Mean arterial pressure drop is an independent risk factor of death in patients with HBV-related cirrhosis ascites

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Original Article

ABSTRACT

Background/Aims: In patients with cirrhosis ascites, mean arterial pressure (MAP) is a credible sign of circulatory dysfunction. There are no studies on the relationship between MAP and long-term prognosis in hepatitis B virus (HBV)-related liver cirrhosis ascites. Therefore, we assessed the association between MAP and prognosis in patients with liver cirrhosis ascites.

Materials and Methods: In total, 110 patients of HBV-related liver cirrhosis ascites were prospectively followed for 5 years. After their admission, the patients underwent laboratory tests and MAP measurements. Multivariate analysis was conducted using backward stepwise Cox proportional hazards regression. Receiver operator characteristic (ROC) curves were used to confirm the best cutoff value of several baseline parameters, including MAP, for predicting death in patients with liver cirrhosis ascites.

Results: In a follow-up period of 5 years, 60 (54.5%) patients survived. MAP (OR 1.176, 95% CI 1.045 to 1.326, p=0.003) was an independent risk factor of death, together with Child–Pugh score (OR 1.204, 95% CI 1.068 to 1.357, p=0.002) and model for end-stage liver disease score (OR 1.297, 95% CI 1.198 to 1.405, p=0.000). The area under the ROC curve of MAP was 0.819 at baseline (95% CI 0.741 to 0.897, p=0.000). A baseline MAP value of ≤83.5 mmHg was an independent risk factor of death.

Conclusion: A decrease in MAP was a valuable predictor of death in patients with HBV-related liver cirrhosis ascites. MAP may be used for determining the prognosis and exploring new treatment measures directed at optimizing the treatment of liver cirrhosis ascites.

Keywords: Mean arterial pressure, cirrhosis, ascites, risk factor, predictor of death

INTRODUCTION

Ascites is a major complication of cirrhosis; over 50% of patients develop ascites within 10 years of the diagnosis of cirrhosis (1). The development of ascites is associated with a poor prognosis and high mortality rate (2). Portal hypertension and splanchnic vasodilation are the primary pathophysiological mechanisms of seroperitoneum. The increase of effective circulatory blood volume is the firstly compensatory of the increase in cardiac output (3). Along with the progression of cirrhosis, this mechanism is not sufficient to maintain the effective circulatory blood volume and leads to vasoconstrictor and antinatriuretic accumulation in vivo. Finally, the redundant fluid gathers in the peritoneal cavity and causes ascites (4).

In clinical practice, mean arterial pressure (MAP) is a reliable index of the dysfunction of circulatory compensation in patients with liver cirrhosis ascites. 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 (5). MAP was found to return from 65 mmHg to the normal range and to be closely associated with microcirculation improvement (6). A recent research also demonstrated that a history of hypertension serves as a protective factor for liver-associated clinical decompensation and mortality (7). Another study also showed that a lower MAP of 50–60 mmHg has a positive correlation with a higher morbidity in case of kidney dysfunction (8).

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Low MAP has been shown to be closely associated with hyperdynamic circulation (5-7), seroperitoneum (5,7), and advancement of hepatorenal syndrome (8), thereby indicating that optimal MAP may be an important factor to ameliorate the prognosis of patients with liver cirrhosis ascites. However, which MAP level should be maintained to ameliorate the prognosis of patients with liver cirrhosis ascites remains controversial, and no prospective studies have determined the long-lasting impact of MAP on the prognosis of these patients. Based on these considerations, in this prospective cohort study, we aimed to demonstrate the long-lasting impact of baseline MAP levels on the prognosis of patients with hepatitis B virus (HBV)-related cirrhosis ascites.

MATERIALS AND METHODS

Patient Characteristics

This was a prospective case–control study involving patients with liver cirrhosis ascites who were enrolled from January 2006 to January 2010 at our hospital. All 110 patients with HBV-related cirrhosis ascites were diagnosed according to the methods described in the literature (4). All the patients had HBV-related decompensated liver cirrhosis, and their Child–Pugh score was B or C grade. Inclusion criteria included shrunken liver and ascites revealed by enhancement computed tomography (CT) scanning of the abdomen. Exclusion criteria included hepatocellular carcinoma, infectious diseases, cardiac or respiratory failure, renal insufficiency, hypertension, diabetes mellitus, and liver transplantation. The research was authorized by our hospital's clinical ethics committee. Signed informed consent forms were collected from all the patients.

