Hepatology International (2019) 13:695–705
https://doi.org/10.1007/s12072-019-09992-x

ORIGINAL ARTICLE

Complications constitute a major risk factor for mortality in hepatitis B virus-related acute-on-chronic liver failure patients: a multi-national study from the Asia–Pacific region

Tao Chen[1] · Zhongyuan Yang[1] · Ashok Kumar Choudhury[2] · Mamun Al Mahtab[3] · Jun Li[4] · Yu Chen[5] · Soek-Siam Tan[6] · Tao Han[7] · Jinhua Hu[8] · Saeed S. Hamid[9] · Lee Guan Huei[10] · Hasmik Ghazinian[11] · Yuemin Nan[12] · Yogesh K. Chawla[13] · Man-Fung Yuen[14] · Harshad Devarbhavi[15] · Akash Shukla[16] · Zaigham Abbas[17] · Manoj Sahu[18] · A. K. Dokmeci[19] · Laurentias A. Lesmana[20] · Cosmas Rinaldi A. Lesmana[20] · Shaojie Xin[8] · Zhongping Duan[5] · Wei Guo[1] · Ke Ma[1] · Zhongwei Zhang[1] · Qiuyu Cheng[1] · Jidong Jia[21] · B. C. Sharma[22] · Shiv Kumar Sarin[2] · Qin Ning[1]

Received: 10 June 2019 / Accepted: 28 September 2019 / Published online: 24 October 2019

Abstract

Background and Aim Cirrhosis is a controversial determinant of mortality in HBV-related acute-on-chronic liver failure (HBV–ACLF). The present study aimed to explore the effects of cirrhosis and the associated risk factors, especially its complications, on the outcome of HBV–ACLF.

Methods A prospective–retrospective cohort of 985 patients was identified from the APASL–ACLF Research Consortium (AARC) database and the Chinese Study Group. Complications of ACLF (ascites, infection, hepatorenal syndrome, hepatic encephalopathy, upper gastrointestinal bleeding) as well as cirrhosis and the current main prognostic models were measured for their predictive ability for 28- or 90-day mortality.

Results A total of 709 patients with HBV–ACLF as defined by the AARC criteria were enrolled. Among these HBV–ACLF patients, the cirrhotic group showed significantly higher mortality and complications than the non-cirrhotic group. A total of 36.1% and 40.1% of patients met the European Association for the Study of Liver (EASL)–Chronic Liver Failure consortium (CLIF-C) criteria in the non-cirrhotic and cirrhotic groups, respectively; these patients had significantly higher rates of mortality and complications than those who did not satisfy the CLIF-C criteria. Furthermore, among patients who did not meet the CLIF-C criteria, the cirrhotic group exhibited higher mortality and complication rates than the non-cirrhotic group, without significant differences in organ failure. The Tongji prognostic predictor model score (TPPMs), which set the number of complications as one of the determinants, showed comparable or superior ability to the Chinese Group on the Study of Severe Hepatitis B–ACLF score (COSSH–ACLFs), APASL–ACLF Research Consortium score (AARC–ACLFs), CLIF-C organ failure score (CLIF–C OFs), CLIF-C–ACLF score (CLIF-C–ACLFs), Model for End-Stage Liver Disease score (MELDs) and MELD–sodium score (MELD–Nas) in HBV–ACLF patients, especially in cirrhotic HBV-–ACLF patients. Patients with two (OR 4.70, 1.88) or three (OR 8.27, 2.65) complications had a significantly higher risk of 28- or 90-day mortality, respectively.

Conclusion The presence of complications is a major risk factor for mortality in HBV–ACLF patients. TPPM possesses high predictive ability in HBV–ACLF patients, especially in cirrhotic HBV–ACLF patients.

Keywords HBV · Acute-on-chronic liver failure · Cirrhosis · Prognostic scores · Mortality

Abbreviations

ACLF	Acute-on-chronic liver failure
HBV–ACLF	HBV-related acute-on-chronic liver failure
AARC	Asia-pacific association for the study of liver ACLF research consortium
APASL	ACLF research consortium score (AARC–ACLFs)

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12072-019-09992-x) contains supplementary material, which is available to authorized users.

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CLIF-C OF	Chronic liver failure consortium organ failure
CLIF-C ACLF	CLIF-C acute-on-chronic liver failure
MELD	Model for end-stage liver disease
MELD–Na	MELD–sodium score
TPPM	Tongji prognostic predictor model
COSSH–ACLF	Chinese Group on the Study of Severe Hepatitis B-ACLF
AUROC	Area under the receiver operating characteristic curve

Introduction

Acute-on-chronic liver failure (ACLF) is a complex clinical syndrome with high morbidity and mortality [1]. HBV infection is the main etiology of ACLF in the Asia–Pacific region, whereas alcohol and HCV infection are the main etiologies in Europe and North America [1]. Most ACLF patients in the Asia–Pacific region have ACLF that was precipitated by hepatic insults, while extrahepatic insults are the precipitants in Europe and North America [1, 2]. Hepatic or extrahepatic insults in HBV–ACLF could result in differences in clinical manifestations and disease prognosis [3].

Complications of ACLF, including ascites, infection, hepatorenal syndrome, hepatic encephalopathy and gastrointestinal bleeding, constitute the main risk factors for disease progression, triggering multi-organ dysfunction and failure in ACLF [4–9] Cirrhosis is a late phase in chronic liver disease. Previous studies have indicated controversial results regarding the use of cirrhosis as a determinant of mortality in HBV–ACLF.

Several prognostic systems were established to evaluate the mortality due to short-term progression in end-stage liver disease regardless of etiology, such as the APASL–ACLF Research Consortium score (AARC–ACLFs), Chronic Liver Failure Consortium organ failure score (CLIF-C OFs), CLIF-C acute-on-chronic liver failure score (CLIF-C ACLFs), Model for End-Stage Liver Disease score (MELDs) and MELD–sodium score (MELD–Nas) [10–12]. Recently, the Tongji prognostic predictor model score (TPPMs) and Chinese Group on the Study of Severe Hepatitis B-ACLF score (COSSH–ACLFs) were developed specifically in HBV–ACLF patients and showed excellent predictive values [5–7].

