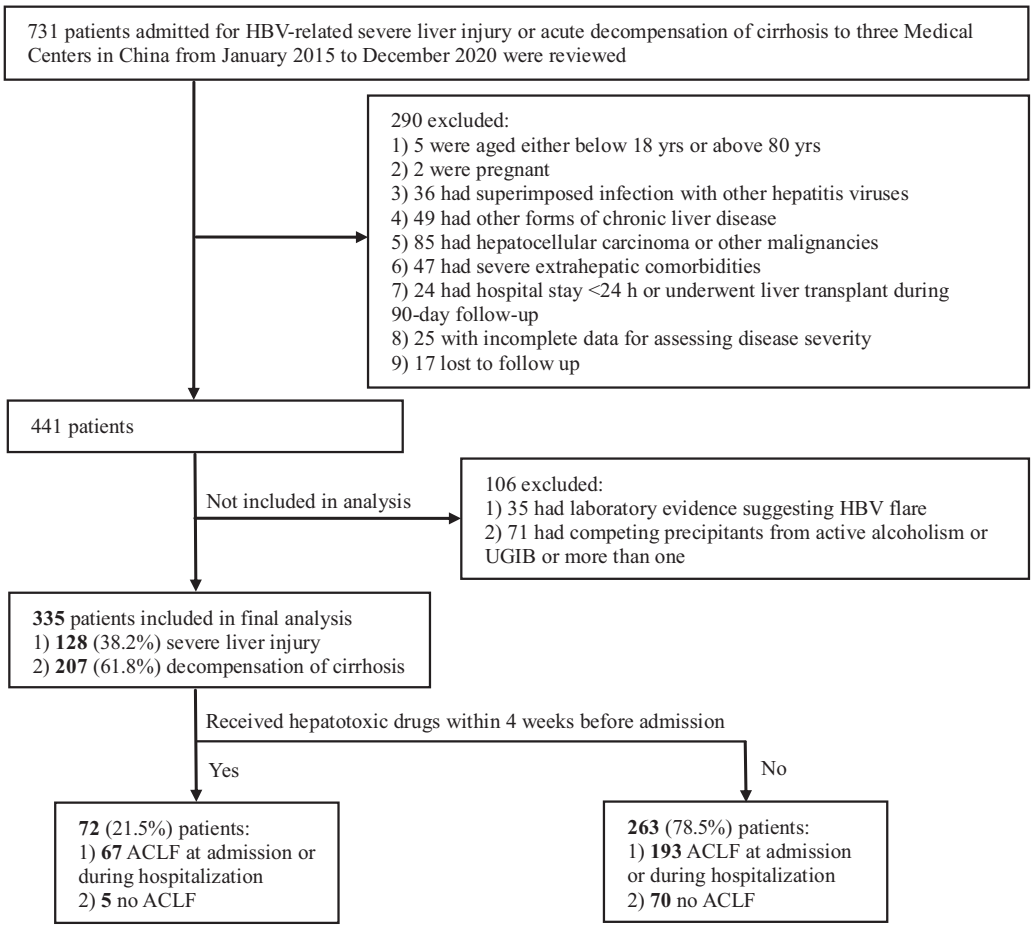

Fig. 1. Flowchart of the study design. Severe liver injury was defined as a total bilirubin level of at least 5 mg/dL and an international normalized ratio of at least 1.5. The diagnosis of ACLF was based on the COSSH criteria. HBV flare was defined as an upsurge of alanine aminotransferase at least five times the upper limit of normal or more than twice the baseline value with HBV DNA detectable within 4 weeks before admission. ACLF, acute-on-chronic liver failure; COSSH, Chinese Group on the Study of Severe Hepatitis B; HBV, hepatitis B virus; UGIB, upper gastrointestinal bleeding.

The cumulative probabilities of survival were compared using the log-rank test. Logistic regression analyses were used to identify risk factors for the development of ACLF. The multivariate model was fitted with a forward stepwise selection method using the factors with $P < 0.1$ in the univariate model. Risk factors for 90-day mortality were identified using the univariate and multivariate Cox regression models likewise. All statistical analyses were performed using the Statistical Package for the Social Sciences version 22.0 (IBM Corporation, Armonk, New York, USA) and GraphPad Prism version 8.1 (GraphPad Software, San Diego, California, USA). A two-tailed P value <0.05 was considered to be statistically significant.

