HBV-related acute-on-chronic liver failure with underlying chronic hepatitis has superior survival compared to cirrhosis

Xiaohui Liu[a,*], Jing Zhang[a,*], Xinhuan Wei[a], Zhongping Duan[a], Hongqun Liu[b], Yu Chen[a], Yali Liu[a,†] and Samuel S. Lee[b]

Background Acute-on-chronic liver failure (ACLF) is divided into three types according to the underlying liver disease: non-cirrhosis (type A), compensated cirrhosis (type B) and decompensated cirrhosis (type C). However, whether the underlying chronic liver diseases impact the ACLF prognosis is not clear. The present study aimed to compare the characteristics and outcomes of type A and type B hepatitis B virus (HBV)-ACLF patients.

Methods According to the European Association for the Study of Liver-Chronic Liver Failure (EASL-CLIF) diagnostic criteria, 86 type A HBV-ACLF and 71 type B HBV-ACLF were prospectively enrolled. The demography and laboratory data, organ failures, ACLF grades and prognosis were evaluated. Univariate and multivariate Cox regression analyses were performed to analyze the prognostic factors.

Results The 28-day and 90-day mortality rates of type A and type B ACLF were 20.9 vs. 60.6% and 34.9 vs. 73.2%, respectively (both $P<0.001$). Patients with type A ACLF were younger, had higher viral load and higher levels of alanine aminotransferase and aspartate aminotransferase, platelet count, serum albumin and sodium, international normalized ratio and alpha-fetoprotein, lower rate of ascites, lower Child-Pugh scores and CLIF sequential organ failure assessment scores, higher rate of coagulation failure. Type B ACLF had more renal and cerebral failure. Cirrhosis was one of the independent prognostic factors [hazard ratio, 2.4 (95% CI, 1.451–3.818) $P<0.001$].

Conclusion ACLF developing on noncirrhotic chronic hepatitis B had more serious liver inflammation but fewer extrahepatic organ failures and better outcome than ACLF developing from compensated HBV cirrhosis. Eur J Gastroenterol Hepatol 33: e734–e739

Background

Acute-on-chronic liver failure (ACLF) is defined as acute decompensation of underlying chronic liver disease with short-term higher mortality rate than 15%. There are four diagnostic criteria of ACLF [1–4], the most accepted diagnostic criteria were proposed by the European Association for the Study of the Liver-chronic Liver Failure (EASL-CLIF) consortium in 2013 [1] and the Asian Pacific Association for Study of the Liver (APASL) in 2019 [4]. One of the crucial differences between the two criteria is the type of underlying chronic liver disease (CLD). The EASL criteria defined compensated and decompensated-vcirrhosis as the underlying CLD. APASL criteria emphasized that ACLF only develops from compensated liver diseases, such as viral hepatitis, compensated cirrhosis, nonalcoholic steatohepatitis, cholestasis liver disease and metabolic liver diseases. Jalan *et al.* [5,6] proposed that ACLF should be classified into three types according to the underlying CLD, namely, noncirrhotic liver disease (type A), compensated cirrhosis (type B) and decompensated cirrhosis (type C). However, whether the underlying CLDs impact the ACLF prognosis is not clear. We aimed to examine the clinical significance of the classification by comparing characteristics and outcomes between the type A and type B hepatitis B virus (HBV)-ACLF cohort.

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Keywords: acute-on-chronic liver failure, cirrhosis, hepatitis B, prognosis

[a]The Third Unit, Department of Hepatology, Beijing Youan Hospital, Capital Medical University, Beijing, People's Republic of China and [b]Liver Unit, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

Correspondence to Samuel S. Lee, MD, Liver Unit, Cumming School of Medicine, University of Calgary, 1869 HSC, 3330 Hospital Dr. NW, Calgary AB T3A 4R2, Canada
Tel: +403 220 8457; e-mail: samlee@ucalgary.ca

*Dr. Xiaohui Liu and Dr. Jing Zhang contributed equally to the writing of this article.
†Yali Liu is the co-correspondence.