The TPPM scoring system was established and validated in HBV–ACLF patients, and it showed superior predictive value compared with the MELD system. Furthermore, so far, it is the only model that includes complications as risk factors. However, the differential effectiveness of the predictive ability of cirrhosis between current models has not yet been fully elucidated.

In the present study, we evaluated ACLF-associated complications and cirrhosis as key determinants in disease progression and compared the predictive values of the TPPMs, AARC–ACLFs, COSSH–ACLFs, CLIF-C OFs, CLIF-C ACLFs, MELDs and MELD–Nas for short-term mortality in an Asia–Pacific multi-national cohort diagnosed with ACLF according to the APASL–ACLF research consortium (AARC) criteria.

Patients and methods

Subjects

A total of 985 patients from the AARC database and the Chinese Study Group who were diagnosed with "chronic severe hepatitis B" or "HBV–ACLF" between 2006 and 2018 were prospectively and retrospectively identified. A total of 709 patients who fulfilled the 2014 AARC ACLF criteria were enrolled, of whom 620 were enrolled between 2014 and 2018, and 89 were enrolled before 2014 [13]. The data were collected using a pre-defined, web-based proforma in the AARC database (http://www.aclf.in). Approval from the institutional ethics committees was obtained. The data were annotated and encrypted before analysis. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Asia–pacific Association for the Study of Liver ACLF Research Consortium) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study. The members of the AARC working party assumed full responsibility for the accuracy and completeness of the data and subsequent analyses. All authors had access to the study data and reviewed and approved the final manuscript.

The country/region and the number of patients contributed are listed as follows:

Country/region	Patients
China	639
India	153
Bangladesh	117
Malaysia	33
Pakistan	19
Singapore	11
Armenia	8
HongKong, China	3
Turkey	1
Indonesia	1
Total	985
Complete data for analysis	709

In detail, the HBV–ACLF diagnostic criteria mainly included jaundice (serum total bilirubin ≥ 5 mg/dl) and coagulopathy (INR ≥ 1.5 or prothrombin activity < 40%), accompanied by ascites and/or encephalopathy within 4 weeks. The screening and enrolment processes are shown in Fig. 1.

Complications of HBV–ACLF included ascites, hepatorenal syndrome (HRS), hepatic encephalopathy (HE), infection, and upper gastrointestinal bleeding [8, 9]. The diagnosis of ascites relied on the patient's history, physical examination, imaging evidence and laboratory assessment of liver function. Ascites was classified into grade 1 or mild ascites, grade 2 or moderate ascites and grade 3 or large ascites [7, 14, 15]. HRS was mainly defined by serum creatinine level (Cr > 1.5 mg/dl) regardless of cirrhosis. It was graded as two types: type 1 HRS, manifested as a rapid and progressive impairment of kidney function, and type 2 HRS, manifested as a stable or less progressive impairment of kidney function [14, 15]. HE was defined by the West Haven criteria. It was graded as 4 levels: I, II, III and IV [15, 16]. Infection was defined by physical examination, laboratory tests, imaging evidence and clinical manifestations [4, 7]. Upper gastrointestinal bleeding was defined by the bleeding history and endoscopic findings [7, 17].

Nucleot(s)ide analogues (NAs) were prescribed according to HBV–DNA levels and patient willingness. A total of 688 patients (97.04%) received oral antiviral treatment: 503 patients (70.94%) were treated with entecavir, 95 patients (13.40%) with lamivudine, 17 patients (2.40%) with adefovir, 16 patients (2.26%) with telbivudine, 10 patients (1.41%) with tenofovir, and 47 patients (6.63%) with a combination of two NAs. All patients were treated with standard medical therapy during their hospital stays. At the attending physicians' discretion, this included but was not limited to glutathione; compound glycyrrhizin; transmetil; hepatocyte growth-promoting factors; vitamin K1; sodium restriction; diuretics and paracentesis combined with albumin infusion for ascites; artificial liver support system (ALSS) with indications; lactulose and L-ornithine aspartate for hepatic encephalopathy; prophylactic antibiotics for bacterial infections and renal replacement for hepatorenal syndrome and uremic symptoms; and coagulation factor supplementation with fresh plasma and cryoprecipitates. Patients were closely monitored during treatment for clinical manifestations, and laboratory examinations were performed as needed.

Study design

A total of 709 AARC HBV–ACLF patients were sub-divided into non-cirrhotic and cirrhotic groups with or without complications. Cirrhosis was diagnosed based on radiological

