Original Article

Risk factors and prognostic model for HBV-related subacute liver failure

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Background: The prognosis for patients with chronic hepatitis B virus (HBV)-related subacute liver failure is poor. Thus, accurate prognostication would facilitate management and optimize liver allocation. This study aimed to explore the risk factors for HBV-related subacute liver failure and establish a risk model.

Methods: A total of 192 patients with HBV-related subacute liver failure treated at the First Affiliated Hospital of Xi'an Jiaotong University during January 2018 to January 2019 were selected and divided into the survival group (n=113) and the death group (n=79) based on their status within 6 months. Patient information were collected, including age, sex, body mass index, complications, hepatitis B e antigen (HBeAg), hepatic encephalopathy, hepatorenal syndrome, infections, ascites, HBV-DNA, Model for End-Stage Liver Disease (MELD), liver function tests, international normalized ratio (INR), serum creatinine and total cholesterol. Binary logistic regression was employed to identify risk factors for risk model establishment. The predictive value of the risk model was assessed with a receiver operating characteristic (ROC) curve.

Results: Compared with the survival group, the patient age, incidence of hepatic encephalopathy and hepatorenal syndrome, infection and ascites rate, MELD score, and alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), INR, and serum creatinine levels were significantly elevated, whereas the total cholesterol level was significantly decreased in the death group (all P<0.05). Patient age [odds ratio (OR) =1.11, P=0.03], hepatic encephalopathy (OR =8.31, P=0.02), infection (OR =4.27, P=0.005), ascites (OR =4.54, P=0.006), MELD score (OR =1.39, P<0.001), INR (OR =5.89, P=0.001), and total cholesterol (OR =0.31, P=0.002) were identified as prognostic factors affecting patient mortality. Although both the MELD score and the risk model established in the present study could differentiate patient outcomes, the area under the curve (AUC) (0.94 *vs.* 0.82, P<0.001) and sensitivity (91.1% *vs.* 58.2%, P<0.001) of the established risk model were significantly higher than those of the MELD score.

Conclusions: Patient age, hepatic encephalopathy, infection, ascites, MELD score, INR, and total cholesterol level were independent prognostic factors. The prognostic model established based on these risk factors may have favorable predictive value.

Keywords: Subacute liver failure; risk factor; model; hepatitis B virus (HBV)

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Introduction

Subacute liver failure is a short-term decompensation of liver function which occurs on the basis of the original liver disease. It is characterized by a high incidence rate and high mortality rate and is a serious burden on the health care system. Chronic hepatitis B virus (HBV) infection is the main cause of subacute liver failure in China (1). The main clinical manifestations of the disease are severe impairment of liver function, complicated with coagulation dysfunction, hepatic encephalopathy, ascites, and jaundice. At present, liver transplantation is an important treatment for HBV-related subacute liver failure, but it is often limited by the high cost of the treatment and shortages of liver resources. Thus, accurate evaluation of the prognosis of such patients is helpful to determine the corresponding treatment plan and optimize the distribution of liver resources. At present, most of the commonly used clinical prognostic evaluation schemes have not been established based on patients with HBV-related subacute liver failure, so the efficacy of evaluating such patients may be unsatisfactory. For example, the Model for End-Stage Liver Disease (MELD), which includes bilirubin, international normalized ratio (INR), serum creatinine, and etiology, is not derived from patients with subacute liver failure caused by HBV. Therefore, this study intends to explore the factors affecting the death in patients with HBV-related subacute liver failure and build a risk model, in order to help medical staff accurately evaluate the prognosis of the disease and provide a reference for early intervention. We present the following article in accordance with the STARD reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-461/rc).

Methods

Research subjects

A total of 192 patients with HBV-related subacute liver failure treated in our hospital from January 2018 to January 2019 were selected as the research subjects. The inclusion criteria were as follows: (I) patients met the diagnostic criteria of subacute liver failure, and HBV infection was the cause of subacute liver failure; (II) patients were 18 years or older. The exclusion criteria were as follows: (I) combined with other types of hemophilic virus infection, such as hepatitis E virus infection; (II) combined with other liver damage, such as alcoholic, autoimmune, drug, or fatty liver damage; (III) combined with other virus infections, such as Epstein-Barr (EB) virus and cytomegalovirus, among others; (IV) patients had other basic diseases that affect survival, such as a malignant tumors and severe heart failure, among others; (V) patients with missing or incomplete data and could not be analyzed. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of The First Affiliated Hospital of Xi'an Jiaotong University (No. XJTUIAF2020LSK-153) and informed consent was obtained from all the patients.