Results

Patient characteristics

From a cohort of 731 patients admitted with HBV-SLI or HBV-AD, 335 patients with HBV flare were finally included in the study population, and were allocated to the drugs group ($n = 72$, 21.5%) or the non-drugs group ($n = 263$, 78.5%) according to whether they had received hepatotoxic drugs in association with disease onset or development (Fig. 1). Among the included patients, the median age was 44 years (IQR, 37–55 years), and 85.7% were male. Additionally, 27.2% had mild extrahepatic comorbidities, including hypertension, diabetes, and non-active tuberculosis, 76.1% were cirrhotic and 61.8% were decompensated cirrhotic. The most common complication was ascites (71.6%), followed by HE (40.9%) and BI (26.6%). Also, 42.7% were HBV envelope antigen (HBeAg)-negative, 45.4% had serum HBV DNA concentrations of greater than 20 000 IU/mL, and 76.1% were antiviral naive (Table 1).

The categories of recorded hepatotoxic drugs are summarized in Table 2. Herbs (44.4%) were the most common form of hepatotoxic drugs, followed by statins (16.7%), hypoglycemic drugs (13.9%), anti-tuberculosis drugs (9.7%), immunosuppressive drugs (5.6%), psychotropic drugs (4.2%), and non-steroidal anti-inflammatory drugs (2.8%). The hepatotoxic constituents of herbs (including *Tripterygium wilfordii* Hook F., *Panax notoginseng*, *Ephedra sinica*, and *Polygonum multiflorum* Thunb.) were identified in only 10 (31.3%) of 32 cases.

Comparison of baseline characteristics between patients with and without hepatotoxic drugs

At admission, patients who had received hepatotoxic drugs differed from those who had not received hepatotoxic drugs in various ways (Table 1). The drugs group had a higher proportion of patients with extrahepatic comorbidities (51.4% vs. 20.5%, P <0.001), particularly non-active

tuberculosis, compared to controls (13.9% vs. 1.1%, P <0.001). HBV flare-related parameters, including HBeAg status and HBV DNA levels, the proportion of cirrhotic patients, and the presence of ascites or BI, were almost equal in the two groups. However, more severe hepatic or extrahepatic dysfunction was observed in the drugs group compared to controls, as indicated by the greater proportion of patients with HE, the higher values of INR, TBIL, and creatinine, and the higher CTP, MELD, MELD-Na, and COSSH scores. No significant differences in other baseline parameters were observed between the two groups.

Development of organ failure and acute-on-chronic liver failure

Of the 335 included patients, 260 (77.6%) patients developed ACLF [ACLF-1, 157 (46.9%); ACLF-2, 61 (18.2%); ACLF-3, 42 (12.5%)], while the remaining 75 (22.4%) patients did not (Fig. 1). In the entire cohort, the proportions of patients with liver, coagulation, cerebral, kidney, circulatory, and respiratory failures were 82.4%, 30.7%, 14.0%, 9.0%, 7.5%, and 4.5%, respectively, with liver failure being the most common type. Compared with controls, patients in the drugs group had a higher prevalence of various organ failures, except respiratory failure (Fig. 2a). Consequently, significantly greater proportions of patients with ACLF, particularly those with ACLF-2 and ACLF-3, were observed in the drugs group (Fig. 2b). There was no significant association between the development of organ failure and the HBeAg status or HBV DNA level (Fig. S1, Supplemental digital content 1, *http://links.lww.com/EJGH/A751*). Also, no significant associations between such two HBV-related parameters and the development of ACLF were observed (Fig. S2, Supplemental digital content 1, *http://links.lww.com/EJGH/A751*).

