Mean arterial pressure drop is an independent risk factor of hepatorenal syndrome in patients with HBV-ACLF

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Background/aims In patients with acute-on-chronic liver failure (ACLF), type 1 hepatorenal syndrome (HRS) is a critical organ failure complication that resulted in rapid mortality. There are no efficient parameters to predict HRS in hepatitis B virus (HBV)-related ACLF. To assess HBV-ACLF risk factors and evaluate the association between mean arterial pressures (MAP), HRS and survival in patients with HBV-ACLF.

Methods A total of 420 ACLF patients were screened from June 2015 to June 2016, and 57 HBV-ACLF patients were included in the study. Clinical data and MAP measurements of these patients were collected. Multivariate analyses, Cox proportional hazards regression and receiver operator characteristic (ROC) curves were used to analyze.

Results In a 30-day study period, 43 (75.44%) patients survived. Patients in the HRS group were older and had higher Model for End-Stage Liver Disease (MELD) scores than patients in the non-HRS group. A MAP drop of ≥9.5 mmHg was an independent predictor of HRS with a sensitivity and specificity of 92.86 and 69.77%, respectively. The baseline MELD score was also an independent risk factor of HRS. MAP drop (OR, 1.582; $P=0.000$), prothrombin time, HRS, MELD and FIB were independent prognostic factors for 30-day mortality. The area under the ROC curve of MAP drop was 0.808 ($P=0.001$).

Conclusion A decrease in MAP was a valuable predictor of HRS in patients with HBV-related ACLF. MAP drop ≥9.5 mmHg may be useful for predicting patient prognosis and exploring new treatment measures in patients with HBV-related ACLF. Eur J Gastroenterol Hepatol 34: 576–584
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Introduction

Acute-on-chronic liver failure (ACLF) is characterized by acute hepatic abnormalities that result from accumulating liver insults in patients with underlying chronic hepatitis or liver cirrhosis [1]. When a liver function fails, the extra-hepatic organs also develop different functional disorders [2]. Specific organ dysfunctions, such as acute kidney injury (AKI), are associated with poor prognosis [2] and necessitate liver transplantation [3]. Due to the high mortality rate of ACLF [1], determining the urgency of liver transplantation is crucial [3,4].

Hepatorenal syndrome (HRS), also called HRS-AKI, is a life-threatening complication of liver cirrhosis [5,6]. HRS is characterized by functional renal failure due to central underfilling, which is caused by the combination of splanchnic arterial and systemic peripheral vasodilation [7] together with inadequate cardiac output [5,7]. Arterial dilation is a key pathogenic event of HRS, leading to reduction of the effective blood volume, homeostatic activation of the renin-angiotensin-aldosterone system, and induction of renal vasoconstriction by the sympathetic nervous system [3,8]. Several lines of evidence also suggest that HRS may be associated with parenchymal kidney damage. HRS is classified as type I or type II. HRS I involves rapidly progressive renal failure with a very poor short-term prognosis, whereas HRS II is a more moderate and stable renal failure with a median survival of about 6 months [3,6].

The management of HRS is still a major challenge. Liver transplantation is the ideal treatment, but organ shortage and the limited window of time for transplants pose important inherent drawbacks [3,9]. Therapies to improve renal perfusion have been tested, including various vasoconstrictors, such as terlipressin, noradrenaline, dopamine and midodrine, with or without the addition of albumin [2,3,6,10]. Unfortunately, these therapies did not demonstrate a survival benefit. At present, most studies focus on how to improve the treatment of patients with HRS [2–6,10,11], and less effort is put into preventing the occurrence of HRS or diagnosis HRS at an early subclinical stage.

Currently, there are no reliable biomarkers that identify the incidence of HRS or predict the prognosis of end-stage

liver disease. Previous studies have shown that liver volume, serum sodium levels, serum creatinine concentration, urine output and high renin activity can predict HRS in patients with alcoholic v cirrhosis [7]. Montoliu *et al.* found that age, basal serum creatinine levels and high ceruplasmin (CP) values were independent predictors of HRS in a study of 263 patients [12]. In the same study, HRS was reported in 55% of patients with a 0.7 increase in the renal resistance index from baseline [12]. While most current biomarker studies are performed in alcoholic liver disease. Creatinine, which is the main component of previous HRS predict models, is affected by many factors associated with creatinine generation and excretion [13], and is a delayed and insensitive biomarker of renal function but not kidney injury [14]. Other biomarkers primarily reflect the severity of chronic liver disease or are difficult to follow-up and observe clinically, so they cannot be effectively used for clinical evaluation.