Research methods

All selected patients received active medical treatment during hospitalization, including antiviral treatment, liver protection, jaundice treatment, promotion of liver regeneration, and immune regulation. An artificial liver support system was used when necessary.

Relevant clinical and laboratory examination data collected at admission were gathered through the electronic medical record system, including patient age, gender, body mass index, comorbidities (hypertension, diabetes), hepatitis B e antigen (HBeAg), hepatic encephalopathy, hepatorenal syndrome, infection, ascites, HBV-DNA, MELD score, total bilirubin, serum albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), hemoglobin, INR, serum creatinine, and total cholesterol. Diagnostic criteria for hepatorenal syndrome: abnormal renal function (serum creatinine >133 μmol/L or urine output <500 mL/24 h) on the basis of severe liver disease, urine osmotic pressure higher than plasma osmotic pressure, dilutional hyponatremia (serum sodium from <130 mmol/L).

The main endpoint of the study was the case fatality rate at 6 months after onset. The patients who were discharged or survived at 6 months after onset were included in the survival group. The patients who were discharged automatically due to exacerbation or died within 6 months of onset were included in the death group.

Statistical analysis

Normally distributed measurement data are expressed as mean ± standard deviation. The independent sample *t*-test was used for intergroup comparisons. Non-normally distributed measurement data are expressed as medians (interquartile range). Intergroup comparisons were also performed by the Mann-Whitney U test. Count data are

Table 1 Comparison of baseline indexes between the survival group and death group

Indexes	Survival group (n=113)	Death group (n=79)	$t/\chi^2/Z$	P
Age (years), mean ± SD	45.07±6.57	50.09±8.39	−4.44	<0.001
Sex (male), n (%)	71 (62.83)	44 (55.70)	0.99	0.32
Body mass index (kg/m^2), mean ± SD	22.96±2.49	23.31±2.80	−0.91	0.36
Hypertension, n (%)	18 (15.93)	16 (20.25)	0.60	0.44
Diabetes mellitus, n (%)	9 (7.96)	6 (7.59)	0.009	0.93
HBeAg (positive), n (%)	56 (49.56)	39 (49.37)	0.001	0.98
Hepatic encephalopathy (positive), n (%)	17 (15.04)	23 (29.11)	4.08	0.04
Hepatorenal syndrome (positive), n (%)	9 (7.96)	14 (17.72)	4.20	0.04
Infection (positive), n (%)	39 (34.51)	47 (59.49)	11.73	0.001
Ascites (positive), n (%)	64 (56.64)	63 (79.75)	11.09	0.001
HBV-DNA ($\log_{10}$ copies/mL), mean ± SD	4.40±1.36	4.71±1.83	−1.27	0.21
MELD score (point), median [IQR]	28 [25, 30]	33 [30, 37]	−7.57	<0.001
Total bilirubin (μmol/L), median [IQR]	286 [235, 352]	311 [243, 363]	−1.67	0.10
Serum albumin (g/L), mean ± SD	32.31±5.41	30.97±4.80	1.77	0.08
ALT (U/L), mean ± SD	359.25±79.73	381.06±61.81	−2.13	0.03
AST (U/L), mean ± SD	261.62±68.23	276.51±63.22	−1.53	0.12
ALP (U/L), mean ± SD	201.07±36.87	212.24±48.60	−1.73	0.09
Hemoglobin (g/L), mean ± SD	127.33±10.36	126.06±10.51	0.83	0.41
INR, mean ± SD	2.00±0.45	2.38±0.51	−5.54	<0.001
Serum creatinine (μmol/L), median [IQR]	74 [65, 81]	90 [74, 109]	−5.19	<0.001
Total cholesterol (mmol/L), mean ± SD	2.52±0.78	1.80±0.62	6.85	<0.001

SD, standard deviation; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; MELD, model for end-stage liver disease; IQR, interquartile range; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase.

expressed by incidence rate and percentage, and the groups were compared by the chi-square test. Taking the patient's death and outcome as the dependent variables, the statistically significant indicators in the univariate analysis were included in the binary logistic regression analysis to identify the factors affecting the 6-month survival rate. Pearson correlation was used to clarify the correlation coefficient r between the constructed risk model in this study and the MELD score. The best cut-off value (cut-off), area under the curve (AUC), sensitivity, and specificity of death at 6 months were identified by evaluating the receiver operating characteristic (ROC) curve and comparing MELD with the risk model constructed in this study. On bilateral tests, P<0.05 indicated that the difference was statistically significant.

