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Predicting 90-day mortality at admission and 7 days post-admission among patients with hepatitis B virus-related acute-on-chronic liver failure

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Abstract

Objective: To investigate the relationship between baseline characteristics and 90-day mortality in hepatitis B virus-related acute-on-chronic liver failure patients.

Methods: The retrospective study was conducted at Fuling Centre Hospital, Chongqing, China, and comprised data from July 2015 to June 2018 of hepatitis B virus-related acute-on-chronic liver failure patients. Demographic characteristics and clinical features at admission and 7 days post-admission were noted. The data was then divided into two groups based on a patient's 90-

day survival status, and their clinical and lab characteristics were compared using SPSS 16.

Results: Of the 120 patients screened, 100(83.3%) were included; 75(75%) males and 25(25%) females. The overall mean age was 50.04±14.61 years. There were 68(68%) in the surviving group and 32(432%) in the non-surviving group. Patients who had hyper-leukocytosis, hypoalbuminemia, lower prothrombin time activity, ascites, hepatic encephalopathy, higher alanine aminotransferase levels and renal dysfunction at admission had poor prognoses ($p<0.05$). At 7 days post-admission, the non-surviving group had lower platelet count, higher aspartate aminotransferase level, lower bilirubin normalisation rate and higher total bile acid levels ($p<0.05$).

Conclusions: Baseline organ failure severity was found to determine the outcome more strongly than the underlying cause.

Key Words: Hepatitis B, Acute-on-chronic liver failure, Prognosis.

Introduction

Hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF) is the most common type of liver failure in China and has attracted increasing attention from liver experts due to its high mortality in the short term (36-86%)[1]. Currently, the artificial liver support system (ALSS) has improved the clinical outcomes of HBV-ACLF, but the condition still cannot be reversed in some patients who may have to undergo liver transplantation and may die[2]. In view

of the shortage of available livers, distinguishing at an early stage the patients who are likely to have a negative outcome from those who will survive with comprehensive management is an urgent issue, as it would enable doctors to distinguish between patients and to allocate the limited liver organs by making decisions regarding the intensity of management needed, which they can then communicate to the patient and family. Unfortunately, currently, there are no sensitive and specific biomarkers for the prognosis of HBV-ACLF.

Various scoring systems are available for use in determining liver function and conducting prognostic evaluations in liver failure patients, including the Model for End-Stage Liver Disease (MELD), the Child-Pugh score, the European Association for the Study of the Liver-chronic liver failure (EASL-CLIF) Consortium Acute-on-Chronic Liver Failure (ACLF) in Cirrhosis (CANONIC) system and the North American Consortium for the Study of End-Stage Liver Disease (NACSELD) systems. MELD and Child-Pugh scores are used mainly to evaluate liver function and the feasibility of using exogenous liver sources[3, 4]. However, all of these systems underestimate the risk of death in patients with ACLF. The CANONIC and NACSELD systems attempt to evaluate the risk of short-term mortality in patients with ACLF [5, 6]. However, these scoring systems are not well-suited for use in China where hepatitis B is the predominant aetiology of ACLF[7]; the most common underlying causes of liver diseases in Europe are alcoholism and hepatitis C[8].

HBV-ACLF is a dynamic disease that may improve or worsen during treatment. Most patients with ACLF have a clear prognosis within 7 days of admission[9].

Thus, the existing scoring systems are useful but imperfect because they lack a means of dynamically assessing patients. The current study was planned to identify valuable early clues in the clinical and laboratory characteristics of hospitalizsed HBV-ACLF patients that can be used to predict 90-day mortality.

Patients and Methods

The retrospective study was conducted at Fuling Centre Hospital, Chongqing, China, and comprised data from July 2015 to June 2018 of HBV-ACLF patients who had been diagnosed in line with the criteria of the Asia Pacific Association for the Study of Liver (APASL)[10]. Those included were positive for hepatitis B surface antigen (HBsAg) for 6 months or longer; had jaundice with serum total bilirubin ≥85.5 μmol/L, had coagulopathy with international normalised ratio (INR) ≥ 1.5 or prothrombin time activity (PTA) ≤40%), and had ascites and/or hepatic encephalopathy (HE) within the preceding 4 weeks.