In clinical practice, mean arterial pressure (MAP) is a reliable index of the dysfunction of circulatory compensation in patients with liver cirrhosis ascites [8]. A previous study revealed that arterial blood pressure was independently associated with survival in patients with liver cirrhosis ascites over a period of 1 year [15]. Xu *et al.* showed that increasing MAP from 65 mmHg to the normal level in septic shock patients with previous hypertension was associated with improved microcirculatory function, characterized by increased perfused vessel density and a higher proportion of small perfused vessels [16]. A recent study demonstrated that hypertension history is a protective factor for liver-associated clinical decomposition and mortality [17]. Another study showed that lower MAPs of 50–60 mmHg are positively correlated with higher morbidity in kidney dysfunction cases [18]. Low MAP is also closely associated with hyperdynamic circulation, seroperitoneum and advancement of hepatorenal syndrome, indicating that optimal MAP may be an important prognostic factor in patients with liver cirrhosis ascites [15–18]. In a prospective cohort study, the long-lasting impact of baseline MAP levels on the prognosis of patients with hepatitis B virus (HBV)-related cirrhosis ascites was demonstrated [13]. More specifically, a decrease in MAP was a valuable predictor of death in patients with HBV-related liver cirrhosis ascites [13]. Together, these studies indicate that MAP may be useful for determining the prognosis and exploring new treatment measures for liver cirrhosis ascites [13]. Although liver cirrhosis is related to HBV-ACLF, the MAP level that should be maintained to determine the prognosis of HBV-ACLF patients remains unclear, and no studies have determined the impact of changes in MAP on HRS occurrence in HBV-ACLF.

Therefore, finding a convenient, noninvasive and clinically accessible indicator is crucial for clinicians to make correct judgments early and conveniently. We propose that researchers should focus on preventing the occurrence of HRS to gain time for improving liver function and maintaining renal function. We anticipate that these efforts will reduce the occurrence of HRS, thereby reducing mortality and extending patient survival.

Materials and methods

Study design

This was a retrospective study of the medical records of patients who were diagnosed with ACLF in the Third Affiliated Hospital of Sun Yat-sen University (Guangzhou, China) between June 2015 and June 2016. Chronic hepatitis B (CHB)-related ACLF patients, aged 18 to 65 years of any gender were included in the study. The diagnoses of CHB and ACLF were made according to the guidelines for CHB and ACLF management as outlined by the American Association for the Study of Liver Diseases and the Asia-Pacific Association for the Study of Liver. CHB was diagnosed according to the following criteria: the presence of hepatitis B surface antigen (HBsAg) for 6 months and includes measuring levels of HBV-DNA, hepatitis B e antigen and serum alanine aminotransferase (ALT) to determine infectivity, and liver biopsy to assess the liver disease. ACLF was diagnosed according to the following criteria: jaundice and coagulopathy resulting from liver insults in patients with underlying CHB or liver cirrhosis, serum total bilirubin (TBIL) ≥5 mg/dL or 85 μmol/L and prothrombin activity < 40% or international normalized ratio >1.5. Exclusion criteria included infection with any other hepatitis virus, alcoholic liver disease, drug-induced liver disease, active gastrointestinal bleeding, septic shock, underlying renal disease, any carcinoma, cardiac or respiratory failure, renal insufficiency history, pregnancy and liver transplantation history. Diagnosis of type 1 HRS was determined using the criteria proposed by the International Ascites Club [4]: (1) low glomerular filtration rate, as indicated by serum creatinine >133 umol/L or 24-h creatinine clearance <40 mL/min; (2) absence of shock, ongoing bacterial infection, fluid losses and treatment with nephrotoxic drugs; (3) no improvement in renal function following diuretic withdrawal and plasma volume expansion; (4) proteinuria <500 mg/day and (5) no ultrasonographic evidence of renal parenchymal disease or urinary tract obstruction. 30-days mortality was defined as the number of patients who died within 30 days of hospitalization. The research was authorized by the clinical ethics committee of the Third Affiliated Hospital of Sun Yat-sen University.

Clinical and laboratory assessment

Clinical and biochemical data from routine examinations were collected at the time of inclusion. Laboratory tests included analysis of biochemical indexes of liver function ALT, gamma glutamyl transpeptidase, and albumin, TBIL, HBV related tests (HBsAg and HBV DNA titer), liver imaging examination, creatinine, potassium and sodium levels, prothrombin time and platelet count. The blood pressure of the patients was measured by professionally trained healthcare workers when the patient was quiet and awake. Blood pressure was measured every day after admission to the hospital using an electronic sphygmomanometer (Omron HEM-6200, Dalian, China). Measurements were performed three times a day, and an average of three measurements in the day was used for further analyses. MAP at every measurement point was calculated (MAP = 1/3 SBP + 2/3 DBP).

Treatment

All the patients were given liver-protecting agents such as adenosylmethoinine, diammonium glycyrrhizinate, phosphatidylcholine and energy mixture. During follow-up, patients with ascites were treated with diuretics

and followed by 10 g albumin infusions daily, if plasma albumin is less than 35 g/L. If plasma albumin is less than 30 g/L in patients with ascites, 20 g albumin was given to the patients daily. All the patients were given antiviral therapy with entecavir for chronic hepatitis B and 400 ml fresh plasma every 2 days.