Short-term survival

Among the 335 transplant-free patients included in this study, the overall survival rate at 90 days from admission was 57.9%. The drugs group had a significantly lower cumulative survival rate at 90 days than controls (44.4% vs. 61.6%, P <0.01) (Fig. 3a). The development of ACLF had a significant negative impact on short-term survival (47.7%), as patients with no ACLF, regardless of using hepatotoxic drugs or not, had a 90-day survival rate of greater than 90% (Fig. 3b). Among 260 patients admitted with or developed ACLF, patients in the drugs group had a lower survival probability at 90 days than controls despite there being no significant difference (40.3% vs. 50.3%, P =0.063) (Fig. 3c). The negative impact of hepatotoxic drugs was further evaluated in different subgroups of ACLF patients according to the status of BI and levels of HBeAg or HBV DNA at admission. Using hepatotoxic drugs was associated with a significant decrease in 90-day survival among 175 ACLF patients without BI at admission (Fig. 4a), but this negative effect was weak among 85 ACLF patients with admission BI (Fig. 4b). No significant associations were observed between 90-day survival and HBeAg status (Fig. S3a, Supplemental digital content 1, *http://links.lww.com/EJGH/A751*) or HBV DNA level (Fig. S3b, Supplemental digital content 1, *http://links.lww.com/EJGH/A751*).

Risk factors for acute-on-chronic liver failure occurrence and 90-day mortality

To identify risk factors for the development of ACLF in 335 included patients, the baseline parameters were analyzed using the logistic regression models. The multivariate logistic model was fitted with a forward stepwise selection method using the clinically and statistically significant variables (P <0.1) in the univariate model. Using hepatotoxic drugs raised the risk of ACLF occurrence by 7.66-fold [95% confidence interval (CI), 1.68–34.86], with HE [odds ratio (OR), 10.63; 95% CI, 3.02–37.36] and TBIL (OR, 1.49; 95% CI, 1.34–1.65) being two other independent risk factors for ACLF occurrence (Table 3). The risk factors for 90-day mortality were analyzed using the Cox regression models likewise, except that cases of ACLF occurrence were defined as patients with ACLF at admission or those who developed ACLF post-admission. The multivariate Cox regression analysis showed that ACLF occurrence was the strongest risk factor for 90-day mortality [hazard ratio (HR), 5.54], followed by HE (HR, 3.22), BI (HR, 2.58), and INR (HR, 1.37) (Table 4).

Discussion

This study is unique in that it assessed the combined effects of hepatotoxic drugs and HBV flare on the development of ACLF in patients with acute deterioration of HBV-related chronic disease. Recent research on HBV-ACLF has confirmed that concurrence of HBV flare and BI contributes to increased organ failures and ACLF development in patients with HBV-AD [9]. However, less is known about whether hepatotoxic drugs are involved in the progression of HBV-ACLF. The present study demonstrated that hepatotoxic drugs were associated with disease onset or development in more than 10% of 731 patients with HBV-SLI or HBV-AD initially screened, and contributed to more organ failures, ACLF development, and increased short-term mortality in 335 patients with HBV flare.

Previous studies on ACLF have focused on patients with AD from alcohol liver disease, with the precipitant events mostly presenting as BI and active drinking [24–26]. However, in China and many other countries in the Asia-Pacific region, chronic HBV infection is the main etiology of ACLF and a significant proportion of ACLF patients are non-cirrhotic [6,8]. A multicenter prospective observational study conducted by the COSSH indicated that 25.3% of 363 patients with HBV-ACLF progressed from HBV-SLI (non-cirrhotic ACLF), and the short-term mortality rates of patients with non-cirrhotic ACLF and cirrhotic-ACLF (developing from HBV-AD), respectively, were equal [5]. In the present study, the study population included patients with HBV-SLI and HBV-AD, and therefore, ACLF was diagnosed per the COSSH criteria. Our data showed that 20.4% of 260 patients with HBV-ACLF were non-cirrhotic, with a similar 90-day mortality rate compared to that of cirrhotic-ACLF (41.5% vs. 50.2%, P >0.05); this was consistent with the findings of the COSSH study.