Those excluded were cases with underlying diseases other than ACLF, such as tumours, pregnancy, obstructive jaundice, patients with liver transplantation and shedding cases. As such, all patients had homogeneous treatment. The study was approved by the institutional ethics review committee,and appropriate informed consent was obtained from patients or their legal heirs before collecting data.

The patients were divided into surviving (S) group and the non-surviving (NS) group according to their 90-day survival status. Those in the S group had recovered from acute hepatic decompensation with comprehensive management, and those in the NS group had died due to hepatic failure without undergoing liver transplantation (LT). We defined recovery from acute hepatic decompensation (AD) as survival >12 weeks after AD. Clinical and laboratory data of HBV-ACLF patients who were hospitalised for at least 7 days was collected and analysed . All laboratory tests were confirmed at admission and 7 days post-admission, and all patients were followed up for >90 days by phone from the day they left the hospital.

In terms of clinical data, the precipitating events for individuals were noted. Reactivation of HBV was defined as an abrupt increase in alanine aminotransferase (ALT) levels >5 times the upper limit of normal, with an HBV deoxyribonucleic acid (DNA) level $>10^3$ IU/ml within the preceding month[11]. Bacterial infections were defined and classified; spontaneous bacterial peritonitis, abdominal pain or tenderness with a concentration of leukocytes in the ascites fluid >250/ml; positive blood culture; pneumonia, respiratory symptoms with fever, pulmonary infiltrate on radiological imaging, or positive sputum cultures, and other bacterial infections of unknown origin. The use of hepato-toxic drugs was defined as the use of drugs with possible hepato-toxicity within the preceding 3 months, and other potential aetiologies were excluded.

Alcohol abuse was defined as consuming alcohol within the preceding month in an amount exceeding 60g/d for men or 40g/d for women.

During hospitalisation, all patients received integrated treatment, including antiviral therapy with first-line nucleoside analogues, ALSS support, antibiotics for bacterial infections, diuretic paracentesis combined with albumin infusion for patients with ascites and lactulose for hepatic encephalopathy (HE).

Baseline clinical characteristics noted included age, gender, status of hepatitis B virus e antigen (HBeAg), ascites and HE. Ascites diagnosis was made by the presence of fluid in the peritoneal cavity on abdominal ultrasonography or abdomen computed tomography (CT). HE was diagnosed using the West Haven criteria[12]. Laboratory measurements, including white blood cell (WBC) count, percentage of neutrophils (NEUT), platelet count (PLT) and levels of ALT, aspartate aminotransferase (AST), total bilirubin (TBIL), direct bilirubin (DBIL), total bile acid (TBA), serum albumin (ALB), serum globulin (GLO), blood urea nitrogen (BUN), serum creatinine (SC), uric acid (UA), serum potassium (K+), serum sodium (Na+) and PTA. These were documented on the admission day and day 7 post-admission.

Data was analysed using SPSS 16.. Univariate analyses, chi-squared test and Fisher's exact test were used as appropriate. Continuous variables were compared using student's t-test, one-way analysis of variance (ANOVA) or a non-parametric analysis depending on the results of the normality test.

Quantitative data was described as median and interquartile ranges (IQRs). P<0.05 was considered statistically significant.

Results

Of the 120 patients screened, 100(83.3%) were included (Figure); 75(75%) males and 25(25%) females. There were 68(68%) patients in the S group and 32(432%) in the NS group.

HBeAgDifferences related to gender, ascites and HE were significant (p<0.05) (Table 1).

Events precipitating HBV-ACLF were noted and infection was the most common reason (Table 2).