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Methods

Study population

From April 2017 to March 2018, 178 patients with HBV-ACLF were prospectively recruited from 7 hospitals in China. They were: Beijing Youan Hospital, Capital Medical University; The Ninth Hospital of Nanchang; The Second People's Hospital of Fuyang; Hepatobiliary Hospital of Jilin Province; The First Teaching Hospital of Xinjiang Medical University; The First Affiliated Hospital of Lanzhou

University and the Sixth People's Hospital of Kaifeng. The research was approved by the Beijing Youan Hospital ethics committee on 30 August 2016 and conformed to the ethical guidelines of the 1975 Declaration of Helsinki. All the other hospitals used the Youan ethics approval. All patients provided written informed consent. If the consent was unable to be provided by the patient with hepatic encephalopathy, it was obtained from the next of kin.

The inclusion criteria: age between 18 and 70 years, acute decompensation, hepatitis B surface antigen positive, met EASL-CLIF ACLF criteria, but the underlying liver disease was chronic hepatitis (noncirrhosis) or compensated cirrhosis. The exclusion criteria: past history of decompensated cirrhosis; co-infection with other viral hepatitis virus such as hepatitis A virus, hepatitis C virus, hepatitis D virus, hepatitis E virus; HIV infection; complicated with other liver diseases (such as autoimmune, alcohol or drug-related diseases, etc.); acute hepatitis B; severe extra-hepatic diseases; pregnancy, malignancy and so on (Fig. 1).

Chronic liver failure-sequential organ failure assessment (CLIF-SOFA) score was applied to evaluate organ failures and organ dysfunction. These were: liver failure, bilirubin ≥12.0 mg/dL; renal failure, serum creatinine ≥2.0 mg/dL or with renal support therapy; cerebral failure, hepatic encephalopathy of grades III–IV; coagulation failure, INR ≥2.5 or platelet $\leq 20 \times 10^9$/L; respiratory failure, PaO_2/FiO_2 ≤200 or SpO_2/FiO_2 ≤214; circulatory failure, vasoconstrictor is required to maintain arterial pressure. In addition, renal dysfunction (serum creatinine of 1.5–1.9 mg/dL) and (or) cerebral dysfunction (hepatic encephalopathy grades I–II) were also used for the diagnosis of EASL-ACLF in patients with single nonrenal organ failure [1]. ACLF grade 1 (ACLF-1) was defined as renal failure, or a nonrenal organ failure with creatinine level of 1.5–2.0 mg/dL and (or) grade I or II hepatic encephalopathy. ACLF-2 had two organ failures, and ACLF-3 involved three or more organ failures.

Treatment and follow-up

All patients received nutrition support (25–30 kcal/kg/d, enteral or parenteral), treatment of complications such as ascites, hepatic encephalopathy, infection and hepatorenal syndrome (HRS). Nucleos(t)ide analogues (NA) were routinely given, including entecavir 0.5–1 mg/d, lamivudine 100 mg/d, adefovir dipivoxil 100 mg/d and tenofovir 300 mg/d, as monotherapy or combined therapy. The type of NA therapy does not affect the prognosis of HBV-induced ACLF [7,8].

Data collection included demographics, history of decompensation, complications, viral load, biochemical examination tests, abdominal ultrasound or computed tomography or MRI and gastroscopy. Hepatic encephalopathy was classified according to the West Haven Criteria [9]. Cirrhosis was diagnosed based on clinical, biochemical, endoscopic (esophageal varices at least grade II in size), radiologic imaging and B-mode ultrasonography [10].