In this study, hepatotoxic drugs were used by 38.2% of 335 included patients; such an association and corresponding patient grouping scheme were largely based on a strong temporal relationship between exposure to

Table 1. Baseline characteristics of 335 included patients

Variable	Total ($N=335$)	Drugs group ($n=72$)	Non-drugs group ($n=263$)	P value
Median age (IQR), years	44 (37–55)	44 (39–61)	43 (36–54)	0.066
Male sex, *n* (%)	287 (85.7)	58 (80.6)	229 (87.1)	0.162
Comorbidities, *n* (%)				
Hypertension	35 (10.4)	15 (20.8)	20 (7.6)	0.002
Diabetes	33 (9.9)	12 (16.7)	21 (8.0)	0.049
Non-active tuberculosis	13 (3.9)	10 (13.9)	3 (1.1)	<0.001
Other	27 (8.1)	8 (11.1)	19 (7.2)	0.283
Total	91 (27.2)	37 (51.4)	54 (20.5)	<0.001
Cirrhosis, *n* (%)	255 (76.1)	53 (73.6)	202 (76.8)	0.573
Decompensated	207 (61.8)	41 (56.9)	166 (63.1)	0.340
Complications, *n* (%)				
Ascites	240 (71.6)	50 (69.4)	190 (72.2)	0.641
Encephalopathy	137 (40.9)	41 (56.9)	96 (36.5)	0.002
Bacterial infection	89 (26.6)	22 (30.6)	67 (25.5)	0.387
Antiviral naive, n (%)	247 (73.7)	54 (75.0)	193 (73.4)	0.782
HBeAg postive, *n* (%)	139 (41.5)	29 (40.3)	110 (41.8)	0.813
HBV DNA, *n* (%)				
<200, IU/mL	80 (23.9)	18 (25.0)	62 (23.6)	0.926
200–2×10^4, IU/mL	99 (29.6)	20 (27.8)	79 (30.0)	
>2×10^4, IU/mL	156 (46.6)	38 (47.2)	122 (46.4)	
Laboratory parameters, median (IQR)				
Hemoglobin, g/L	123 (108–137)	120 (108–133)	124 (108–138)	0.076
White blood cell count, $\times10^9$ /L	6.3 (4.7–8.5)	6.4 (5.1–8.5)	6.3 (4.7–8.8)	0.686
Platelet, $\times10^9$ /L	93 (61–128)	91 (52–118)	93 (65–130)	0.237
International normalized ratio	1.9 (1.6–2.6)	2.3 (1.8–3.1)	1.8 (1.5–2.4)	0.004
Total bilirubin, mg/dL	17.7 (12.1–23.5)	20.7 (14.1–24.5)	16.6 (10.5–23.2)	0.004
Alanine aminotransferase, IU/L	241 (89–736)	233 (94.5–608)	245 (88–786)	0.672
Aspartate aminotransferase, IU/L	190 (99–453)	182 (98.3–395.8)	197 (99–459)	0.589
Albumin, g/L	32 (29–35)	32.3 (29.5–35.9)	31.9 (29–35.6)	0.444
Creatinine, mg/dL	0.8 (0.6–1.0)	0.9 (0.7–1.1)	0.7 (0.6–0.9)	<0.001
Sodium, mmol/L	136 (133–139)	136 (132.3–139.8)	137 (133–139)	0.785
Severity score, median (IQR)				
CTP	11 (10–12)	11 (10–13)	11 (9–12)	0.017
MELD	23.2 (17.9–27.7)	23.8 (20.9–29.4)	21.2 (17.1–26.5)	<0.001
MELD-Na	22.9 (17.8–30.2)	26.8 (21.8–33.0)	22.2 (17.0–29.3)	<0.001
COSSH ACLF score	3.5 (2.6–4.9)	4.3 (3.5–5.6)	3.2 (2.5–4.5)	<0.001

A patient was allocated to the drugs group or the non-drugs groups according to whether he or she received hepatotoxic drugs associated with disease onset or development (within 4 weeks before admission). Categorical variables are expressed as numbers (%), and continuous variables are expressed as median (interquartile range) values.
ACLF, acute-on-chronic liver failure; COSSH, the Chinese Group on the Study of Severe Hepatitis B; CTP, Child–Turcotte–Pugh; HBeAg, hepatitis B envelope antigen; HBV, hepatitis B virus; MELD, model for end-stage liver disease.