Clinical and laboratory characteristics of patients with HBV-ACLF at admission (Table 3) and of day 7 post-admission (Table 4) were noted and compared

Discussion

HBV-ACLF is commonly defined as an acute deterioration in liver function that can be accompanied by extra-hepatic organ failure in patients with pre-existing chronic hepatitis B infection[5]. HBV-ACLF has unique characteristics that differentiate it from liver failure due to alcohol-related or non-viral aetiologies[13]. The current study investigated 100 patients who were hospitalised due to HBV-ACLF. The first main finding of the study was the common demographic characteristics. Patients of ages ranging from 9 to 84

years with HBV infections could develop ACLF. With the widespread use of antiviral treatments, the proportion of HBeAg-positive patients has gradually decreased, resulting in a larger sample of HBeAg-negative patients with chronic hepatitis B; 75% of patients in this study were HBeAg-negative individuals. However, the proportions of HBeAg-positive patients were not significantly different between the groups. Furthermore, the study demonstrated that the incidence and mortality rates of HBV-ACLF were higher in males than in females. ALSS can effectively improve the short-term mortality of patients, and we found that the 90-day mortality rate of patients with HBV-ACLF was 32%, which was lower than the rates previously reported (36.7-50%)[14-16].

The aetiology of ACLF is multifactorial, including bacterial infections, excessive alcohol intake, drug toxicity or viral hepatitis[17]. The early recognition of risk factors is very important to precisely control disease progression to enhance the survival rate. The current study investigated the precipitating events of HBV-ACLF and found that the most common causes of ACLF were the reactivation of hepatitis B, bacterial infections, alcohol consumption, drug toxicity mainly related to Traditional Chinese Medicine (TCM) or herbs in China[18], chemotherapy and flare-ups of autoimmune hepatitis. The findings were consistent with those of a previous study[7]. More than 40% of patients developed ACLF due to infections in the current study. Bacterial infection was the primary precipitating event of ACLF and plays pivotal role in the development and progression of ACLF either as a cause or a

specific complication[19]. Early diagnosis, prompt detection, and appropriate antibiotic treatment are essential for managing bacterial infections. Concurrent viral infections, such as hepatitis A and E infections, should also be taken into account, especially in the Middle East and Asia[20]. It is worth noting that autoimmune hepatitis (AIH) is not uncommon in the Asia Pacific region and plays an important role in the incidence of HBV reactivation. Therefore, the awareness of antiviral for hepatitis B before using chemotherapy or immunosuppressive agents must be encouraged. Differences in the precipitating events between the two groups were not found in this study. Similar results were obtained in the CANONIC study[5].

Meanwhile, the 90-day mortality in patients with organ dysfunction was greater than in those without organ dysfunction, which suggests that once ACLF develops, host organ dysfunction severity determines the outcome more strongly than does the underlying cause. Therefore, although the rapid identification and treatment of the precipitating event can improve the prognosis, the key factor determining the prognosis is the degree of organ dysfunction in the host. Ascites is usually considered a marker of decompensation of liver function. The percentage of patients with ascites was significantly higher in the NS group than in the S group. Renal dysfunction is closely linked to the prognosis of ACLF. In our 100 HBV-ACLF patients, blood urea nitrogen (BUN) and serum creatinine (SC) levels were significantly higher in the NS group than in the S group both at admission and 7 days post-

196 hospitalisation. In those with ACLF, HE is strongly and independently related to
197 an increased risk of death, and the proportion of patients with HE was
198 significantly higher in the NS group than in the S group in the current study.
199 The presence of single or multiple organ failure is associated with a higher
200 short-term mortality rate[21]. The 28-day mortality rate was only 20.2% in
201 patients without kidney dysfunction and/or HE[22]. Mortality increased with an
202 increasing degree of organ failure[23]. The current study demonstrated that the
203 90-day mortality rate was higher in patients with ascites, HE and failure of the
204 extra-hepatic organs than in those without those characteristics at admission.
205 Therefore, disease severity and outcome can be predicted by both hepatic and
206 extra-hepatic organ failures[13]. Those patients with abnormal extra-hepatic
207 organ function should be given supportive care and priority for LT.
208 HBV-ACLF patients have complex and heterogeneous prognoses, and LT is the
209 most effective curative treatment to date. The identification of prognostic
210 factors for HBV-ACLF patients is critical because emergency LT is not readily
211 available due to organ shortage. Furthermore, prognostic factors would help
212 medical teams decide whether to manage patients in intensive care units (ICUs)
213 or regular wards. However, until now, sensitive and specific biomarkers were
214 lacking. Further discrimination of priority treatment groups in the context of the
215 scarcity of liver sources depends on the early recognition of high-risk patients.
216 Alternative evaluation models, including the Child-Pugh, MELD, CANONIC
217 and NACSELD systems[3-6], are inadequate because they focus on one time