Statistical analyses

The results are expressed as mean with SD or as median with range. Comparisons between groups were performed using Student's t-test, Mann–Whitney U test or Fisher's exact test. A value of $P < 0.05$ on both sides was considered significant. The survival curves were generated using the COX method and compared with the log-rank test. Logistic analyses were performed to determine baseline predictors of HRS. A receiver operating characteristic (ROC) curve was generated, and the area under the curve was calculated. All statistical analyses were performed using the SPSS 23.0 statistical package (SPSS Inc., Chicago, Illinois, USA) and R package [R version 3.6.1 (2019-07-05)].

Results

Baseline patient characteristics

During the study period from June 2015 to June 2016, a total of 420 ACLF patients were admitted to the 3rd affiliated hospital of Sun-yat Sen University. Of these patients, 335 patients were included according to the including criteria. Totally 91 were excluded based on complicated with other primary diseases or other causes of ACLF besides HBV infection (Fig. 1). In the remaining 244 patients, 187 patients were excluded based on severe complications related to ACLF or BP data incomplete. In total 57 patients were assessed for eligibility (Fig. 1).

Total 57 final identified HBV-related ACLF patients were divided into HRS group ($n = 14$) and non-HRS group ($n = 43$). The baseline clinical characteristics of all patients are shown in Table 1. The average age of the HRS patients was 53.21 ± 13.38 years, with a male predominance (12/14, 85.71%). And in non-HRS patients were 45.02 ± 11.74 years, which was significantly younger than the patients in the HRS group ($P = 0.033$), with a male predominance(37/43, 86.05%). Model for end-stage liver disease (MELD) score, albumin, Fib and blood urea nitrogen (BUN) values for patients in the HRS group were 36.09 ± 8.36, 29.09 ± 9.41 mg/l, 1.17 ± 0.39 g/l and 8.44 ± 8.12 µmol/l, respectively, and those in the non-HRS group were 27.64 ± 5.87, 33.30 ± 5.19 g/l, 1.50 ± 0.52 g/l and 4.08 ± 2.38 µmol/l, respectively, all of these parameters were significantly different between the two groups. In conclusion, patients in the HRS group were older and had higher MELD scores than patients in the non-HRS group. There was no difference in viral load levels between the HRS and non-HRS groups ($P = 0.233$), and none of the patients in the HRS group received anti-HBV treatment prior to hospital admittance. One patient in the non-HRS group received anti-HBV therapy, and the HBV DNA level was below the detective level in this patient. There was no difference in cases of HBsAg level between the two groups ($P = 0.052$) (Table 1). The 30-day mortality rates were 57 and 20% in the HRS and non-HRS groups, respectively.
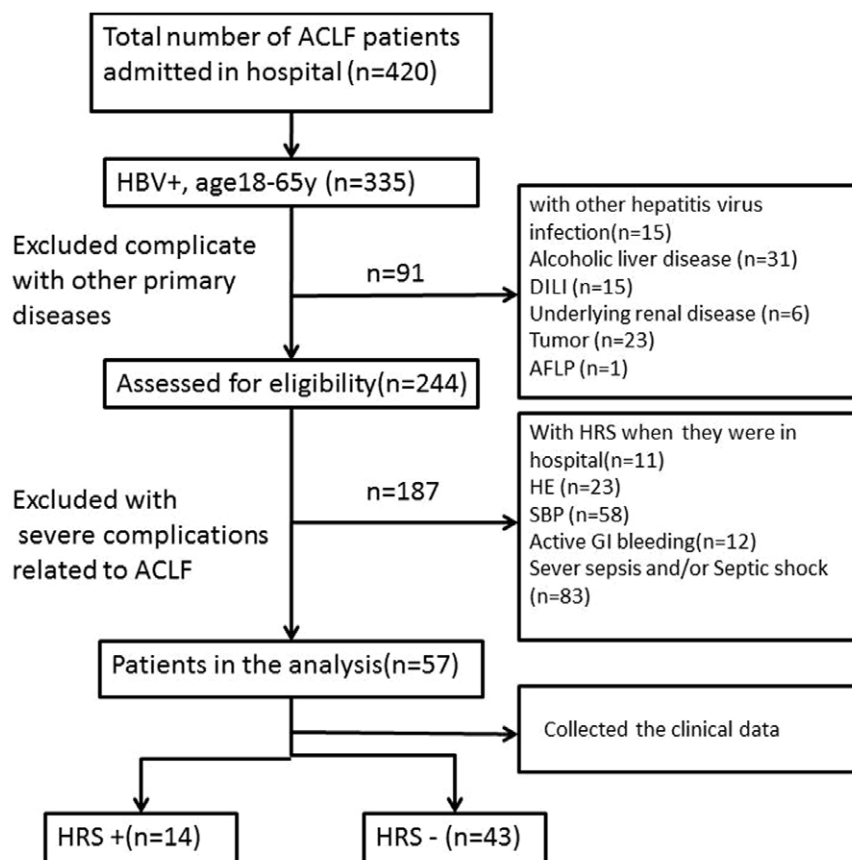

Fig. 1. Flow diagram of the patients screening and enrollment process.