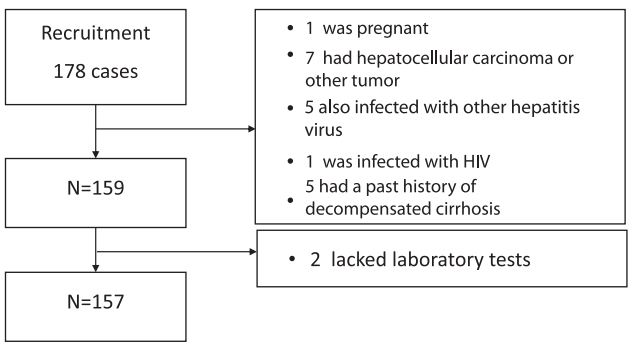

Fig. 1. Screening, enrollment and flow of patients.

Statistical analysis

Statistical analysis was performed with SPSS 16.0 software for windows (Chicago, Illinois, USA). Normally distributed data were expressed as mean ± SD and differences between two groups were assessed by a Student's *t*-test. Non-normally distributed data were expressed as medians (range) and differences between two groups were assessed by a Wilcoxon rank-sum test. Numerical counts were expressed as the number (percentage) and the differences among groups were assessed by a chi-square test. The Kaplan–Meier method was used to estimate the overall survival rates. Univariate and multivariate Cox regression analyses were performed for quantitative and qualitative data to evaluate the prognostic factors on overall survival. Significance was determined at $P < 0.05$.

Results

Clinical characteristics at enrollment and outcome

A total of 178 patients with HBV-ACLF were screened and 21 patients were excluded. Eighty-six patients who developed ACLF from chronic hepatitis B were assigned to the type A group. Seventy-one with compensated cirrhosis were assigned to the type B group.

Compared with type B, patients with type A ACLF were significantly younger, had higher HBV DNA load, platelet count, and higher levels of alanine aminotransferase (ALT), aspartate aminotransferase, international normalized ratio (INR), serum albumin and sodium. The levels of bilirubin were comparable between the two groups (23.8 ± 7.9 mg/dL vs. 24.5 ± 6.9 mg/dL; $P = 0.577$). The median AFP level of type A ACLF was 229.4 mg/L (3.6, 2980), which was significantly higher than that of type B [42.4 mg/L (1.1, 3500); $P < 0.001$]. The type A patients also had lower rates of ascites (58.1 vs. 95.8%; $P < 0.001$), Child-Turcotte-Pugh score [11 (9, 14) vs. 13 (10, 14); $P < 0.001$] and CLIF-SOFA score [8 (7, 13) vs. 9 (7, 14); $P < 0.001$]. The model of end-stage liver disease (MELD) &&scores of the two groups were similar (28.1 ± 4.5 vs. 28.4 ± 6.2; $P = 0.752$). The 28-day and 90-day mortality rates were significantly lower in type A ACLF than type B ACLF (20.9 vs. 60.6%, 34.9 vs. 73.2%, both $P < 0.001$). (Table 1). Kaplan–Meier analysis showed that the survival curves were significantly different between the two groups ($P < 0.001$, Fig. 2).

Organ failures in type A and type B groups

The most common type of organ failure in both type A and type B groups were liver and coagulation failure. The proportions of liver failure in both groups were similar (100% vs. 98.6%, $P = 0.452$). Coagulation failure rates were significantly higher in type A ACLF than type B (82.6 vs. 62.0%), $P = 0.004$). The proportion of renal failure (1.2%) and cerebral failure (7.0%) in type A were much less than type B (16.9 and 18.3%, both $P < 0.05$). Compared with type A, type B ACLF tends to develop multiple organ failures (Table 1).