Table 2. Category of hepatotoxic drugs involved in this study

Category	Frequency (%)
Herbs	32 (44.4)
Identified constituents[a]	10 (31.3)
Unidentified constituents	22 (68.8)
Statins	12 (16.7)
Hypoglycemic drugs	10 (13.9)
Anti-tuberculosis drugs	7 (9.7)
Immunosuppressive drugs	4 (5.6)
Antiepileptic drugs	3 (4.2)
Non-steroidal anti-inflammatory drugs	2 (2.8)
Others	2 (2.8)

Hepatotoxic drugs involved in the analysis were largely based on a strong temporal relationship between exposure to hepatotoxic drugs and disease onset or development (within 4 weeks before admission).
[a]Four types of hepatotoxic herbs, including *Tripterygium wilfordii* Hook F. ($n=4$), *Panax notoginseng* ($n=3$), *Ephedra sinica* ($n=2$), and *Polygonum multiflorum* Thunb ($n=1$).

hepatotoxic drugs and disease onset or development (within 4 weeks before admission) because of a wide variety of constituents of hepatotoxic drugs (particularly herbs) and the absence of effective laboratory tests to establish the definitive diagnosis of drug-induced liver injury. Although nearly half of 52 patients with mild comorbidities (e.g. hypertension and diabetes) in the control group undertook relevant medications with potential hepatotoxicity, they were not allocated to the study group because there was no evidence suggesting the presence of hepatotoxic drugs, or there was no significant relationship between the onset or development of disease and patient exposure to drugs with potential hepatotoxicity. Moreover, among the 335 included patients, some of them had insignificant elevated ALT levels or undetectable HBV DNA levels at admission because of receiving complimentary and antiviral treatment at outpatient or local hospitals; their medical history and laboratory data outside were taken to support HBV flare.

Although HBV flare is regarded as the main trigger of HBV-ACLF, the host's immune dysregulation, not direct damage caused by HBV leads to the development of the disease, and controversies persist regarding the specific role of HBV flare in ACLF development [27]. In the 335 patients (all patients with HBV flare) included in this study, there were significant disparities in disease severity, development of organ failure and ACLF, and 90-day mortality between patients with and without hepatotoxic drugs, whereas such differences were not observed when considering HBV-related parameters (including HBeAg status and HBV DNA levels) between the two groups. Our findings suggested that, compared to HBV flare alone, hepatotoxic drugs accelerated the progression of HBV-SIL/AD to HBV-ACLF. Moreover, 71 patients with other forms of competing precipitants (including active alcoholism and