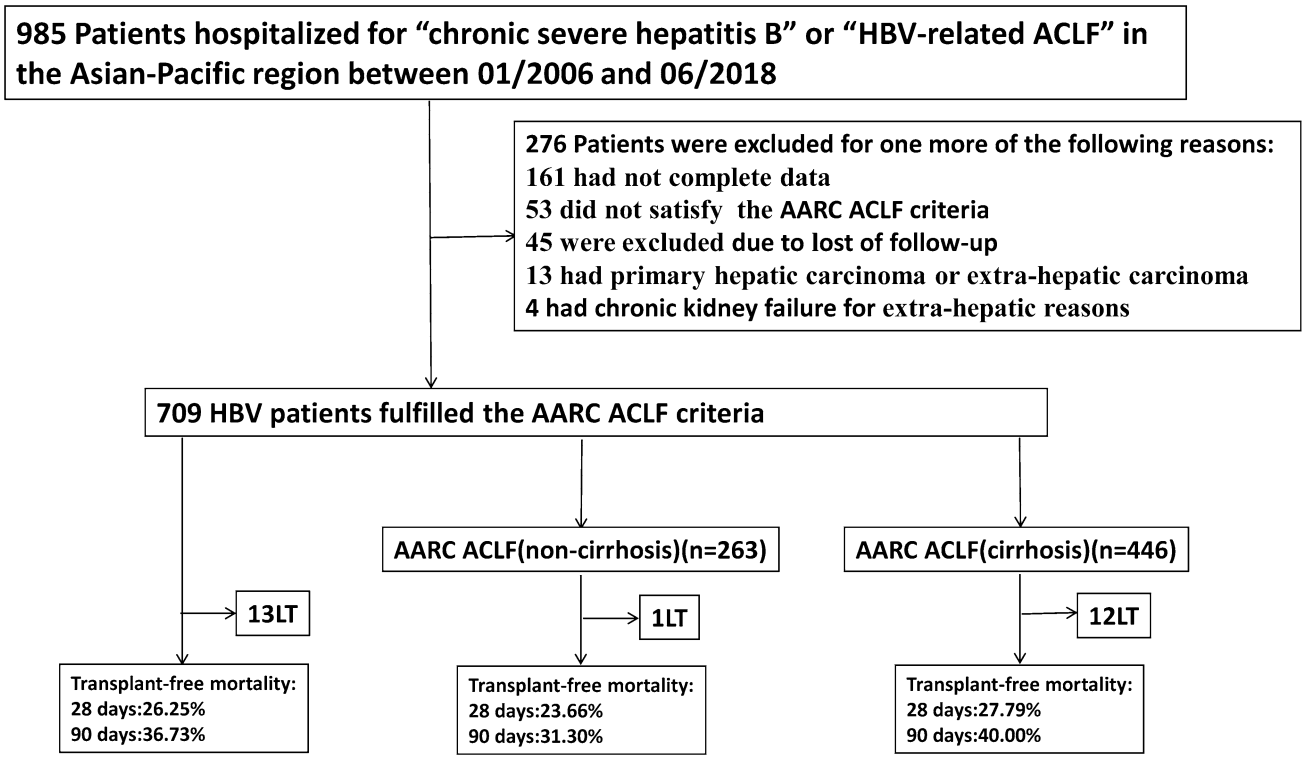

Fig. 1 Screening and enrollment of patients with HBV–ACLF as defined by AARC criteria. A total of 985 patients who were diagnosed with "chronic severe hepatitis B" or "HBV–ACLF" from the AARC database and the Chinese Study Group between 2006 and 2018 were screened. A 709 of patients who fulfilled the 2014 AARC ACLF criteria were enrolled

imaging and endoscopy results regarding liver nodularity and/or portal hypertension or the clinical evidence of previous hepatic decompensation and laboratory tests and/or liver biopsy in patients with CHB [3]. According to the CLIF-C criteria [18], patients in the non-cirrhotic and cirrhotic groups were further sub-divided into non-CLIF-C ACLF and CLIF-C ACLF groups for subgroup analysis. Organ failure was diagnosed by the CLIF-C SOFA criteria [18]. Clinical characteristics and short-term mortality rates were analysed in all patients according to their definitions. The area under the receiver operating characteristic curve (AUROC) was used to compare the superiority of the models among the TPPM, AARCs, COSSH–ACLF, CLIF-C OF, CLIF-C ACLF, MELD, and MELD–Na.

The TPPMs uses the TBIL, INR, HBV–DNA and number(s) of complications as parameters [5, 6], which showed good prognostic ability in patients with HBV–ACLF. The AARC–ACLFs include the TBIL, HE grade, PT-INR, lactate and creatinine as parameters that showed adequate prognostic value in the overall AARC database [19]. The COSSH–ACLF was created based on the TBIL, INR, age and HBV–SOFA, and it was modified according to the CLIF–SOFA criteria and verified in a Chinese HBV–ACLF cohort [7]. The CLIF-C OF score was established based on the sequential organ failure assessment (SOFA), and it showed comparable ability to the CLIF–SOFA and was superior to the MELDs and MELD–Nas in ACLF patients in intensive care units [12]. The CLIF-C OFs and two other independent predictors of mortality (age and white blood cell count) were combined to develop a specific prognostic score for ACLF, the CLIF Consortium–ACLF score (CLIF-C ACLFs) [12]. The MELD score (serum bilirubin, serum creatinine and international normalized ratio for prothrombin time) and MELD–Na score (Meld score and serum sodium) are scoring systems used to assess the severity of chronic liver disease [10, 11]. They are prognostic models that are used to determine the severity and extent of liver disease to support decisions regarding specialist medical interventions, such as specific medical treatments and liver transplantation.

Data collection

The following clinical data were collected at enrolment: demographic data, vital signs, physical examination results, history, complications, precipitating events, antiviral treatment plan, and laboratory measurements, e.g., white blood cell (WBC) count, hemoglobin (Hb) level, platelet (PLT) count, alanine aminotransferase (ALT) level, aspartate aminotransferase (AST) level, serum albumin (ALB) level, total bilirubin (TBIL) level, serum sodium (Na) level, serum creatinine (Cr) level, the international normalized ratio (INR), pulse oximetry, HBV infection biomarker levels, and HBV–DNA levels. Telephone follow-up calls helped confirm the prognosis at 28 and 90 days and information regarding liver transplantation after hospital discharge.

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation, and they were compared by Student's *t* tests and/or the Mann–Whitney *U* test. Categorical variables are presented as frequencies and percentages, and they were compared by the Chi square test or Fisher's exact test. The AUROCs were used to compare the predictive ability of the TPPMs, AARCs, COSSH–ACLFs, CLIF-C OFs, CLIF-C ACLFs, MELDs and MELD–Nas with regard to the short-term mortality rate. Values were also compared by DeLong's test. A p value less than 0.05 was considered statistically significant, and all statistical analyses were performed with SPSS release 23.0 for Windows (SPSS, Inc., Chicago, IL) and MedCalc software (version 11.4, Ostend, Belgium).