Table 1. Comparison of baseline clinical characteristics of patients in Hepatorenal syndrome (HRS) and non-HRS group

Parameters	Patients without HRS ($n = 43$)	Patients with HRS ($n = 14$)	P Value
Age (years)	45.02 ± 11.74	53.21 ± 13.38	0.033
WBC ($\times 10^9$/L)	7.19 ± 2.85	7.85 ± 2.35	0.445
Platelet ($\times 109$/L)	108.70 ± 46.26	98.57 ± 47.70	0.483
AST (U/L)	451.72 ± 649.27	241.79 ± 163.37	0.058
GGT (U/L)	75.446 ± 49.306	61.79 ± 35.91	0.344
ALP (U/L)	138.98 ± 39.116	125.79 ± 42.69	0.288
Albumin (g/L)	33.30 ± 5.596	29.09 ± 9.41	0.038
TBIL (umol/L)	375.99 ± 149.75	473.58 ± 202.89	0.058
BS (mmol/L)	5.296 ± 2.20	6.39 ± 3.05	0.147
HBV DNA	$3.5 \log 7 \pm 6.14 \log 7$	$1.36 \log 7 \pm 4.52 \log 7$	0.233
HBsAg (IU/ml)	9911.76 ± 17680.97	2784.75 ± 2679.87	0.022
PCT (ng/ml)	1.046 ± 1.15	2.30 ± 4.39	0.369
Prothrombin time (S)	30.69 ± 9.36	34.02 ± 9.64	0.256
Fibrinogen (g/L)	1.50 ± 0.52	1.17 ± 0.39	0.032
NA (mmol/L)	135.58 ± 5.85	132.00 ± 8.59	0.083
MAP (mm/Hg)	87.48 ± 11.41	89.12 ± 11.19	0.641
K (mmol/L)	$3.71 \pm 0\ 0.48$	4.04 ± 1.02	0.251
HCO_3 (mmol/L)	23.46 ± 3.42	21.90 ± 3.87	0.160
MELD	27.64 ± 5.89	36.09 ± 8.36	0.000
HGB (g/L)	112.26 ± 26.32	102.50 ± 20.13	0.210
BUN (umol/l)	4.08 ± 2.38	8.44 ± 8.12	0.000
Creatinine (umol/l)	74.74 ± 20.41	102.63 ± 29.39	0.004
Survival (days)	28.88 ± 2.66	17.86 ± 11.20	0.030

ALP, alkaline phosphate; AST, aspartate amiotransferase; BS, blood sugar; BUN, blood urea nitrogen; GGT, gamma glutamyl transpeptidase; HBsAg, hepatitis B surface antigen; HBV DNA: hepatitis B virus DNA; HCO_3, plasma bicarbonate concentration; HGB, hemoglobin; K, potassium; MAP, mean artery pressure; MELD, model for end-stage liver disease; NA, natrium sodium;, PCT, plateletocrit, TBIL, total bilirubin; WBC, white blood cell count.

Analysis of baseline variables predicting hepatorenal syndrome

To assess the association of baseline variables and HRS, the following parameters were tested by the logistic regression analyses: age, albumin, Fib, MELD score and BUN. These variables showed significant differences between the HRS and non-HRS groups. Creatinine was not used in the logistic regression, as the MELD score was calculated using the creatinine values. We found that only the MELD score was associated with a significantly increased risk of HRS [odds ratio (OR), 1.182; 95% confidence interval (CI), 1.067–1.309].

Analysis of baseline variables predicting survival

All patients were divided into survival and nonsurvival groups, and data were collected for 30 days to calculate the in-hospital mortality rate. Prothrombin time, Fib and the MELD score were significantly different in the survival and nonsurvival groups (Table 2). Eight patients were diagnosed with HRS in the nonsurvival group, and seven patients without HRS died during the follow-up period. There was a significant difference in HRS diagnosis between the survival and nonsurvival groups ($X^2 = 9.095$; $P = 0.003$).

To assess baseline variables that predict survival, the following parameters were tested by forward stepwise Cox proportional hazards regression analysis: prothrombin time, Fib, MELD score and HRS diagnosis. We found that prothrombin time, HRS, MELD and Fib independently predicted 30-day survival in HBV-ACLF patients (Table 3).

Mean arterial pressures falls before hepatorenal syndrome development

Although the baseline MELD score predicted HRS in HBV-ACLF patients, it was unclear when the patients developed HRS and whether treatment could prevent HRS occurrence. As baseline MAP was not different between the HRS and non-HRS groups, we collected MAP measurements during the course of the hospital stay. We found that MAPs dropped 12.02 ± 2.98 mmHg before HRS diagnosis. In contrast, MAPs only dropped 7.89 ± 3.80 mmHg in non-HRS patients throughout the in-hospital period ($P < 0.05$) (Fig. 2). In the HRS group, MAP-drop lasted for 3.79 ± 1.528 days, whereas in the non-HRS group, MAP-drop lasted for 1.58 ± 0.932 days ($P < 0.01$). For the 14 patients in the HRS group, the average time from MAP drop to HRS happen is 5.36 ± 1.865 days.