Table 1. Baseline characteristics of HBV-acute-on-chronic liver failure

Characteristic	Type A ACLF ($n=86$)	Type B ACLF ($n=71$)	*P* value
Age (years)	39.7±11.0	45.9±10.3	<0.001
Male sex (*n*, %)	75 (87.2%)	64 (90.1%)	0.566
Ascites (*n*, %)	50 (58.1%)	68 (95.8%)	<0.001
Laboratory data			
WBC (×10^9/L)	6.6 (3.5,24.5)	8.7±4.7	0.629
Platelet (×10^9/L)	112.0 (22.0,282.0)	83.5±5.7	<0.001
ALT (U/L)	407.3 (37.9,3169.0)	145.2 (15.9,1858.0)	<0.001
AST (U/L)	276.5 (45.0,2291.0)	182.5 (30.4,1765.2)	0.002
Bilirubin (mg/dL)	23.8±7.9	24.5±6.9	0.577
Albumin (g/L)	30.8±5.0	29.1±5.0	0.038
SCr (mg/dL)	0.8 (0.3,4.2)	0.8 (0.3,3.7)	0.854
Na (mmol/L)	134.5±4.6	132.1±5.0	0.002
PT (s)	33.7±7.2	31.8±8.2	0.110
PTA (%)	25.1±7.0	25.9±8.4	0.471
INR	3.0±0.7	2.7±0.7	0.020
AFP (ng/mL)	229.4 (3.63,2980.0)	42.4 (1.12,3500)	<0.001
HBV DNA (log_{10} IU/ml)	5.5±1.5	4.7±1.6	0.002
Organ failures			
Liver	86 (100%)	70 (98.6%)	0.452
Kidney	1 (1.2%)	12 (16.9%)	<0.001
Cerebral	6 (7.0%)	13 (18.3%)	0.03
Coagulation	71 (82.6%)	44 (62.0%)	0.004
Circulation	0	0	–
Lungs	0	0	–
Kidney dysfunction	2 (2.3%)	3 (4.2%)	0.827
Mild to moderate hepatic encephalopathy	15 (17.4%)	34 (47.9%)	<0.001
CTP score	11 (9,14)	13 (10,14)	<0.001
MELD score	28.1±4.5	28.4±6.2	0.752
CLIF-SOFA score	8 (7,13)	9 (7,14)	<0.001
28-day mortality rate	18/86 (20.9 %)	43/71 (60.6%)	<0.001
90-day mortality rate	30/86 (34.9%)	52/71 (73.2%)	<0.001

The normal distribution data were expressed as mean±SD and non-normal distributed data were expressed as median (minimum, maximum).
ACLF, acute-on-chronic liver failure; AFP, alpha fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLIF SOFA, chronic liver failure-sequential organ failure assessment; CTP, Child-Tureotte-Pugh score; HBV, hepatitis B virus; INR, international normalized ratio; MELD, model of end-stage liver disease; PT, prothrombin time; PTA, prothrombin activity; SCr, Serum creatinine; WBC, white blood cell.

Multiorgan failures in different acute-on-chronic liver failure grades

The proportions of grades 1, 2, 3 in type A ACLF were 15.1, 80.2 and 4.7%, respectively. The proportions were 29.6, 45.1 and 25.3% in type B, respectively ($P<0.001$). Totally, 18 of 22 grade 3 patients were in the type B group. The results showed that type B ACLF was more severe than type A. The types of multiorgan failures and death rates in each grade of type A and B groups are shown in Table 2.

Mortality rates in different acute-on-chronic liver failure grades

The 90-day mortality rates were different among the ACLF grades in the whole group (52.9% for grade 1, 45.5% for grade 2 and 81.8% for grade 3, $P=0.008$). In the type B group, the mortality rate was significantly lower in ACLF grade 1 (57.1%) than in ACLF 3 (94.4%, $P=0.031$). But there were no mortality differences among the three grades in the type A group (Table 3).