Results

More complications and high mortality in cirrhotic HBV–ACLF

Among a total of 709 HBV patients who fulfilled the AARC ACLF criteria, 446 (62.90%) patients had cirrhosis. HBV–DNA, ALT, AST, ALB, TBIL, Hb, PLT, and serum Na levels were significantly higher in the non-cirrhotic group than in the cirrhotic group. However, age and Cr, AFP, and CRP levels were significantly higher in the cirrhotic group. Patients in the cirrhotic group had more complications, including ascites, bacterial or fungal infections and upper gastrointestinal bleeding. Similarly, a significantly higher 90-day mortality rate was observed in cirrhotic patients, although there was no difference in 28-day mortality between the cirrhotic and non-cirrhotic groups (Table 1). However, organ failure as defined by the CLIF-C criteria in patients with and without cirrhosis was not significantly different (Supplementary Table 1).

High mortality in cirrhotic HBV–ACLF patients who did not meet the CLIF-C criteria

In total, 709 patients had ACLF according to the AARC criteria, and 274 patients were diagnosed with ACLF according to the CLIF-C criteria. Patients from the CLIF-C ACLF group exhibited more severe laboratory indexes regardless of the presence of cirrhosis when compared with those from the non-CLIF-C ACLF group. CLIF-C ACLF patients had worse levels of ALB, TBIL, Cr, serum Na, INR, WBC; a higher incidence of complications (especially HRS and HE);

Table 1 Baseline characteristics of the HBV–ACLF patients defined by AARC criteria with and without cirrhosis

Variates	AARC ACLF (non-cirrhosis) ($n=263$)	AARC ACLF (cirrhosis) ($n=446$)	p value
Age (years)	44.66 ± 13.43	46.78 ± 12.86	0.015
Male sex	228 (86.69)	375 (84.08)	0.346
HBV–DNA ($\log_{10}$(copies/ml))	6.24 ± 1.99	5.50 ± 1.74	0.000
ALT (U/L)	646.26 ± 912.08	373.46 ± 511.65	0.000
AST (U/L)	677.00 ± 885.05	393.01 ± 572.97	0.000
ALB (g/L)	32.09 ± 23.05	28.85 ± 6.41	0.002
TBIL (mg/dl)	19.12 ± 8.57	19.86 ± 9.75	0.531
Cr (mg/dl)	1.08 ± 1.39	1.11 ± 1.01	0.014
Na (mmol/L)	135.19 ± 5.76	134.12 ± 6.38	0.001
INR	2.41 ± 1.11	2.34 ± 0.93	0.712
WBC ($\times 10^9$/L)	8.36 ± 4.45	8.27 ± 4.94	0.294
Hb (g/L)	124.15 ± 27.74	115.67 ± 25.55	0.000
PLt ($\times 10^9$/L)	142.67 ± 67.23	117.09 ± 82.14	0.000
AFP (ng/ml)	185.11 ± 337.31	209.91 ± 1359.99	0.003
CRP (mg/L)	15.60 ± 15.52	18.56 ± 16.55	0.014
Complications			
Ascites	172 (65.40)	393 (88.12)	0.000
Bacterial or fungal infection	46 (17.49)	144 (32.29)	0.000
Hepatorenal syndrome	30 (11.41)	65 (14.57)	0.232
Hepatic encephalopathy	44 (16.73)	90 (20.18)	0.257
HE (I–II)	32 (12.17)	68 (15.25)	0.255
HE (III–IV)	12 (4.56)	22 (4.93)	0.824
Upper gastrointestinal bleeding	10 (3.80)	40 (8.97)	0.009
Transplant-free mortality			
28 days	62 (23.66)	122 (27.79)	0.230
90 days	82 (31.30)	174 (40.00)	0.021

Data are expressed as mean ± standard deviation or number of patients (%)

AARC Asian Pacific Association for the Study of Liver (APASL)ACLF Research Consortium, *WBC* white blood cell, *Hb* hemoglobin, *PLT* blood platelet, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ALB* albumin, *TBIL* total bilirubin, *Na* sodium, *Cr* creatinine, *INR* international standardization ratio, *AFP* alpha-fetoprotein, *CRP* c-reactive protein, *HE* hepatic encephalopathy

a higher incidence of organ failure (liver, coagulation, kidney and cerebral); and eventually, higher 28-day and 90-day mortality rates (Table 2).

The 274 patients who met the CLIF-C ACLF criteria included 95 non-cirrhotic ACLF patients (non-cirrhotic CLIF-C ACLF group) and 179 cirrhotic ACLF patients (cirrhotic CLIF-C ACLF group). When compared with non-cirrhotic patients, the cirrhotic CLIF-C ACLF group had lower HBV–DNA, ALT, AST, Hb, PLT and INR levels and a higher incidence of complications (ascites, bacterial or fungal infection and upper gastrointestinal bleeding), while there was no difference in the incidence of organ failure or the short-term mortality rate (Table 2).

However, in the majority of patients (63.9% in the non-cirrhotic group and 59.9% in the cirrhotic group) who did not meet the CLIF-C criteria, cirrhotic patients exhibited higher mortality rates and incidence of complications than non-cirrhotic patients, without a significant difference in organ failure (Table 2).

TPPMs shows adequate predictive value in HBV–ACLF patients

Among all patients, the predictive abilities of the TPPMs (0.847, 0.804) and COSSH–ACLFs (0.851, 0.804) were superior to those of the CLIF-C OFs (0.835, 0.783, $p=0.472$, 0.221), AARC–ACLFs (0.790, 0.766, $p=0.096$, 0.219),CLIF-C ACLFs (0.773, 0.738, $p=0.001$, 0.005), MELDs (0.789, 0.748, $p=0.001$, 0.002) and MELD–Na (0.783, 0.756, $p<0.001$, 0.013) in predicting 28-day and 90-day mortality, respectively. Notably, the TPPMs (0.847, 0.804) and COSSH–ACLFs (0.851, 0.804) showed equivalent effectiveness in predicting short-term mortality in the entire cohort of patients (Table 3).