Mean arterial pressures drop is an independent risk factor for hepatorenal syndrome development in hepatitis B virus - acute-on-chronic liver failure patients

To evaluate whether the drop in MAP could predict HRS, a ROC curve was constructed. MAP drop was a very good predictor of HRS in patients with HBV-ALCF (AUROCs = 0.808). Creatinine level, BUN and MELD were also markers of HRS in patients with HBV-ALCF (AUROCs > 0.70 and > 0.80) (Fig. 3). However, creatinine and BUN cannot predict HRS prior to the occurrence and MELD cannot be corrected rapidly. As MAP was predictive of HRS and can be improved in a relatively short time, we went on to determine the specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR−) for different cutoff MAP drop values. We found that a cutoff MAP drop value of ≥9.5 mmHg predicted the risk of HRS in patients with HBV-ACLF with a sensitivity, specificity, PPV, NPV, LR+ and LR− of 92.86, 69.77, 50.0, 96.77%, 0.10 and 3.07, respectively (Table 4).

Table 2. Comparison of baseline clinical characteristics of patients in survival and non- survival group

Parameters	Patients survival (n = 43)	Patients non- survival (n = 14)	P Value
Age (years)	49.60 ± 8.92	46.12 ± 13.59	0.361
WBC (×10^9/L)	7.46 ± 2.73	7.32 ± 2.76	0.860
Platelet (×109/L)	93.20 ± 48.75	110.86 ± 45.21	0.209
AST (U/L)	472.53 ± 786.44	374.31 ± 487.69	0.575
GGT (U/L)	53.13 ± 39.95	78.86 ± 47.16	0.065
ALP (U/L)	128.73 ± 53.39	138.24 ± 34.53	0.435
Albumin (g/L)	31.06 ± 9.22	32.70 ± 5.52	0.417
TBIL (umol/L)	434.86 ± 207.78	387.50 ± 152.09	0.353
BS (mmol/L)	5.55 ± 8.59	4.35 ± 1.95	0.972
HBV DNA	3.40lg7 ± 6.47lg7	2.85lg7 ± 5.65lg7	0.753
HBsAg (IU/ml)	11372.06 ± 21210.59	6770.23 ± 12836.34	0.352
PCT (ng/ml)	1.82 ± 4.038	1.17 ± 1.29	0.439
Prothrombin time (S)	39.79 ± 10.47	28.55 ± 7.11	0.001
Fibrinogen (g/L)	1.08 ± 0.44	1.55 ± ± 0.48	0.002
NA (mmol/L)	133.46 ± 8.68	135.15 ± 5.94	0.410
MAP (mm/Hg)	87.34 ± 9.46	88.08 ± 11.96	0.829
K (mmol/L)	4.15 ± 0.87	3.66 ± 0.52	0.056
HCO_3 (mmol/L)	22.48 ± 4.75	23.29 ± 3.08	0.456
MELD	35.17 ± 7.28	27.77 ± 27.77	0.001
HGB (g/L)	108.27 ± 26.92	110.43 ± 24.77	0.778
BUN (umol/l)	7.42 ± 8.59	4.35 ± 1.95	0.000
Creatinine (umol/l)	80.26 ± 26.26	85.7 ± 24.29	0.482

ALP, alkaline phosphate; AST, aspartate amiotransferase; BS, blood sugar; BUN, blood urea nitrogen; GGT, gamma glutamyl transpeptidase; HBsAg, hepatitis B surface antigen; HBV DNA: hepatitis B virus DNA; HCO_3, plasma bicarbonate concentration; HGB, hemoglobin; K, potassium; MAP, mean artery pressure; MELD, model for end-stage liver disease; NA, natrium sodium;, PCT, plateletocrit, TBIL, total bilirubin; WBC, white blood cell count.

Table 3. Cox regression analyses of baseline variables predicting survival

	βcoefficient	Z	P value	Exp(B)	EXP(B) 95% confidence interval Low	Up
FIB	−2.230	−3.027	0.002	0.107	0.025	0.455
Prothrombin time	0.085	3.775	0.000	1.088	1.042	1.137
MELD	0.120	3.618	0.000	1.128	1.057	1.204
HRS	1.787	3.419	0.000	5.973	2.144	16.638

FIB, fibrinogen; HRS, Hepatorenal syndrome; MELD, model for end-stage liver disease; PT, prothrombin time.

Mean arterial pressures drop is an independent risk factor for the 30-day mortality of hepatitis B virus - acute-on-chronic liver failure patients

Next, we performed forward stepwise Cox proportional hazards regression analysis in all patients and found that the MAP drop (OR, 1.582; 95% CI, 1.317–1.900; $P = 0.000$) could predict 30-day mortality.

Discussion

The present study demonstrated that patients who developed HRS were older, had greater drops in MAP, and had higher MELD scores than those who did not have HRS ($P < 0.05$). A MAP drop ≥9.5 mmHg was an important independent predictor of HRS in HBV-ACLF patients. The results of this retrospective study suggest that reversal of MAP may be effective and well tolerated preventive measures for type 1 HRS in HBV-ACLF patients. This study also provides new insight into the role of circulation dysfunction in the development of HRS in HBV-ACLF.