Prognostic factors

The underlying CLD, age, bilirubin and platelet counts were found to be independently associated with the 90-day mortality in the total cohort of ACLF patients. The prognostic factors for 28-day mortality of all ACLF patients were

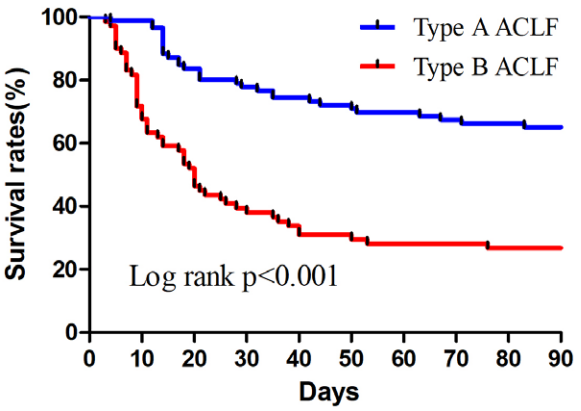

Fig. 2. Survival curves of HBV-ACLF patients. Type A ACLF, $n=86$; Type B ACLF, $n=71$. Type A: ACLF patients with hepatitis B as underlying liver disease. Type B: ACLF patients with HBV-related compensated cirrhosis as underlying liver disease. ACLF, acute-on-chronic liver failure; HBV, hepatitis B virus.

underlying CLD, age, bilirubin and INR. The hazard ratio of underlying cirrhosis was 2.4 [(95% CI, 1.451–3.818) $P=0.001$] when compared to non-cirrhosis (Table 4).

In the type A group, age and bilirubin were the independent factors for both 28-day and 90-day prognosis. In the type B group, the factors were age and INR. The detailed univariate and multivariate analysis are shown in Supplementary Table 1-4, Supplemental digital content 1, *http://links.lww.com/EJGH/A707*.

Discussion

No global consensus has yet been achieved on whether ACLF should be classified into three subtypes according to the underlying liver disease, perhaps in part due to a paucity of studies specifically examining the prognostic value of such a classification system. We thus aimed to examine this concept in our Chinese population of ACLF patients. In East Asia, most ACLF develops from underlying hepatitis B-related liver disease, either chronic hepatitis or cirrhosis [11–13]. In the present study, we focused only on the HBV-related ACLF cohorts to make the groups as homogeneous as possible because it is now well recognized that ACLF with underlying alcoholic cirrhosis as seen in the West is significantly different from HBV-related ACLF [1,4,11,14]. Additionally, we chose the CLIF-C EASL classification system rather than the APASL ACLF Research Consortium system because other Asian studies [13] as well as our previous studies [11,12] showed that the CLIF ACLF system provides superior short-term prognostication ability. The risk of death increased about 2.4-fold if the underlying liver disease was compensated cirrhosis rather than chronic hepatitis.

According to the EASL criteria, ACLF has three major characteristics: acute decompensation, multiorgan failure and a high 28-day mortality rate (predefined threshold of 15%). In our cohort, type A ACLF had a multiorgan failure and the 28-day mortality rate was 20.9%, suggesting that chronic hepatitis can be an underlying liver disease predisposing to ACLF. Li *et al.* [15] analyzed 183 HBV-ACLF liver transplantation patients and found that the livers from nine patients presented only pathologic massive hepatocyte necrosis without cirrhosis. Thus, their

Table 2. The multi-organ failure types of total and deceased patients in different acute-on-chronic liver failure grades

	Type A ACLF		Type B ACLF	
ACLF grades	Types of organ failure	Total/deceased number (%)	Types of organ failure	Total/deceased number (%)
Grade 1	Liver failure and mild to moderate hepatic encephalopathy	11 (12.8)/5 (16.7)	Liver failure and mild to moderate hepatic encephalopathy	18 (25.4)/10 (19.2)
	Liver failure and kidney dysfunction	2 (2.3)/1 (3.3)	Liver failure and kidney dysfunction	3 (4.2)/2 (3.8)
Grade 2	Liver and coagulation failure	67 (77.9)/22 (73.3)	Liver and coagulation failure	26 (36.6)/19 (36.5)
	Liver and cerebral failure	2 (2.3)/1 (3.3)	Liver and kidney failure	3 (4.2)/2 (3.8)
			Liver and cerebral failure	2 (2.8)/2 (3.8)
			Coagulation and kidney failure	1 (1.4)/0 (0.0)
Grade 3	Liver, coagulation, cerebral and kidney failure	1 (1.2)/1 (3.3)	Liver, coagulation and kidney failure	7 (9.9)/6 (11.5)
			Liver, coagulation and cerebral failure	10 (14.1)/10 (19.2)
	Liver, coagulation and cerebral failure	3 (3.5)/0 (0.0)	Liver, coagulation, kidney and cerebral failure	1 (1.4)/1 (1.9)
	Total	86/30		71/52