Table 2 Baseline characteristics of the HBV–ACLF patients and comparison of the clinical variables according to varies definitions

Variates	AARC ACLF (non-cirrhosis)		AARC ACLF (cirrhosis)	
	Non-CLIF-C ACLF ($n=168$)	CLIF-C ACLF ($n=95$)	Non-CLIF-C ACLF ($n=267$)	CLIF-C ACLF ($n=179$)
Age (years)	43.65 ± 12.93	46.42 ± 14.18	46.75 ± 12.19[♯]	46.83 ± 13.84
Male sex	147 (87.50)	81 (85.26)	220 (82.40)	155 (88.59)
HBV–DNA ($\log_{10}$(copies/ml))	6.21 ± 1.92	6.30 ± 2.13	5.53 ± 1.74[♯]	5.46 ± 1.73[§]
ALT(U/L)	558.46 ± 669.37	803.17 ± 1221.19	308.67 ± 402.55[♯]	470.83 ± 630.53[§,‡]
AST(U/L)	651.87 ± 774.63	720.91 ± 1053.70	338.97 ± 465.74[♯]	473.62 ± 696.91[§]
ALB (g/L)	34.27 ± 28.17	28.28 ± 7.37[†]	29.25 ± 6.11[♯]	28.25 ± 6.81
TBIL (mg/dl)	17.19 ± 8.03	22.54 ± 8.47[†]	17.20 ± 9.03	23.83 ± 9.45[‡]
Cr (mg/dl)	0.76 ± 0.22	1.65 ± 2.19[†]	0.83 ± 0.28[♯]	1.53 ± 1.47[‡]
Na (mmol/L)	136.41 ± 4.57	133.07 ± 6.92[†]	134.69 ± 5.47[♯]	133.28 ± 7.47[‡]
INR	1.92 ± 0.44	3.28 ± 1.38[†]	1.97 ± 0.52	2.90 ± 1.11[§,‡]
WBC ($\times 10^9$/L)	7.20 ± 3.60	10.38 ± 5.06[†]	6.98 ± 3.39	10.21 ± 6.14[‡]
Hb (g/L)	126.43 ± 29.36	120.13 ± 24.23[†]	118.59 ± 24.02[♯]	111.32 ± 27.17[§,‡]
PLt ($\times 10^9$/L)	138.75 ± 62.96	149.52 ± 73.96	113.37 ± 77.83[♯]	122.60 ± 88.07[§]
AFP(ng/ml)	224.05 ± 382.63	85.97 ± 134.06[†]	168.13 ± 284.30[♯]	288.70 ± 2281.26[‡]
CRP(mg/L)	16.34 ± 16.00	13.50 ± 14.06	17.36 ± 14.03	20.97 ± 20.67
Complications				
Ascites	111 (66.87)	61 (64.21)	234 (87.64)[♯]	159 (88.83)[§]
Bacterial or fungal infection	24 (14.29)	22 (23.16)	67 (25.09)[♯]	77 (43.02)[§,‡]
Hepatorenal syndrome	2 (1.19)	28 (16.67)[†]	9 (3.37)	56 (31.28)[‡]
Hepatic encephalopathy (HE)	0	44 (46.32)[†]	4 (1.50)	86 (48.04)[‡]
HE (I–II)	0	32 (33.68)[†]	3 (1.12)	65 (36.31)[‡]
HE (III–IV)	0	12 (12.63)[†]	1 (0.37)	21 (11.73)[‡]
Upper gastrointestinal bleeding	4 (2.38)	6 (6.32)	9 (3.37)	31 (17.32)[§,‡]
Organ failures				
Liver failure	115 (68.45)	86 (90.53)[†]	168 (62.92)	165 (92.18)[‡]
Coagulation failure	5 (2.98)	46 (48.42)[†]	14 (5.24)	99 (55.31)[‡]
Kidney failure	0	19 (20.00)[†]	0	33 (18.44)[‡]
Cerebral failure	0	12 (12.63)[†]	1 (0.37)	21 (11.73)[‡]
Lung failure	0	1 (1.05)	0	2 (1.12)
Transplant-free mortality				
28 days	13 (7.74)	49 (52.13)[†]	33 (12.45)	89 (51.15)[‡]
90 days	24 (14.29)	58 (61.70)[†]	67 (25.57)[♯]	107 (61.85)[‡]

Data are expressed as mean ± standard deviation or number of patients (%)

AARC Asian Pacific Association for the Study of Liver (APASL)ACLF Research Consortium, *WBC* white blood cell, *Hb* hemoglobin, *PLT* blood platelet, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ALB* albumin, *TBIL* total bilirubin, *Na* sodium, *Cr* creatinine, *INR* international standardization ratio, *AFP* alpha-fetoprotein, *CRP* c-reactive protein

[♯] p value (< 0.05) for comparisons between non-CLIF-C ACLF patients with and without cirrhosis

[§] p value (< 0.05) for comparisons between CLIF-C ACLF patients with and without cirrhosis

[‡] p value (< 0.05) for comparisons between non-CLIF-C ACLF and CLIF-C ACLF patients with cirrhosis

[†] p value (< 0.05) for comparisons between non-CLIF-C ACLF and CLIF-C ACLF patients without cirrhosis

We then stratified HBV–ACLF patients with and without cirrhosis. In the cirrhotic HBV–ACLF group, the TPPMs (0.870, 0.792) had the highest predictive ability compared with the COSSH–ACLFs (0.843, 0.773, $p=0.135$, 0.354),CLIF-C OFs (0.819, 0.753, $p=0.025$, 0.072), AARC–ACLFs (0.807, 0.759, $p=0.013$, 0.074), CLIF-C ACLFs (0.735, 0.698, $p<0.0001$, 0.002), MELDs (0.784, 0.727, $p<0.001$, 0.008) and MELD–Nas (0.773, 0.733, $p<0.001$, 0.026)in predicting day 28 and day 90, respectively (Table 3).