ACLF develops in acute decompensation of cirrhosis and is defined by hepatic and extra-hepatic organ failure [2,3]. ACLF is also characterized by high mortality, ranging from 23 to 74% [1,2]. In critically ill patients, the severe complications of ACLF (e.g. HRS, hepatic encephalopathy, hepatopulmonary syndrome, spontaneous bacterial peritonitis, etc.) are associated with poor quality of life and short survival [13,19]. This study evaluated a drop in MAP as a predictor of HRS, which is a very severe complication of ACLF. HRS occurs in 25–50% of patients with cirrhosis admitted to the hospital with an episode of acute decompensation [20]. HRS is a strong predictor of poor survival in both the short and long term [2]. Hospitalized cirrhotic patients with HRS do not survive their admission, and demonstrate1- and 12-month mortality rates of 58 and 63%, respectively. In our study, 57.14% of HRS patients (8/14) died during the 30-day observation period in the hospital. In contrast, the 30-day mortality rate of ACLF patients who did not have HRS was 13.95% (6/43). Thus, preventing HRS may significantly improve the survival of ACLF patients.

There are many new parameters besides the traditional biomarkers that predict HRS. Urinary sodium excretion is a common indicator of HRS [4,7], however, sodium excretion can be affected by many factors, such as diuretic administration. Other biomarkers associated with HRS include serum cystatin C, urinary and serum neutrophil gelatinase-associated lipocalin (NGAL), urinary IL-18, kidney injury molecule 1, liver-type fatty acid-binding protein, insulin-like growth factor and tissue inhibitor metalloproteinase [21]. These novel biomarkers increase
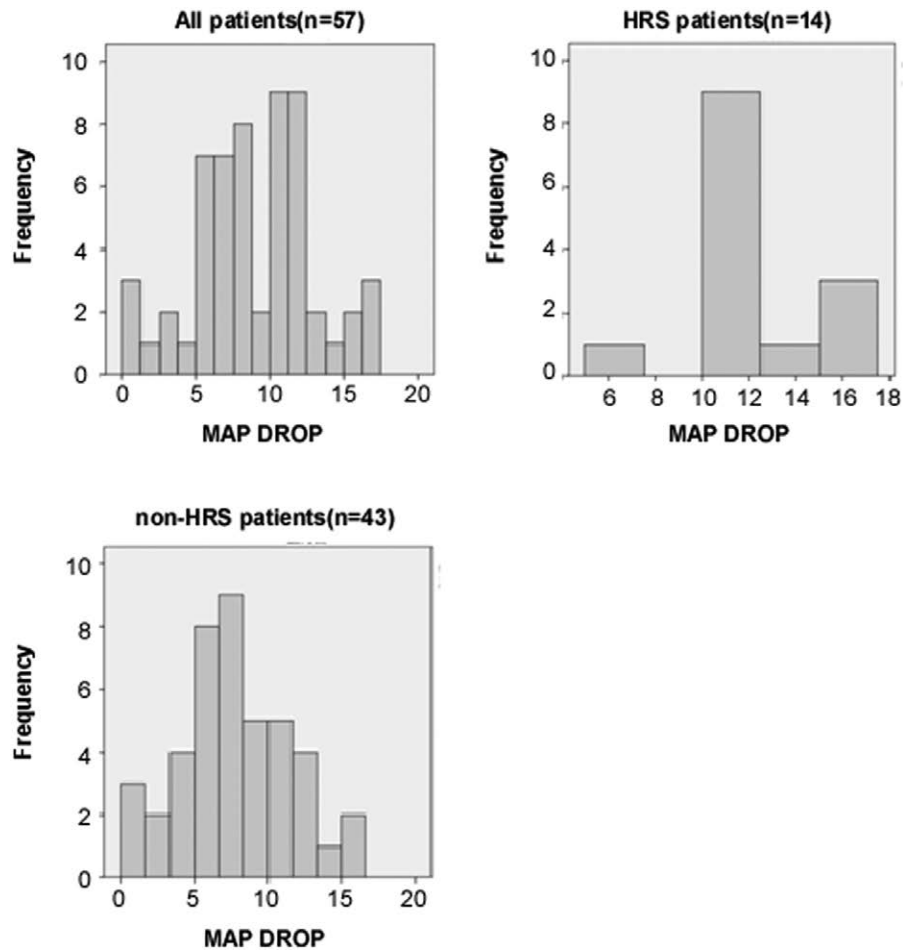
Fig. 2. Distribution of mean artery pressure (MAP) drops in different groups. (a) all patients; (b) Hepatorenal syndrome (HRS group); (c) non-HRS group.