ACLF, acute-on-chronic liver failure.

Table 3. The 90-day mortality of patients with different acute-on-chronic liver failure grades

	Grade 1	Grade 2	Grade 3	*P* value	*P1*	*P2*	*P3*
Type A ACLF	46.2% (6/13)	33.3% (23/69)	25% (1/4)	0.666	0.568	1.000	0.603
Type B ACLF	57.1% (12/21)	71.9% (23/32)	94.4% (17/18)	0.031	0.804	0.366	0.033
All ACLF patients	52.9% (18/34)	45.5% (46/101)	81.8% (18/22)	0.008	0.455	0.006	0.084

P value is for comparisons between all the three grades of ACLF; *P*1 value is for comparisons between grade 1 and grade 2, *P*2 value is for comparisons between grade 2 and grade 3, *P*3 value is for comparisons between grade 1 and grade 3.
ACLF, acute-on-chronic liver failure.

Table 4. Multivariate Cox regression analysis of risk factors for 28-day and 90-day mortality

		Multivariable analysis for 28-day mortality			Multivariable analysis for 90-day mortality		
		Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Total groups	Age (years)	1.035	1.010–1.060	0.006	1.029	1.009–1.050	0.004
	CLD	3.904	2.196–6.938	<0.001	2.354	1.451–3.818	0.001
	Platelet ($\times 10^9$/L)	–	–	–	0.995	0.990–1.000	0.044
	Bilirubin (mg/dL)	1.038	1.001–1.077	0.043	1.040	1.009–1.073	0.005
	INR	1.498	1.053–2.130	0.024	–	–	–
Type A group	Age (years)	1.045	1.002–1.090	0.039	1.035	1.002–1.070	0.036
	Bilirubin (mg/dL)	1.076	1.023–1.133	0.005	1.089	1.044–1.137	<0.001
Type B group	Age (years)	1.031	1.001–1.062	0.046	1.035	1.008–1.062	0.011
	INR	1.662	1.101–2.509	0.016	1.542	1.056–2.251	0.025

CI, confidence interval; CLD, chronic liver disease; INR, international normalized ratio..

study also indicated that chronic hepatitis can be one of the underlying conditions of ACLF. A similar phenomenon was also described [16].

The manifestations were significantly different between the two groups in our study. The patients with type A ACLF were younger and had higher virus loads, which are consistent with the natural history of hepatitis B. Levels of transaminases, INR and the proportion of coagulation failure were significantly higher in type A ACLF than type B. These parameters suggest that liver inflammation was more severe in type A. AFP was increased significantly in the type A group, suggesting that these patients had a strong liver-regenerative ability, which may be a major explanation for the improved prognosis compared to the cirrhotic patients. In type B ACLF, the higher rates of ascites, renal failure and cerebral failure, and lower levels of albumin, serum sodium and platelets could be explained by underlying cirrhosis.

The common features of two groups were prominently elevated ALT, bilirubin, INR and high proportion of liver failure and coagulation failure. These results were consistent with previous studies. In Wu's study, the rates of liver failure and coagulation failure in type A HBV-ACLF were 100 and 75% respectively; these rates were 93.7 and 68.3% in cirrhotic patients (both compensated and decompensated cirrhosis) [16]. A similar result was also seen in the study of Choudhury *et al.*, [17]. These results are consistent with the idea that a significant proportion of HBV-ACLF is characterized by massive or submassive necrosis, regardless of whether the ACLF develops from hepatitis or cirrhosis [15]. But in Western cohorts, such as the CANONIC study [1], the most common organ failure is renal failure. The reason may be that the causes of western ACLF are mainly alcohol, sepsis and hepatitis C, and all patients have underlying cirrhosis. The preexisting portal hypertension may thus predispose to hepatic encephalopathy and renal failure.