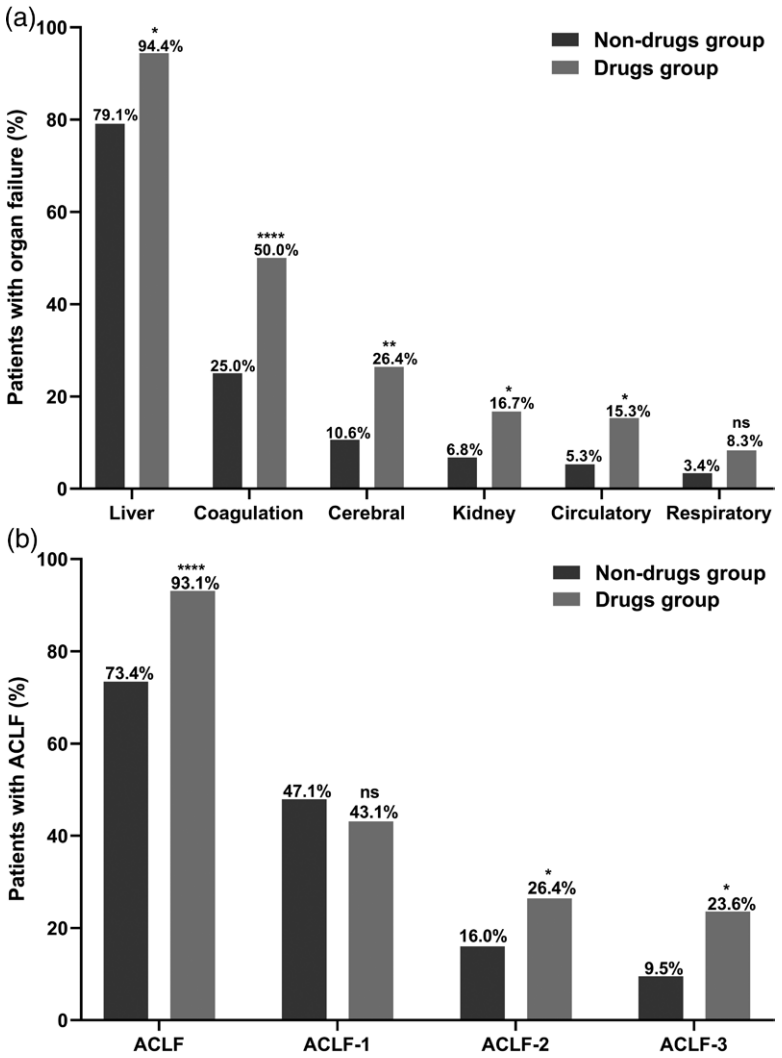

Fig. 2. Comparisons of the development of organ failure (a) and acute-on-chronic liver failure (ACLF) (b) between patients who have and have not been administered hepatotoxic drugs. Organ failures and ACLF development were counted only once using the first encountered decompensation episode within 4 weeks during hospitalization. Diagnosis of organ failure was based on the CLIF-C criteria. ACLF was diagnosed and graded according to the COSSH criteria. Categorical variables were compared using the Chi-squared test, followed by Fisher's exact test, as appropriate. ACLF, acute-on-chronic liver failure; CLIF-C, Chronic Liver Failure Consortium; COSSH, the Chinese Group on the Study of Severe Hepatitis B.

UGIB) were excluded from the study population because these acute insults have been recognized as having negative impacts on short-term survival in patients with AD or ACLF [23,26,28].

In the Asia-Pacific region, especially in China and India, herbs are very popular for cultural and economic reasons and have been increasingly used in the management of numerous diseases, including CLD [16]. However, there are limited data available on the negative effects of herbs on the development of ACLF. Our data showed that herbs accounted for more than 40% of hepatotoxic drugs taken by 72 patients involved in this study population, and the hepatotoxic constituents (including *Tripterygium wilfordii* Hook F., *P. notoginseng*, *E. sinica*, and *P. multiflorum* Thunb.) [16,29] were identified in only 31.3% of these herbs. This finding was consistent with the research conducted by APASL and suggested the difficulty in diagnosis of herbs-induced liver injury because of a wide variety of their constituents [18]. Moreover, statins (16.7%) and oral hypoglycemic drugs (13.9%) were two other types of hepatotoxic drugs involved in this study; this was consistent with the higher proportions of patients with hypertension or non-end-stage diabetes observed in the drugs group. Anti-tuberculosis drugs and immunosuppressive drugs only composed 15.3% of involved hepatotoxic drugs because many patients with active tuberculosis or other severe comorbidities were excluded to minimize any potential interference with short-term survival data.

Numerous studies have suggested that in patients with AD or ACLF from alcoholic-related liver cirrhosis, BI is the most frequent precipitant event and significantly contributes to ACLF development [24,30–32]. Recent research on HBV-ACLF have also confirmed this negative impact and corresponding elevated inflammatory indexes like the neutrophil-to-lymphocyte ratio on short-term mortality [33,34]. However, because of objective limitations (e.g. long-term management in local hospitals before admission; administration of prophylactic antibiotics, particularly extra-broad spectrum antibiotics), it is difficult to accurately identify the role of BI (acute insults of ACLF development or mere secondary infections after