point, and lack the capacity for dynamic evaluation of the patient. The Chronic **Liver** Failure-consortium (CLIF-C) ACLF score is a prognostic model used to predict survival, and it discriminates between survivors and non-survivors significantly better than the MELD and Child-Pugh systems[24]. These scoring systems are not suitable for application in China because the most common underlying aetiologies of ACLF are alcoholism and hepatitis C (16.3%) in Europe[8].

There is a short "golden window" in the early phase of ACLF. Most patients with ACLF will have a clear prognosis within 7 days of hospital admission[9]. **I**n addition to the baseline characteristics, dynamic changes in clinical parameters during hospitalisation are useful prognostic factors for patients with HBV-ACLF[25]. The current study suggests that repeated assessments of curative effects and outcomes are linked to appropriate critical care for patients who might deteriorate quickly. This study demonstrated that increased WBC counts and NEUT percentages at admission and 7 days post-hospitalisation were key factors associated with a high mortality rate. A low PLT level and rebounding of the TBIL level 7 days post-admission indicated poor prognosis. With the exception of the status of the extra-hepatic organs during the initial days of hospitalisation, repeated evaluations seem better at predicting the outcome than a single observation at the time of admission[26].

Patients with ACLF are considered to have a higher than normal risk of abnormal PTA because of the decreased synthesis of coagulation factors[27]. The coagulation profile was evaluated in patients with ACLF, and the PTA was

lower than normal (<40%) in those patients; a lower PTA (<40%) is considered one of the critical criteria for ACLF[28]. The current study showed that the NS group had lower PTA than the S group both at admission and 7 days later. Thrombocytopenia is common during the progression of ACLF. This study demonstrated that the platelet parameters were not different between the groups at admission, but that differences appeared 7 days later. These findings simply indicate that the association of PLT counts with the prognosis of ACLF patients should be given more attention.

Another prognostic risk factor is the TBA level. BAs are signalling molecules that activate nuclear factor signalling to maintain metabolic homeostasis. However, the accumulation of toxic BAs promotes liver injury by initiating inflammation, inducing apoptosis and causing oxidative stress that leads to cirrhosis and liver failure[29]. It is noteworthy in the current study that the level of BAs 7 days post-admission was much higher in the NS group than in the A group. Patients with high BA levels, as such, should receive particular attention.

Conclusions

Overall 90-day mortality rate of HBV-ACLF patients was 32%. Organ failure severity affected the outcome more strongly than did the precipitating event. Serial measurement of relevant parameters at admission and 7 days post-admission is a simple way of predicting the prognosis.

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Conflicts of Interest: None.

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Table 1: Clinical characteristics.

Characteristics		Surviving (n=68)	Non-surviving (n=32)	χ^2 value	*p* value
Gender	Male (n.)	69.1% (47)	30.9% (28)	3.922	0.048
	Female (n.)	87.5% (21)	12.5% (4)		
HBeAg	Positive (n.)	29.4% (20)	15.6% (5)	2.206	0.215
	Negative (n.)	70.6% (48)	84.4% (27)		
Ascites	Yes (n.)	14.7% (10)	43.8% (14)	10.064	0.002
	No (n.)	85.3% (58)	56.2% (18)		
HE	Yes (n.)	2.9% (2)	37.5% (12)	21.585	<0.001
	No (n.)	97.1% (66)	62.5% (20)		

HE: Hepatic encephalopathy; HBeAg: Hepatitis B surface antigen.