Table 3 Comparisons of varies models in predicting short-term mortality in patients with HBV–ACLF

Variates	28-day mortality				90-day mortality			
	AUROC	95% CI	*Z*	*p* value vs. TPPM	AUROC	95% CI	*Z*	*p* value vs. TPPM
Total ACLF patients								
TPPMs	0.847	0.814–0.877			0.804	0.768–0.837		
COSSH–ACLFs	0.851	0.818–0.880	0.247	0.8051	0.804	0.768–0.836	0.008	0.9938
CLIF-C OFs	0.835	0.801–0.865	0.720	0.4718	0.783	0.746–0.818	1.224	0.2210
AARC–ACLFs	0.790	0.718–0.850	1.666	0.0957	0.766	0.692–0.829	1.229	0.2190
CLIF-C ACLFs	0.773	0.735–0.807	3.228	0.0012	0.738	0.699–0.775	2.824	0.0047
MELDs	0.789	0.753–0.823	3.203	0.0014	0.748	0.709–0.784	3.035	0.0024
MELD–Nas	0.783	0.746–0.817	3.481	0.0005	0.756	0.718–0.792	2.486	0.0129
All cirrhotic patients								
TPPMs	0.870	0.829–0.903			0.792	0.745–0.834		
COSSH–ACLFs	0.843	0.800–0.880	1.496	0.1346	0.773	0.724–0.817	0.926	0.3544
CLIF-C OFs	0.819	0.774–0.859	2.235	0.0254	0.753	0.703–0.798	1.802	0.0715
AARC–ACLFs	0.807	0.714–0.880	1.246	0.0128	0.759	0.661–0.840	1.625	0.0741
CLIF-C ACLFs	0.735	0.685–0.782	4.569	0.0000	0698	0.646–0.747	3.046	0.0023
MELDs	0.784	0.737–0.827	3.656	0.0003	0.727	0.676–0.774	2.646	0.0081
MELD–Nas	0.773	0.724–0.816	3.921	0.0001	0.733	0.683–0.780	2.225	0.0261
All non-cirrhotic patients								
TPPMs	0.812	0.752–0.863			0.826	0.767–0.875		
COSSH–ACLFs	0.865	0.811–0.909	2.537	0.0112	0.858	0.802–0.903	1.522	0.1280
CLIF-C OFs	0.863	0.808–0.907	1.940	0.0523	0.844	0.787–0.891	0.709	0.4782
AARC–ACLFs	0.772	0.647–0.869	0.708	0.4792	0.787	0.664–0.881	0.860	0.3897
CLIF-C ACLFs	0.832	0774–0.880	0.556	0.5779	0.809	0.748–0.860	0.502	0.6156
MELDs	0.795	0.733–0.848	0.558	0.5767	0.782	0.719–0.836	1.551	0.1210
MELD–Nas	0.802	0.741–0.854	0.347	0.7284	0.788	0.726–0.842	1.412	0.1580

AUROC area under the receiver operating characteristic curve, *TPPMs* Tongji prognostic predictor model score, *AARC–ACLFs* APASL–ACLF Research Consortium–ACLF score, *COSSH–ACLFs* Chinese Group on the Study of Severe Hepatitis B-ACLF score, *CLIF-C* chronic liver failure consortium, *OFs* organ failure score, *MELDs* model for end-stage liver disease score, *MELD–Nas* MELD–sodium score

Cirrhotic HBV–ACLF patients with complications exhibited a significantly higher mortality rate than those without complications

To understand the contributions of complications to mortality in HBV–ACLF patients, patients were stratified according to the occurrence of complications. As shown in Fig. 2, cirrhotic HBV–ACLF patients with complications had a significantly higher mortality rate than those without complications. However, no significant difference in mortality was found between non-cirrhotic patients with or without complications.

Two and more than two complications were independent risk factors for mortality in cirrhotic HBV–ACLF patients

Risk factors associated with transplant-free 28- or 90-day mortality were evaluated according to a multivariate logistic regression model in cirrhotic HBV–ACLF patients. Odds ratios of two (OR 4.701, 1.881) or three (OR 8.266, 2.648) complications showed a significantly higher risk of 28-day (Supplementary Table 2) or 90-day (Supplementary Table 3) mortality, which were four- and eightfold higher, respectively.

Discussion

In recent decades, the APASL (AARC) and EASL (CLIF-C) consecutively defined ACLF with independent criteria based on the Eastern and Western populations, respectively. [13, 18] Each definition may apply to different patient populations. Understanding ACLF patient characteristics in various definitions is essential for management consensus. Although ACLF etiology may have changed in recent years, with trends towards more alcohol insults and fewer chronic HBV infections, the latter is still the leading cause of ACLF in many Asian countries [20]. The AARC criteria cover the