Results

Comparison of baseline indexes between the survival group and death group

Compared with the survival group, the age, incidence of hepatic encephalopathy and hepatorenal syndrome, infection rate, ascites ratio, MELD score, and ALT, AST, ALP, INR, and blood creatinine levels in the death group increased significantly, while the blood cholesterol level decreased significantly (all P<0.05; *Table 1*).

Risk factors for patient mortality

The factors with significant differences between the

Table 2 Binary logistic regression analysis of factors affecting the risk of death in patients with subacute liver failure

Variables	B	Standard error	Wald	OR (95% CI)	P
Age (years)	0.10	0.03	9.00	1.11 (1.04, 1.18)	0.03
Hepatic encephalopathy (positive =1; negative =0)	2.12	0.67	9.98	8.31 (2.34, 30.90)	0.02
Hepatorenal syndrome (positive =1; negative =0)	1.05	1.01	1.06	2.84 (0.39, 20.72)	0.30
Infection (positive =1; negative =0)	1.45	0.52	7.95	4.27 (1.56, 11.73)	0.005
Ascites (positive =1; negative =0)	1.51	0.56	7.43	4.54 (1.53, 13.48)	0.006
MELD score (point)	0.33	0.06	26.85	1.39 (1.23, 1.58)	<0.001
ALT (U/L)	0.006	0.04	2.59	1.01 (1.00, 1.01)	0.11
INR	1.77	0.54	10.64	5.89 (2.03, 17.07)	0.001
Serum creatinine (μmol/L)	0.004	0.007	0.28	1.00 (0.99, 1.02)	0.59
Total cholesterol (mmol/L)	−1.19	0.38	9.76	0.31 (0.15, 0.64)	0.002

OR, odds ratio; CI, confidence interval; MELD, model for end-stage liver disease; ALT, alanine aminotransferase; INR, international normalized ratio.

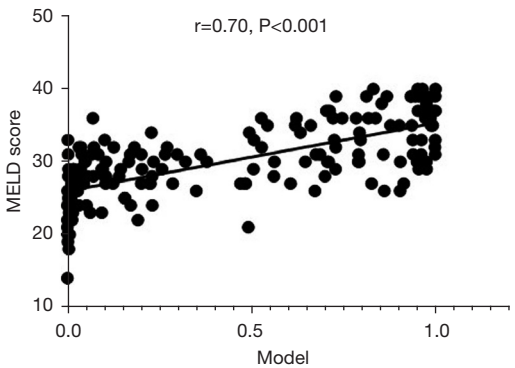

Figure 1 Correlation between the subacute liver failure risk model constructed in this study and MELD score. MELD, model for end-stage liver disease.

survival group and death group in the univariate analysis were included in the binary logistic regression analysis. It was found that age [odds ratio (OR) =1.11], hepatic encephalopathy (OR =8.31), infection (OR =4.27), ascites (OR =4.54), MELD score (OR =1.39), INR (OR =5.89), and total cholesterol level (OR =0.31) were risk factors for patient mortality (*Table 2*). Based on this, the regression equation was constructed as follows: F =−15.40 + 1.11× age (years) +8.31 × hepatic encephalopathy (positive =1; negative =0) + 4.27× infection (positive =1; negative =0) + 4.54× ascites (positive =1; negative =0) + 1.39× MELD score (score) + 5.89× INR + 0.31× total cholesterol (mmol/L). The risk model of death in patients with subacute liver failure was further obtained as follows: Y = ExP (F)/[1 + ExP (F)], where Y is the probability of death risk in patients with subacute liver failure.

The correlation between the risk model and MELD score

As shown in *Figure 1*, the correlation analysis demonstrated that the risk model of subacute liver failure constructed in this study had a significant positive correlation with the MELD score (r=0.70, P<0.001).

The effectiveness of the model constructed in this study vs. the MELD score

As shown in *Table 3* and *Figure 2*, although the MELD score and the risk model constructed in this study could distinguish the death in patients with subacute liver failure, the AUC and sensitivity of the risk model constructed in this study were significantly higher than the MELD score.