with the severity of the liver injury and are predictive of outcomes. In addition, urinary infection, which is more prevalent in patients with ACLF, can also increase urinary biomarker excretion. Therefore, further study is required to develop efficient and controllable biomarkers to aid in diagnosing HRS early to improve clinical outcomes. In our study, we analyzed clinical markers and found that Fib, prothrombin time, MELD score, albumin and BUN were significantly different in the HRS and non-HRS groups. Interestingly, only the MELD score was a predictor of HRS. These results are similar to a previous study, which found that patients with a poor liver condition and severe ACLF will develop more complications, including HRS [1,5,8,13,22]. More importantly, these parameters cannot be corrected rapidly, which limits the treatment potential for patients suspected to be at risk of developing HRS. Based on the effect of MAP in reflecting circulation volume and can be improved in a short time, we consider it an interesting factor to look at. Then, we compared the baseline MAP in the two groups and found no significant difference or the predictive ability for HRS. However, we discovered that HRS patients suffered a MAP drop prior to HRS occurrence. Using ROC curve analysis, we selected a cutoff for MAP drop ≥9.5 mmHg to predict HRS.

ACLF patients show evidence of severe cardiovascular dysfunction. They can have both increased and decreased cardiac output [3,4,6]. Increased cardiac output is a compensation period performance and will be developed into decreased cardiac output, which may result in renal hypoperfusion and ischemia [3,4,9,13]. A significant change in patients with cirrhosis is portal hypertension, which accelerates the release and generation of endogenous vasodilators into visceral blood circulation. The release of these vasodilators results in splanchnic vasodilatation, blood volume expansion and increased mesenteric blood flow [3,13,22]. Finally, the total effective arterial blood volume decreases, and leads to systemic circulatory dysfunction. Renal perfusion is one of the most affected organs [2,13]. Studies on arterial hypertension in patients with cirrhosis have shown that the prevalence of hypertension is reduced [23] and that high arterial blood pressure is a beneficial predictive factor of hepatic decompensation and liver disease-associated death [15,17]. The vasodilatory complications of hepatorenal syndrome and hepatopulmonary syndrome can be prevented in patients with high arterial blood pressure [13]. MAP is regarded as the perfusion pressure required maintaining blood flow to the organs and is considered the most important hemodynamic measure of the function of the circulation system [13]. MAP is also the determining factor for maintaining cerebral and renal blood flow [16,18]. A previous study revealed that arterial blood pressure was independently associated with survival in patients with liver cirrhosis ascites over a period of 1 year [15]. Another study reported that baseline MAP was an independent correlative factor of 5-year mortality in patients with HBV-related liver cirrhosis ascites [13].
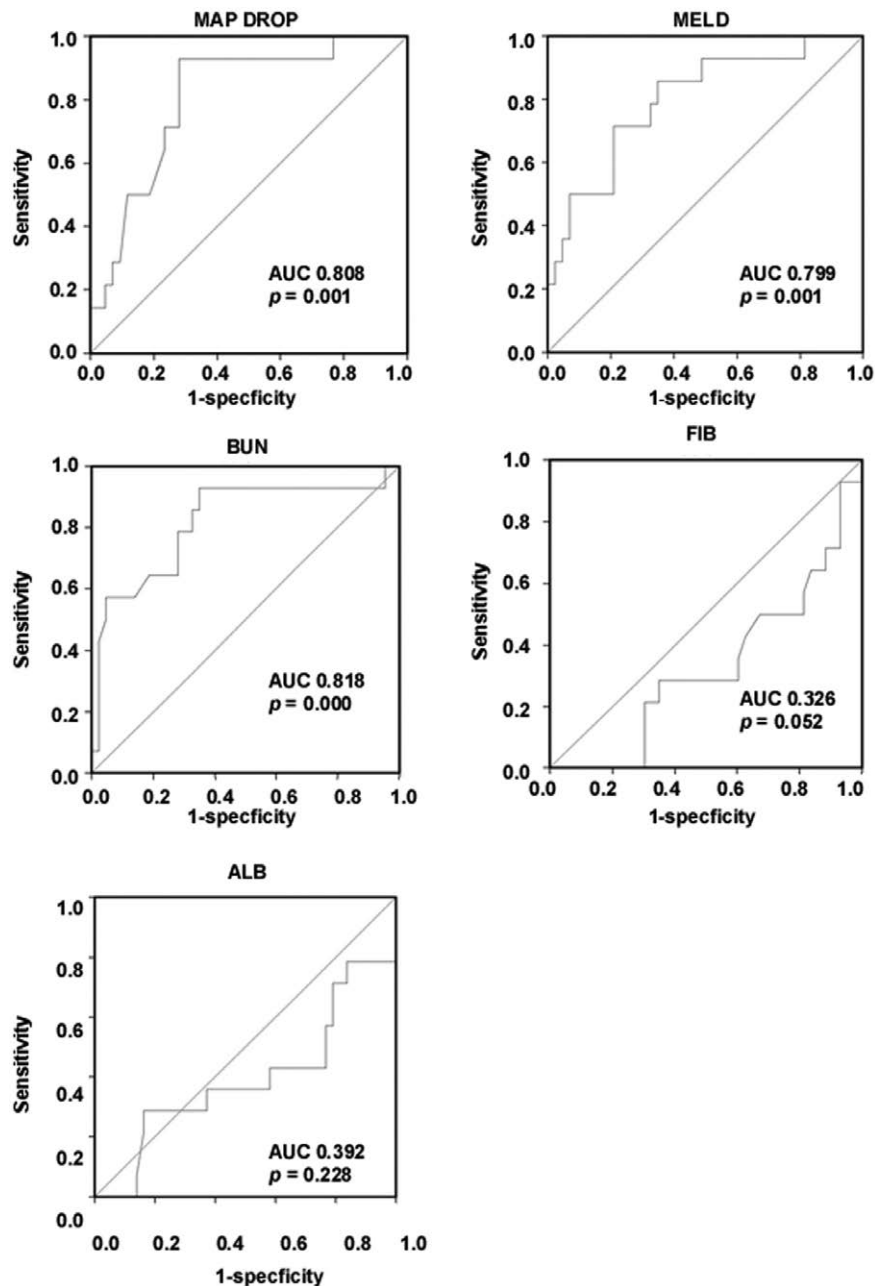
Fig. 3. Area under the receiver-operating characteristic (ROC) curves of different variables for predicting Hepatorenal syndrome (HRS) in patients with hepatitis B virus- Acute-on-chronic liver failure (HBV-ALCF). Mean artery pressure (MAP) drop (a), model for end-stage liver disease (MELD) scores (b), blood urea nitrogen (BUN) (c), fibrinogen (FIB) (d) and albumin (e).