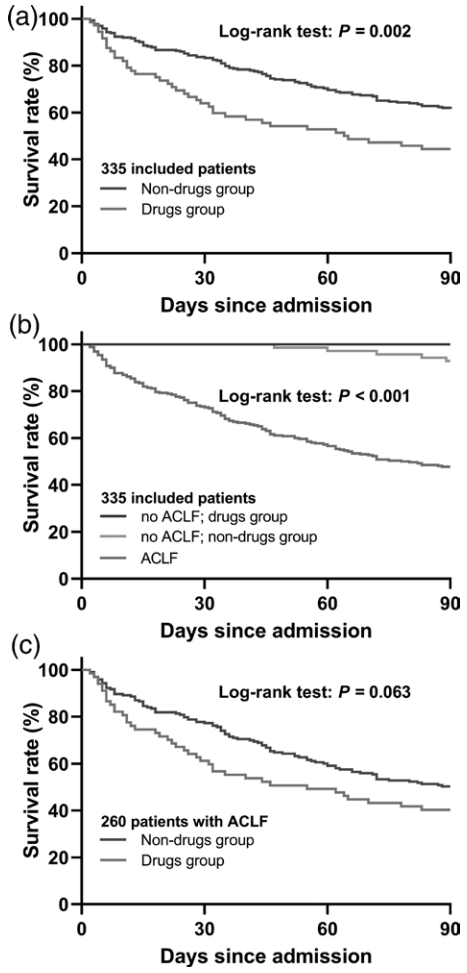

Fig. 3. Cumulative survival rates at 90 days after admission were analyzed using the Kaplan–Meier method. Rates were compared between the following patient subgroups: (a) patients who received and did not receive hepatotoxic drugs within 4 weeks before admission (drugs group, $n = 72$; non-drugs group, $n = 263$); (b) patients with no acute-on-chronic liver failure (ACLF) in the drugs group ($n = 5$), those with no ACLF in non-drugs group ($n = 70$), and those admitted with or developed ACLF ($n = 260$); and (c) ACLF patients in the drugs group ($n = 67$) and in the non-drugs group ($n = 193$). ACLF was diagnosed and graded according to the COSSH criteria. ACLF, acute-on-chronic liver failure; COSSH, the Chinese Group on the Study of Severe Hepatitis B.

ACLF occurrence) in some patients, especially in non-cirrhotic patients with ACLF. Of the 335 patients included in the analysis, nearly 25% were non-cirrhotic, more than 40% received prophylactic antibiotics before admission, and more than 25% had BI upon admission; therefore, we did not exclude those with admission BI. Of note, our data showed that patients with and without hepatotoxic drugs had similar incidence rates of admission BI, and that hepatotoxic drugs, not admission BI, were highly predictive of ACLF occurrence in the multivariate regression model. Our data also showed that, for the entire cohort, admission BI was highly predictive of 90-day mortality; this finding was consistent with previous research.

Although patient data were systematically collected and strictly interpreted per the cross-checking protocol, this study has some limitations other than its retrospective design. First, the patient grouping scheme was largely based on medical history (use of hepatotoxic drugs within 4 weeks before admission) because of objective limitations. Second, episodes of HBV flare may not have been accurately captured in some participants because of irregular outpatient examinations and interference owing to antiviral therapy before admission. Moreover, it was difficult to entirely eliminate the effects of competing participants like BI on short-term survival among the study participants, although there was no significant difference in the incidence of admission BI between the drugs and non-drugs groups. Only 72 patients with hepatotoxic drugs were included in the study population, possibly resulting in a statistical bias (e.g. there was no significant difference in 90-day survival rates between ACLF patients in the two groups). Our findings need to be validated in future prospective research and a larger cohort.

In summary, there is a strong correlation between hepatotoxic drugs and the development or progression of HBV-ACLF. Hepatotoxic drugs contribute to more organ failures, the development of ACLF, and a higher 90-day mortality rate among patients with acute decompensation of HBV-CLD. Restricting the use of hepatotoxic drugs may be beneficial for preventing disease progression and improving short-term survival among these patients.