Clinical and Laboratory Assessment

All the patients used nucleoside/nucleotide analog (NUC)-based treatment for at least 5 years. The patients underwent clinical and biochemical analyses and blood routine examination at baseline. Baseline diastolic blood pressure (DBP) and systolic blood pressure (SBP) were recorded for further studies, and MAP at every measurement point was calculated (MAP=1/3SBP+2/3DBP). The blood pressure of the patients was measured every morning by professional trained healthcare workers before the patients woke up. Blood pressure was measured using an electronic sphygmomanometer (Omron HEM-6200, Dalian, China) after admission to the hospital. Measurements were performed for 3 consecutive days, and an average of three measurements was used for further analyses. Child–Pugh scores and model for end-stage liver disease (MELD) scores were recorded at the time of inclusion. Laboratory tests included analysis of albumin, total bilirubin, creatinine, potassium, and sodium levels; international normalized ratio (INR) for prothrombin time (PT); and platelet count. Our study describes the death time during 5 years of follow-up.

Statistical Analyses

Statistical analyses were performed using Statistical Package for the Social Sciences PASW Statistics 18 (SPSS Inc; Chicago, IL, USA). Comparisons of laboratory indices between two groups were made using paired-samples *t* test. Proportions between two groups were compared using chi-square test. Survival was analyzed by Kaplan–Meier curves. Regression of binary logistic analysis was used to determine the risk factor of death. Multivariate analysis was conducted using backward stepwise Cox proportional hazards regression. To evaluate the MAP level and the relationship between MAP change and mortality, areas under the receiver operator characteristic curves (AUROCs) were calculated. All tests were 2-tailed. P<0.05 were regarded as statistically significant.

RESULTS

Patient Baseline Characterizations and Survival Rate

Baseline clinical characteristics of 110 patients are shown in Table 1. The average age of the 50 patients in the death group was 54.8±7.2 years, with a male predominance [44 (88.0%)]. The average age of the 60 patients in the survival group were 52.9±5.7 years, with a male predominance [50 (83.3%)]. The parameters of age; gender; albumin, total bilirubin, potassium, and sodium levels; and platelet counts between the two groups showed no significant differences. Child–Pugh score, MELD score, MAP, creatinine level, and INR of patients in the death group were 10.9±1.5, 14.7±3.1, 81.1±7.0 mmHg, 71.5±11.7 mmol/L, and 1.71±0.11, respectively, and those in the survival group were 9.3±1.5, 10.1±1.7, 90.6±7.7 mmHg, 65.7±9.0 mmol/L, and 1.54±0.16, respectively; all these parameters were significantly different between the two groups (p=0.000, p=0.000, p=0.000, p=0.004, and p=0.000, respectively). The 5-year survival rate of patients with HBV-related cirrhosis ascites was 54.5% (Figure 1).

Table 1. Baseline Characteristics of patients with HBV-related cirrhosis and ascites

Parameter	Death group	Survival group	p
Total	50	60	-
Age, year	54.8±7.2	52.9±5.7	NS
Male sex	44 (88.0%)	50 (83.3%)	NS
Child-Pugh score	10.9±1.5	9.3±1.5	0.000
MELD score	14.7±3.1	10.1±1.7	0.000
MAP, mmHg	81.1±7.0	90.6±7.7	0.000
Laboratory data			
Albumin, g/L	24.2±2.7	24.6±2.8	NS
Total bilirubin, μmol/L	43.0±15.9	38.9±12.9	NS
Creatinine, μmol/L	71.5±11.7	65.7±9.0	0.004
Potassium, mmol/L	4.12±1.56	3.98±1.67	NS
Sodium, mmol/L	131.0±3.1	131.7±3.8	NS
INR	1.71±0.11	1.54±0.16	0.000
Platelets, $\times 10^9$/L	47.4±17.0	48.2±13.3	NS

Data are presented as number, mean±SD or n (%).
NS: not significant; MELD: model for end-stage liver disease; MAP: mean arterial pressure; INR: international normalized ratio

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Analysis of Baseline Variables Predicting Death

In order to assess baseline variables predicting death in 5 years, binary logistic regression analysis was performed to determine the involvement of age; gender; albumin, total bilirubin, creatinine, and sodium levels; platelet count; INR; Child–Pugh score; MELD score; and MAP level in this model. Regression analysis indicated that the baseline MAP level was a significant factor predicting death in all the patients (OR 0.869, 95% CI 0.787 to 0.959, p=0.005). Apart from baseline INR, MELD score and Child–Pugh score were independent predictors of death in all the patients (INR: OR 0.000, 95% CI 0.000 to 0.155, p=0.010; Child–Pugh score: OR 0.503, 95% CI 0.314 to 0.804, p=0.004; MELD score: OR 0.518, 95% CI 0.365 to 0.736, p=0.000) (Table 2).