Moreover, a meta-analysis suggested that the use of terlipressin or noradrenaline improves MAP, which results in higher urine output and reversal of both types of HRS [11]. These results indicate that once HRS has occurred, hemodynamic and renal function disorders may develop. Therefore, preventing or correcting pre-clinical HRS may be more valuable than treating HRS.

Our results revealed that a MAP decrease of at least 9.5 mmHg was a notable predictor of HRS occurrence in patients with HBV-ALCF. Like the baseline MELD score[1], the MAP drop proved to be an independent correlative factor of 30-day mortality during hospital stays. The AUROC values were all greater than 0.8, indicating a satisfactory predictive ability. MAP drop was one of the most consistent and independent predictors of HRS in

patients. Therefore, MAP should be monitored for drops as an optimal predictor of HRS in patients with HBV-ACLF. In addition, changes in MAP are indicative of treatment efficacy when using albumin and vasoconstrictors to improve blood pressure.

Our study has a number of limitations. First, we did not calculate a sample size a priori. For this is a retrospect study, many clinical data were incomplete. The relatively low number of patients included in this study necessitates validation of our results in larger cohorts. Our study only included one hospital, limiting the external generalizability of our results. The use of cardiac output monitoring or central venous pressure values was not used to aid with volume assessment in this study. Thus, we did not have a direct indicator of the effective circulating blood

Table 4. Different cutoff mean artery pressure, drop values to evaluate the risk of Hepatorenal syndrome in patients with Hepatitis B virus-Acute-on-chronic liver failure

MAP drop (mmHg)	Specificity	Sensitivity	NPV	PPV	LR+	LR-
0.5	0.047	1	1	0.255	0	1.049
1.5	0.069	1	1	0.259	0	1.075
2.5	0.093	1	1	0.264	0	1.103
3.5	0.116	1	1	0.269	0	1.132
4.5	0.163	1	1	0.280	0	1.194
5.5	0.209	1	1	0.292	0	1.265
6.5	0.372	0.929	0.941	0.325	0.192	1.479
7.5	0.465	0.929	0.952	0.361	0.154	1.736
8.5	0.605	0.929	0.963	0.433	0.118	2.349
9.5	**0.698**	**0.929**	**0.968**	**0.500**	**0.102**	**3.071**
10.5	0.744	0.714	0.889	0.476	0.384	2.79
11.5	0.837	0.5	0.837	0.500	0.597	3.071
12.5	0.907	0.286	0.796	0.500	0.788	3.071
14	0.930	0.214	0.784	0.500	0.845	3.071
15.5	0.953	0.143	0.774	0.500	0.899	3.071
16.5	1	0.143	0.782	1	0.857	NA

Bold indicates MAP drop value.
ACLF, Acute-on-chronic liver failure; HRS, Hepatorenal syndrome; LR+, positive likelihood ratio; LR–, negative likelihood ratio; MAP, mean artery pressure; NPV, negative predictive value; PPV, positive predictive value.

volume. Finally, whether MAP drop is a cause or consequence of renal dysfunction in HBV-ACLF and organ failure development is not understood. Therefore, additional studies addressing whether elevated MAP prevents HRS occurrence are necessary and require a randomized controlled clinical design. To this end, we have registered a clinical study to evaluate the effect of terlipressin on the prevention of HRS by improving mean arterial pressure (NCT02489864).

In conclusion, the most important discovery of this retrospective study was that a MAP drop ≥9.5 mmHg was one of the most important predictors of HRS in patients with HBV-ACLF during short-term follow-up. Our results may be extended to predict patient prognosis and to explore new treatment measures directed at optimizing the treatment of HBV-ACLF patients.

Conflicts of interest

There are no conflicts of interest.

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