Discussion

HBV remains the main cause of subacute liver failure in China. The clinical condition of HBV-related subacute liver failure is dangerous and sudden, and has a poor prognosis. A previous study found that the short-term mortality rate of HBV-related subacute liver failure in China can be as high as 50% to 90% (2). The short-term mortality rate of patients in this study was 41.1%, slightly lower than

Table 3 ROC curve results of the MELD score and the model constructed in this study to identify the death in patients with subacute liver failure

Variables	Cut-off	AUC (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	P
MELD (points)	32	0.82 (0.76, 0.87)	58.2 (46.6, 69.2)	92.0 (85.4, 96.3)	<0.001
Research model	0.2983	0.94 (0.90, 0.97)	91.1 (82.6, 96.4)	83.2 (75.0, 89.6)	<0.001

AUC, area under the curve; CI, confidence interval; cut-off, split value; MELD, model for end-stage liver disease; ROC, receiver operating characteristic.

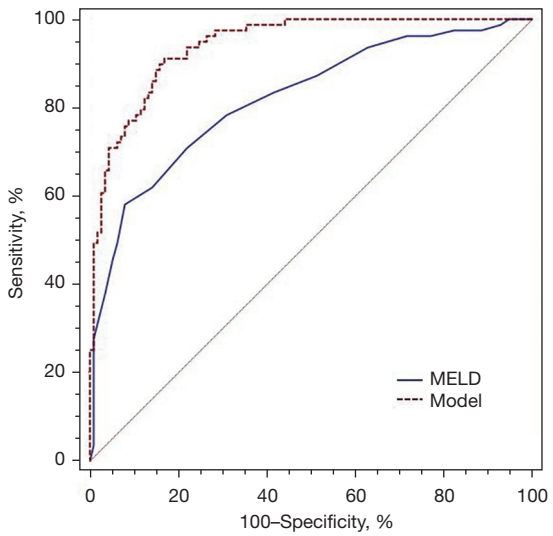

Figure 2 ROC curve of the risk model and MELD score to identify the death in patients with subacute liver failure. ROC, receiver operating characteristic; MELD, model for end-stage liver disease.

that reported in the literature, which may be related to the small sample size included in this study. In addition, after active medical treatment, some patients can finally recover. Therefore, accurately evaluating the prognosis of this disease through the analysis of relevant risk factors has huge clinical significance.

This study reported that age, hepatic encephalopathy, infection, ascites, MELD score, INR, and total cholesterol level are risk factors affecting the prognosis of subacute liver failure. Previous studies (3,4) have shown that age is an independent risk factor affecting the prognosis of acute liver failure, chronic acute liver failure, and liver cirrhosis. This may be related to the decline of organ reserve function and the weakening of liver regeneration in the elderly. Therefore, special attention should be paid to subacute liver failure in the elderly in order to diagnose and treat it in time.

Hepatic encephalopathy is a neurological disorder related to the severe decline of liver function. Tapper *et al.* (5) found that 21% of cirrhotic patients with Child-Pugh grade A and B liver function developed hepatic encephalopathy within 1 year. The research of Cordoba *et al.* (6) showed that the mortality of patients with chronic and acute liver failure complicated with hepatic encephalopathy was significantly higher than that of patients without hepatic encephalopathy, which is consistent with the results of this study. Yu *et al.* conducted a meta-analysis of 13 studies and 2,071 patients with liver failure (7) and found that the number of patients with liver failure complicated with hepatic encephalopathy was 4.62 times higher than those without hepatic encephalopathy.

Infection is very common in patients with liver failure. Fernández *et al.* found that 37% of patients with subacute liver failure had a bacterial infection at admission, and 46% of the remaining patients had a bacterial infection within 4 weeks after discharge (8), which was roughly consistent with the incidence of infection in this study. Spontaneous peritonitis, pneumonia, urinary tract infection, and skin infection are more common in patients with liver failure (9). Mücke *et al.* confirmed that infection could significantly increase the 30- and 90-day mortality in patients with chronic and acute liver failure (10). In addition, ascites was also a risk factor for death in this study, which may be related to the fact that ascites can easily cause infection or that ascites themselves are a manifestation of bacterial peritonitis.