To our knowledge, this is one of the few studies to compare the clinical manifestations and outcomes among subtypes of ACLF. Tang *et al.* [18] found that type A ACLF were younger, had higher platelet counts, aminotransferase levels, less renal failure and more active HBV replications. Those results were similar to the present studies. However, in Tang's cohort, 28-day mortality rates were

similar between the type A and B ACLF (48.7 vs. 48.4%; $P=0.941$). The 90-day mortality rate differences between the two groups did not reach statistical significance [54.5 vs.62.8% ($P=0.08$)]. Thus the mortality data in the Tang study differ from ours. We speculate that there may be two reasons for the discrepancy. The first reason may be the sample size: it is possible that a larger sample size may have made the 90-day mortality differences statistically significant at the p+0.05 level. The second reason may be differences in patient selection. Noteworthy is that the MELD score of the type A patients in the Tang study was significantly higher than our type A patients (mean 33.3 vs. 28.1, respectively)

Three other studies also investigated the survival in different ACLF subtypes. The large multicenter, multinational study of Chen *et al.* [14] reported that there were no significant differences in 28-day or 90-day mortality rates between cirrhotic and noncirrhotic groups. That study lumped all cirrhosis, both compensated and decompensated, into one category. Therefore, their results are not directly comparable to ours. Two other studies, one from Korea [14], another from China [16], also showed no survival difference between cirrhotic and noncirrhotic ACLF patients. Similarly, both these studies also lumped both compensated and decompensated cirrhotics into one category.

In our study, the mortality rates increased with the ACLF grades in the overall ACLF cohort and in the type B ACLF cohort, which was consistent to the previous studies [1]. But the mortality rates were similar among the three grades in type A ACLF. We assumed two possible reasons. First, there were only four patients with grade 3 in type A ACLF which may not reflect the real mortality of such patients. Second, type A patients appeared to have stronger liver regeneration. That may offset the effect of the severity of liver injury on mortality. But these assumptions need to be confirmed by further research.

Multivariate analysis showed that underlying liver disease was one of the independent risk factors of death. It was well known that cirrhotic liver has fewer hepatocytes and lower ability of regeneration. Portal hypertension and portosystemic shunt cause hepatic encephalopathy, ascites, HRS and other complications. Type B ACLF therefore had more organ failure and higher mortality rate.

Limitations of the present study include the following: the total number of cases was relatively small and the diagnosis of underlying compensated cirrhosis was not based on pathology. All the patients had HBV-related ACLF, so whether our results are applicable to other causes of ACLF needs further verification.

Conclusions

In conclusion, our study showed that type A ACLF without cirrhosis was clearly distinct from type B with underlying compensated cirrhosis. The noncirrhotic patients had more severe liver inflammation, less extrahepatic organ failures and better prognosis. Our results support the concept that ACLF should be classified into three types according to the underlying liver disease. Different types of ACLF may have different pathogenesis, clinical characteristics, management and prognosis. Further research based on type of ACLF may help physicians improve predictive and prognostic ability in patients with ACLF.

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The research was approved by the Beijing Youan Hospital ethics committee on 30 August 2016 and conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. All patients provided written informed consent. If the patient had encephalopathy or was unable to provide consent, it was obtained from the next of kin.

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All patients provided written informed consent.

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

J. Z. and Z.D. designed the study. X.L. collected and analyzed the data, X.L. and H.Q.L. drafted the article. S.S.L. revised the article critically.

Conflicts of interest

There are no conflicts of interest.

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