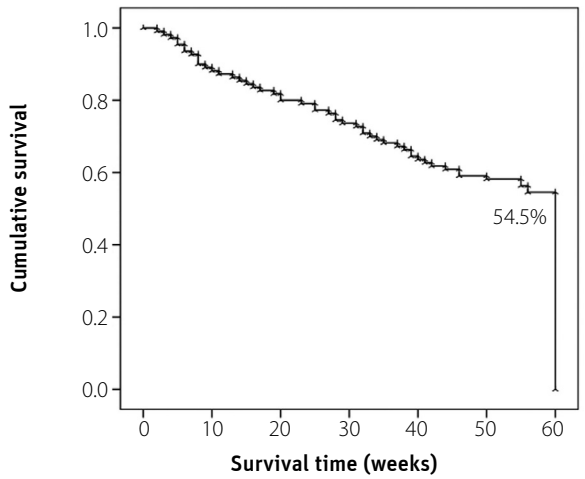
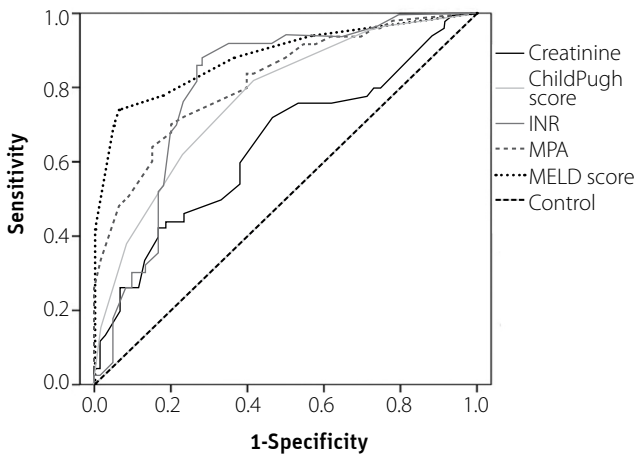


Figure 1. The survival curve of patients with HBV-related cirrhosis and ascites at follow-up five years



			95% Confidence Interval	
Baseline variables	**Area**	***P* value**	**Lower Bound**	**Upper Bound**
Creatinine level	0.644	0.010	0.539	0.749
Child-Pugh score	0.773	0.000	0.686	0.859
INR level	0.802	0.000	0.716	0.888
MAP level	0.819	0.000	0.741	0.897
MELD score	0.884	0.000	0.819	0.950

Figure 2. AUROCs of baseline variables as predictors of death in patients with HBV-related cirrhosis and ascites
INR: international normalized ratio; MAP: mean arterial pressure; MELD: Model for end-stage liver disease; AUROC: areas under the receiver operator characteristic curve

Next, we performed backward stepwise Cox proportional hazards regression analysis in all the patients; and the results indicated that the baseline MAP level was an important independent predictor of death in the patients (OR 1.176, 95% CI 1.045 to 1.326, p=0.003). Child–Pugh score (OR 1.204, 95% CI 1.068 to 1.357, p=0.002) and MELD score (OR 1.297, 95% CI 1.198 to 1.405, p=0.000) were also factors predicting death in the patients (Table 3).

MAP Level as Predictor of Death

The MAP levels and changes at baseline were tested using the receiver operating characteristic (ROC) curves. Of these, INR and MAP level and MELD score were found to be very good predictive factors of death in patients with HBV-related cirrhosis and ascites (AUROCs>0.80). Creatinine level and Child–Pugh score were regular predictors of death in patients with HBV-related cirrhosis ascites (AUROCs>0.60 and <0.80) (Figure 2).

We determined the specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR^+), and negative likelihood ratio (LR^-) for different cutoff MAP values. We found that a cutoff MAP value of ≤83.5 mmHg was the best to evaluate the risk factor of death in patients with HBV-related cirrhosis ascites, with a sensitivity, specificity, PPV, NPV, LR^+ and LR^- of 70%, 80%, 42.2%, 44.4%, 3.50, and 0.38, respectively (Table 4).