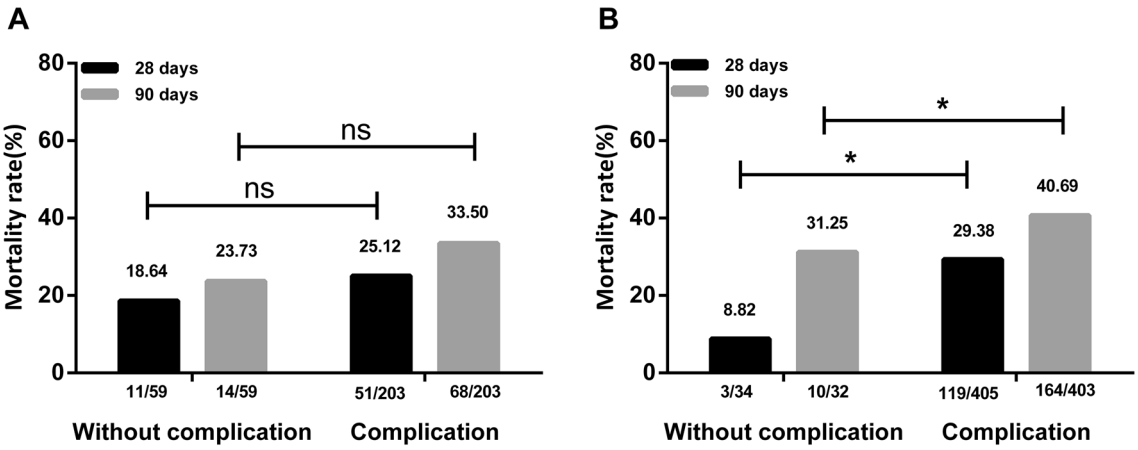

Fig. 2 Complication is an important risk factor for short-term mortality rate in patients with HBV–ACLF. **a** Comparison of 28-day and 90-day transplant-free mortality in all the non-cirrhotic patients with or without complication. **b** Comparison of 28-day and 90-day transplant-free mortality in all the cirrhotic patients with or without complication

early stage of ACLF, with a golden window for the reversal of disease progression.

The impact of cirrhosis on the mortality of ACLF patients remains controversial. Several studies have indicated that cirrhosis is not an independent risk factor for ACLF mortality [5, 21, 22]. However, some studies demonstrated that cirrhosis independently predicted 3-month mortality [23, 24]. Cirrhosis is still a controversial determinant of mortality in HBV–ACLF. Our data from patients across 10 Asian countries revealed that patients with cirrhotic HBV–ACLF exhibited significantly higher 90-day transplant-free mortality than those without cirrhosis, indicating that cirrhosis could be regarded as a risk factor for disease progression and could perhaps be used for patient stratification. According to the COSSH criteria, cirrhotic HBV–ACLF patients had a significantly higher risk (1.02- to 1.94-fold) than non-cirrhotic patients for 28-day mortality [7], and this result further confirmed the important role of cirrhosis in HBV–ACLF. Further analyses demonstrated that cirrhotic patients have more complications than non-cirrhotic patients, mainly presenting as ascites, bacterial or fungal infections and upper gastrointestinal bleeding. However, there was no difference in extrahepatic organ failure in cirrhotic versus non-cirrhotic HBV–ACLF patients. These data suggested that complications, ascites, bacterial or fungal infections and upper gastrointestinal bleeding are major risk factors for the mortality of cirrhotic HBV–ACLF patients. When the CLIF-C criteria were applied to Asian HBV–ACLF patients, they only captured 36.1% in the non-cirrhotic patients and 40.1% in the cirrhotic patients, with no significant differences in 28-day and 90-day mortality. This indicated that cirrhosis was not a risk factor for short-term mortality based on the CLIF-C criteria in HBV–ACLF patients. Second, the 63.9% of non-cirrhotic and 59.9% of cirrhotic HBV–ACLF patients who were not captured by the CLIF-C criteria had short-term mortality rates of 7.7% and 25.6%, respectively.

To evaluate the disease severity and predict the mortality of ACLF, several models have been explored. Initially, the MELDs and MELD–Nas were established based on patients with end-stage liver disease and have traditionally been used as prognostic assessments [10, 11]. Nevertheless, there are approximately 15–20% of patients whose survival could not be accurately predicted by the MELD score. Recently, the CLIF-C OFs and CLIF-C ACLFs were developed based on the CLIF-C ACLF in cirrhosis (CANONIC) studies, regardless of etiology [12], which were shown to be poor at predicting effectiveness in HBV–ACLF [7]. Generally, the main limitations of the existing predictive models were not etiology-specific; thus, they might vary significantly with different causes such as HBV versus alcoholic ACLF.

The effects of complications (ascites, infection, hepatorenal syndrome, hepatic encephalopathy and gastrointestinal bleeding) on 28-day and 90-day TFM were assessed by univariate analysis. As shown in Supplementary Table 4, HE, HRS, GI bleeding and infection were independent risk factors for 28-day and 90-day TFM in all and cirrhotic HBV–ACLF patients. Moreover, HE and HRS were observed to be the most crucial risk factors for short-term TFM.

Several predictive models were well developed in HBV–ACLF patients. We recently established and evaluated the TPPM model in HBV–ACLF patients from a large single-centre cohort, and it has a superior predictive ability when compared with the MELD and MELD–Na models [5, 6]. The TPPMs used TBIL, INR, HBV–DNA and complications as parameters. Recently, the COSSH–ACLF was created based on the TBIL, INR, age and HBV–SOFA and was modified according to the CLIF–SOFA criteria [7]. These

models are superior to the MELD in HBV–ACLF patients. Nevertheless, no detailed comparisons and subgroup analyses have been performed with the present models.

Based on the current multi-national cohort, the TPPMs was shown to be comparable to the COSSH–ACLFs and superior to the AARC–ACLFs, CLIF-C OFs, CLIF-C ACLFs, MELDs and MELD–Nas in predicting 28-day and 90-day mortality in HBV–ACLF patients, with the highest predictive value when compared with the existing models in cirrhotic HBV–ACLF patients. Our data also indicated that cirrhotic HBV–ACLF patients had a significantly higher mortality rate and more complications than non-cirrhotic patients. Complications usually occur earlier than organ failure [2]. Thus, a prompt recognition and intervention in complications are vital for cirrhotic HBV–ACLF patients. This may explain the higher predictive value of the TPPMs in all patients diagnosed by the AARC criteria, particularly in cirrhotic individuals.