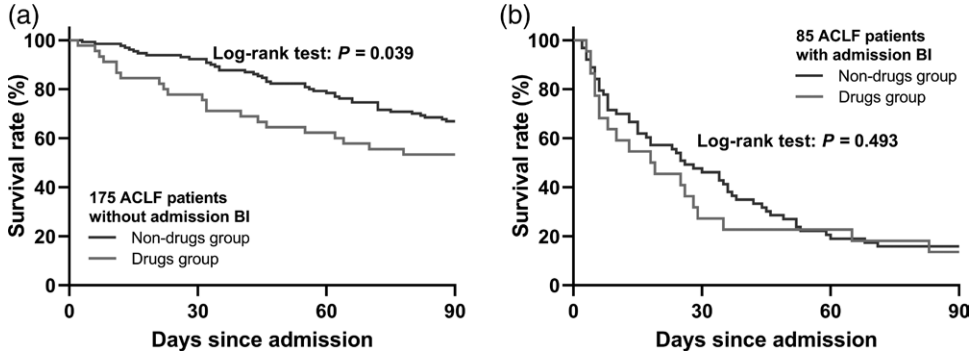

Fig. 4. Kaplan–Meier curves were used to analyze the 90-day survival rates in 260 patients admitted with or who developed HBV-ACLF. Rates were compared between the following patient subgroups: (a) 175 HBV-ACLF patients without admission BI (drugs group, $n = 45$; non-drugs group, $n = 130$) and (b) 85 HBV-ACLF patients with admission BI (drugs group, $n = 22$; non-drugs group, $n = 63$). ACLF was diagnosed and graded according to the COSSH criteria. BI, bacterial infection; COSSH, the Chinese Group on the Study of Severe Hepatitis B; HBV-ACLF, hepatitis B virus-related acute-on-chronic liver failure.

Table 3. Logistic regression analysis of risk factors for the development of acute-on-chronic liver failure in 335 included patients

	Univariate		Multivariate	
Parameter	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.03 (1.02–1.03)	<0.001		
Cirrhosis	4.31 (3.15–5.90)	<0.001		
Ascites	4.85 (3.47–6.79)	<0.001		
Hepatic encephalopathy	25.52 (7.84–83.09)	<0.001	10.63 (3.02–37.36)	<0.001
Bacterial infection	8.62 (3.05–24.40)	<0.001		
INR	3.09 (2.10–4.55)	<0.001		
Total bilirubin	1.65 (1.47–1.84)	<0.001	1.49 (1.34–1.65)	<0.001
HBeAg positive	3.09 (2.10–4.55)	<0.001		
HBV DNA level	1.65 (1.47–1.84)	<0.001		
Antiviral naive	3.18 (2.38–4.27)	<0.001		
With hepatotoxic drugs	13.4 (5.40–33.25)	<0.001	7.66 (1.68–34.86)	0.008

The multivariate logistic regression model was fitted with a forward stepwise selection method using the risk factors (admission parameters) with $P<0.01$ in the univariate model.
ACLF, acute-on-chronic liver failure; HBeAg, hepatitis B envelope antigen; HBV, hepatitis B virus; CI, confidence interval; INR, international normalized ratio; OR, hazard ratio.

Table 4. Cox regression analysis of risk factors for the 90-day mortality in 335 included patients

	Univariate		Multivariate	
Parameter	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.03 (1.01–1.04)	<0.001		
Cirrhosis	2.10 (1.32–3.34)	0.002		
Ascites	2.57 (1.63–4.05)	<0.001		
Hepatic encephalopathy	8.90 (5.99–13.21)	<0.001	3.22 (1.36–7.66)	0.009
Bacterial infection	6.23 (4.44–8.74)	<0.001	2.58 (1.84–4.56)	<0.001
INR	1.84 (1.68–2.02)	<0.001	1.37 (1.22–1.54)	<0.001
Total bilirubin	1.08 (1.06–1.10)	<0.001		
HBeAg positive	0.74 (0.52–1.05)	0.088		
HBV DNA level	1.14 (0.93–1.41)	0.217		
Antiviral-naive	0.74 (0.52–1.05)	0.090		
With hepatotoxic drugs	1.79 (1.24–2.58)	0.002		
ACLF development	11.08 (4.54–27.06)	<0.001	5.54 (3.48–8.91)	<0.001

The Cox regression model was fitted with a forward stepwise selection method using the risk factors with $P<0.01$ in the univariate model. All factors were calculated using admission parameters, except ACLF development (including ACLF diagnosed at admission and within 4 weeks during hospitalization).
ACLF, acute-on-chronic liver failure; CI, confidence interval; HBeAg, hepatitis B envelope antigen; HBV, hepatitis B virus; HR, hazard ratio; INR, international normalized ratio.

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J.S. and X.P.Y. designed the study and constructed the framework. Z.Y.W., L.J., J.Y., H.T.Z., J.G., N.W., and J.H.Y. performed data collection and patient follow-up. Z.Y.W. and L.J. performed data interpretation and statistical analysis. J.S. drafted the article. X.P.Y. critically reviewed the article. All authors have read and approved the final version of the article.

Conflicts of interest

There are no conflicts of interest.

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