Table 2. Binary Logistic regression analysis for baseline variables associated with death risk

Factors	**β coefficient**	**Wald**	**OR (95% CI)**	**p**
INR	-7.826	6.622	0.000 (0.000-0.155)	0.010
Child-Pugh score	-0.688	8.228	0.503 (0.314-0.804)	0.004
MELD score	-0.657	13.540	0.518 (0.365-0.736)	0.000
MAP	-0.141	7.778	0.869 (0.787-0.959)	0.005

OR: odds ratio; CI: confidence interval; INR: international normalized ratio; MELD: model for end-stage liver disease; MAP: mean arterial pressure

Table 3. Cox regression analysis for baseline variables associated with death risk

Factors	**β coefficient**	**Wald**	**OR (95% CI)**	**p**
Child-Pugh score	0.186	9.195	1.204 (1.068-1.357)	0.002
MELD score	0.260	41.084	1.297 (1.198-1.405)	0.000
MAP	0.033	5.908	1.176 (1.045-1.326)	0.003

OR: odds ratio; CI: confidence interval; MELD: model for end-stage liver disease; MAP: mean arterial pressure

Table 4. Performance of baseline MAP level in predicting death in patients

Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR-
≤86.5	80.0	60.0	52.6	70.6	2.00	0.33
≤85.5	74.0	71.7	46.3	56.7	2.61	0.36
≤84.5	72.0	76.7	43.9	50.0	3.09	0.37
≤83.5	70.0	80.0	42.2	44.4	3.50	0.38
≤82.5	68.0	80.0	41.5	42.9	3.40	0.40
≤81.5	64.0	85.0	38.6	33.3	4.27	0.42

PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio

DISCUSSION

The most frequent complication of patients with cirrhosis is ascites; it appears in approximately 85% of patients and is combined with many complications, including hepatorenal syndrome, hypovolemia, hepato-hydrothorax, and spontaneous bacterial peritonitis. Almost all these complications are associated with a poor quality of life and short survival (2,9,10). A significant finding in patients with cirrhosis is portal hypertension, which accelerates the release and generation of endogenous vasodilators into visceral blood circulation. This results in splanchnic vasodilatation, blood volume expansion, and increased mesenteric blood flow. Finally, the effective arterial blood volume decreases and there is an increase in the reduction of arterial pressure and in splanchnic and systemic circulatory dysfunction (11,12).

Studies on arterial hypertension in patients with cirrhosis have shown that the frequency of prevalence of hypertension is reduced (13) and that high arterial blood pressure is a beneficial predictive factor of hepatic decompensation and deaths associated with liver diseases (5,7). The vasodilatory complications of hepatorenal syndrome and hepatopulmonary syndrome can be preventable in these patients with high arterial blood pressure (13). Electronic integration of the pressure signal determines MAP, which reflects the mean value of arterial blood pressure. MAP is regarded as perfusion pressure of the organs required to maintain blood flow and is considered as the most important hemodynamic parameter for the function of the circulation system. MAP is the determinant factor for maintaining cerebral and renal blood flow (6,8).

The present study showed that the patients who died had lower MAP values than those who survived. The results indicated that the baseline MAP level is an important independent predictor of death in patients, similar to Child-Pugh score and MELD score. Then, we analyzed the risk of different cutoff points of MAP in all the patients in order to confirm the best cutoff point. Our results revealed a notable increase in death when MAP was under 83.5 mmHg in patients with cirrhosis ascites. Like the baseline INR level and MELD score, the baseline MAP level proved to be an independent correlative factor of mortality in patients during 5 years of our study; the AUROC values were all more than 0.8, indicating that their whole predictability evaluation was very satisfactory. MAP was one of the most consistent and independent predictors of death in patients; therefore, MAP should be used as the optimal predictor of death in patients with HBV-related cirrhosis ascites. Some studies have found serum potassium level to be a prognostic factor and have revealed that it directly correlates with renal function in patients with cirrhosis (14,15). In our study, all the patients showed normal renal function at baseline, and the serum potassium level was not significantly different between the two groups. Therefore, we think that an elevated serum potassium level predicts mortality in case of advanced cirrhosis only in patients with renal dysfunction.

In conclusion, the principal pathophysiological mechanisms of cirrhosis ascites are splanchnic vasodilation and portal hypertension. Along with the progression of cirrhosis, vasoconstrictor and antinatriuretic accumulation in vivo decreases the effective circulatory blood volume. The exuded fluid accumulates in the peritoneal cavity and leads to ascites to further promote the reduction of the effective circulatory blood volume. MAP can reflect the effective circulatory blood volume and arterial blood pressure and is a definite indicator of circulatory dysfunction in patients with cirrhosis. The most important discovery of this prospective study is that baseline MAP is one of the most important predictors of death in patients with HBV-related cirrhosis ascites during long-term follow-up. Our results may be used for determining the prognosis and exploring new treatment measures directed at optimizing the treatment of these patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of the Bethune International Peace Hospital (2006/12).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – L.H.; Design – L.H., G.Z.; Supervision – S.D.; Materials – L.H., Y.X.; Data Collection and/or Processing – L.H., Y.X.; Analysis and/or Interpretation – L.H., G.Z.; Literature Review – L.H., G.Z.; Writer – L.H., G.Z.; Critical Review – S.D.

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