HBV genotypes are associated with disease progression and the long-term outcome of HBV infection [25]. They may serve as viral genetic markers for the risk stratification of chronic hepatitis B patients in clinical practice. HBV genotypes C, D and F carry a higher lifetime risk of cirrhosis and HCC development than genotype A. However, the relationship between HBV genotypes and ACLF development was not involved in the current study, and it needs to be fully examined in future studies.

In conclusion, the presence of complications is a major risk factor for mortality in HBV–ACLF patients, particularly in cirrhotic individuals. The TPPMs possesses high predictive ability for mortality in HBV–ACLF patients. The importance of complications as an early risk factor is worth exploring in alcohol- and autoimmune hepatitis-related ACLF.

Acknowledgements The authors would like to thank Professor Osamu Yokosuka, Prof. Sombat Treeprasertsuk and Prof. Gamal Shiha for their support in valuable discussion and editing.

Funding This study was partially supported by the National Thirteenth "Five Years" Project in Science and Technology of China (2017ZX10202201, 2018ZX10302-206).

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest about this work.

Informed consent in studies with human subjects The data were collected using a pre-defined, web-based proforma in the Asia–pacific Association for the Study of Liver ACLF Research Consortium (AARC) database (http://www.aclf.in). Approval from the institutional ethics committees was obtained. The data were annotated and encrypted before analysis. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Asia–pacific Association for the Study of Liver ACLF Research Consortium) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

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Affiliations

Tao Chen[1] · Zhongyuan Yang[1] · Ashok Kumar Choudhury[2] · Mamun Al Mahtab[3] · Jun Li[4] · Yu Chen[5] · Soek-Siam Tan[6] · Tao Han[7] · Jinhua Hu[8] · Saeed S. Hamid[9] · Lee Guan Huei[10] · Hasmik Ghazinian[11] · Yuemin Nan[12] · Yogesh K. Chawla[13] · Man-Fung Yuen[14] · Harshad Devarbhavi[15] · Akash Shukla[16] · Zaigham Abbas[17] · Manoj Sahu[18] · A. K. Dokmeci[19] · Laurentias A. Lesmana[20] · Cosmas Rinaldi A. Lesmana[20] · Shaojie Xin[8] · Zhongping Duan[5] · Wei Guo[1] · Ke Ma[1] · Zhongwei Zhang[1] · Qiuyu Cheng[1] · Jidong Jia[21] · B. C. Sharma[22] · Shiv Kumar Sarin[2] · Qin Ning[1]

✉ Shiv Kumar Sarin
shivsarin@gmail.com

✉ Qin Ning
qning@vip.sina.com

Tao Chen
chentao_tjh@vip.sina.com

Zhongyuan Yang
1049446560@qq.com

Ashok Kumar Choudhury
doctor.ashokchoudhury@gmail.com

Mamun Al Mahtab
shwapnil@agni.com

Jun Li
lijun2009@zju.edu.cn

Yu Chen
chybeyond@163.com

Soek-Siam Tan
tansoeksiam@yahoo.com

Tao Han
hantaomd@126.com

Jinhua Hu
13910020608@163.com

Saeed S. Hamid
saeed.hamid@aku.edu

Lee Guan Huei
guan_huei_lee@nuhs.edu.sg

Hasmik Ghazinian
ghazinian@gmail.com

Yuemin Nan
nanyuemin@163.com

Yogesh K. Chawla
ykchawla@gmail.com

Man-Fung Yuen
mfyuen@hku.hk

Harshad Devarbhavi
harshad.devarbhavi@gmail.com

Akash Shukla
drakashshukla@yahoo.com

Zaigham Abbas
zaigham.abbas@aku.edu

Manoj Sahu
manojsahu427@gmail.com

A. K. Dokmeci
akdokmeci@hotmail.com

Laurentias A. Lesmana
llesmana.id@gmail.com

Cosmas Rinaldi A. Lesmana
medicaldr2001id@yahoo.com

Shaojie Xin
xinshaojie302@163.com

Zhongping Duan
duan2517@163.com

Wei Guo
294571240@qq.com

Ke Ma
6811976@qq.com

Zhongwei Zhang
1552315681@qq.com

Qiuyu Cheng
1226271272@qq.com

Jidong Jia
jiamd@263.net

B. C. Sharma
drbcsharma@hotmail.com

[1] Department of Infectious Disease, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095, Jiefang Avenue, Wuhan 430030, People's Republic of China

[2] Departments of Hepatology and Transplant, Institute of Liver and Biliary Sciences, New Delhi 110070, India

[3] Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

[4] State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

[5] Youan Hospital, Capital Medical University, Beijing, China

[6] Department of Hepatology, Selayang Hospital, Batu Caves, Malaysia

[7] Department of Gastroenterology, Third Central Hospital, Tianjing, China

[8] Liver Failure Treatment and Research Center, the Fifth Medical Center, Chinese PLA General Hospital, Beijing, China

[9] Department of Medicine, Aga Khan University Hospital, Karachi, Pakistan

[10] National University of Singapore and National University Hospital, Singapore, Singapore

[11] Department of Hepatology, Nork Clinical Hospital of Infectious Diseases, Yerevan, Armenia

[12] Department of Hepatology, Hebei Medical University, Shijiazhuang, China

[13] Department of Hepatology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

[14] Department of Medicine, Queen Mary Hospital, Hong Kong, China

[15] Department of Gastroenterology and Hepatology, St John Medical College, Bangalore, India

[16] Department of Hepatology, KEM Hospital, Mumbai, India

[17] Department of Hepatogastroenterology, Ziauddin University, Karachi, Pakistan

[18] Department of Gastroenterology and Hepatology, IMS and SUM Hospital, Odisa, India

[19] Department of Gastroenterology, Ankara University School of Medicine, Ankara, Turkey

[20] Medistra Hospital, Digestive Disease and GI Oncology Center, Jakarta, Indonesia

[21] Liver Research Center, Beijing Friendship Hospital, Beijing, China

[22] Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India