Table 2: Precipitating events and prognostic factors

Precipitating events	Surviving (n=68)	Non-surviving (n=32)	χ^2 value	*p* value
HBV reactive	26.5% (18)	18.8% (6)		
Infection events	41.2% (28)	43.8% (14)	4.642	0.461
Drug	17.6% (12)	12.5% (4)		

Alcohol	11.8% (8)	12.5% (4)
Flare of autoimmune hepatitis	1.5% (1)	3.1% (10)
Chemotherapy	1.5% (1)	9.4% (3)

HV: Hepatitis B virus

Table 3: Laboratory parameters at admission

Factors	Unit	Surviving group	Non-surviving group	t value	*p* value
Age	years	50.18±15.59	49.75±12.50	0.135	0.893
WBC	$*10^9$/L	6.54±4.11	8.96±6.07	-2.049	0.046
NEUT	%	67.47±9.92	76.79±9.18	-4.486	<0.001
PLT	$*10^9$/L	140.19±64.02	127.12±85.19	0.771	0.444
ALT	u/L	965.78±1170.46	459.94±779.81	2.221	0.029
AST	u/L	681.78±559.50	477.86±125.64	1.552	0.124
TBIL	μmol/L	281.96±105.86	303.21±146.73	-0.824	0.412
DBIL	μmol/L	219.47±93.82	234.85±121.10	-0.695	0.489
TBA	μmol/L	191.81±79.52	168.76±79.01	1.355	0.179
ALB	g/L	35.08±5.03	30.91±6.43	3.527	0.001
GLO	g/L	28.57±12.31	27.61±10.06	0.384	0.702
BUN	mmol/L	4.89±3.52	8.86±9.56	-2.342	0.025
SC	μmol/L	71.49±32.70	131.01±177.30	-2.687	0.008
UA	μmol/L	229.61±74.77	282.05±159.54	-1.77	0.085
K+	mmol/L	4.25±0.79	3.97±0.82	1.683	0.095
Na+	mmol/L	137.81±6.12	136.26±3.49	1.604	0.112
PTA	%	31.61±6.67	21.58±6.44	7.086	<0.001

WBC, white blood cell; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; TBA, total bile acid; ALB, serum albumin; GLO, serum globulin; BUN, blood urea nitrogen; SC, serum creatinine; UA, uric acid; K+, serum calcium; Na+, serum sodium; PTA, prothrombin time activity.

Table 4: Laboratory features at day 7.

Factors	Unite	Surviving group	Nonsurviving group	t value	P value
WBC	$*10^9$/L	6.76±4.30	10.50±7.32	-2.681	0.01
NEUT	%	65.91±12.95	79.19±13.75	-4.69	<0.001
PLT	$*10^9$/L	144.5±68.88	103.94±92.11	2.458	0.016
ALT	u/L	157.15±195.37	209.28±366.00	-0.929	0.355
AST	u/L	102.20±107.52	170.98±177.85	-2.398	0.018
TBIL	μmol/L	119.64±122.37	322.55±220.19	-4.871	<0.001
DBIL	μmol/L	93.28±78.88	233.46±140.35	-5.272	<0.001
TBA	μmol/L	122.54±115.47	172.03±103.78	-2.063	0.042
ALB	g/L	34.97±5.68	30.04±3.43	4.528	<0.001
GLB	g/L	25.17±5.92	23.86±6.24	1.018	0.311
BUN	mmol/L	5.30±3.25	7.58±4.87	-2.779	0.007

SC	μmol/L	72.53±39.64	91.04±75.69	-1.302	0.201
UA	μmol/L	227.02±87.22	215.46±109.33	0.569	0.571
K+	mmol/L	4.36±0.61	4.11±0.99	1.339	0.188
Na+	mmol/L	138.44±5.19	135.24±3.84	3.109	0.002
PTA	%	71.13±17.28	49.86±24.19	5.03	<0.001

WBC, white blood cell; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; TBA, total bile acid; ALB, serum albumin; GLO, serum globulin; BUN, blood urea nitrogen; SC, serum creatinine; UA, uric acid; K+, serum calcium; Na+, serum sodium; PTA, prothrombin time activity.

Figure: Screening, enrollment and grouping of the cohort