The MELD score is a scoring system for predicting death within 3 months in patients with liver cirrhosis. The scoring system is derived from European and American patients. Most of their liver cirrhosis is caused by alcohol or hepatitis C, which is different from Chinese patients. For example, Xun *et al.* found that the AUC of the MELD score in 77 patients with HBV-related subacute liver failure was only 0.72 (11). Follow-up studies have shown that improving this MELD scoring system based on the MELD score can better predict the prognosis of patients with liver failure (12-14). In this study, we found that although the MELD score was helpful in distinguishing the risk of death in patients with subacute liver failure, its efficacy and sensitivity were significantly

lower than the model constructed in this study, which again indicates that the model constructed in this study may be more suitable for domestic patients with subacute liver failure.

INR and total cholesterol are important indicators of liver synthetic function. Similar to previous studies (15,16), these 2 indicators in this study were independent risk factors of mortality in patients with subacute liver failure. Therefore, it is necessary to observe the dynamic changes of these 2 indexes in the clinic and implement timely and effective interventions.

In conclusion, this study found that age, hepatic encephalopathy, infection, ascites, MELD score, INR, and total cholesterol level were risk factors affecting the prognosis of patients with subacute liver failure. The death risk model constructed according to these 7 indicators is highly effective in evaluating the prognosis of such patients. The risk model constructed in this study needs to be verified and extended in a prospective, multicenter cohort.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-461/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-461/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-461/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of The First Affiliated Hospital of Xi'an Jiaotong University (No. XJTUIAF2020LSK-153) and informed consent was obtained from all the patients.

References

1. Liu Q, Liu Z, Wang T, et al. Characteristics of acute and sub-acute liver failure in China: nomination, classification and interval. J Gastroenterol Hepatol 2007;22:2101-6.
2. Mahmud N, Kaplan DE, Taddei TH, et al. Incidence and Mortality of Acute-on-Chronic Liver Failure Using Two Definitions in Patients with Compensated Cirrhosis. Hepatology 2019;69:2150-63.
3. Hernaez R, Kramer JR, Liu Y, et al. Prevalence and short-term mortality of acute-on-chronic liver failure: A national cohort study from the USA. J Hepatol 2019;70:639-47.
4. Schiødt FV, Chung RT, Schilsky ML, et al. Outcome of acute liver failure in the elderly. Liver Transpl 2009;15:1481-7.
5. Tapper EB, Zhao L, Nikirk S, et al. Incidence and Bedside Predictors of the First Episode of Overt Hepatic Encephalopathy in Patients With Cirrhosis. Am J Gastroenterol 2020;115:2017-25.
6. Cordoba J, Ventura-Cots M, Simón-Talero M, et al. Characteristics, risk factors, and mortality of cirrhotic patients hospitalized for hepatic encephalopathy with and without acute-on-chronic liver failure (ACLF). J Hepatol 2014;60:275-81.
7. Yu H, Chen Y, Jiang P. Prognostic value of hepatic encephalopathy for survival of patients with liver failure: A systematic review and meta-analysis. Ann Hepatol 2019;18:607-12.
8. Fernández J, Acevedo J, Wiest R, et al. Bacterial and fungal infections in acute-on-chronic liver failure: prevalence, characteristics and impact on prognosis. Gut 2018;67:1870-80.
9. Yang L, Wu T, Li J, et al. Bacterial Infections in Acute-on-Chronic Liver Failure. Semin Liver Dis 2018;38:121-33.
10. Mücke MM, Rumyantseva T, Mücke VT, et al. Bacterial infection-triggered acute-on-chronic liver failure is associated with increased mortality. Liver Int 2018;38:645-53.

11. Xun YH, Shi JP, Li CQ, et al. Prognostic performance of a series of model for end-stage liver disease and respective Δ scores in patients with hepatitis B acute-on-chronic liver failure. Mol Med Rep 2014;9:1559-68.
12. Xia Q, Dai X, Zhang Y, et al. A modified MELD model for Chinese pre-ACLF and ACLF patients and it reveals poor prognosis in pre-ACLF patients. PLoS One 2013;8:e64379.
13. He WP, Hu JH, Zhao J, et al. Comparison of four prognostic models and a new Logistic regression model to predict short-term prognosis of acute-on-chronic hepatitis B liver failure. Chin Med J (Engl) 2012;125:2272-8.
14. Chen W, You J, Chen J, et al. Modified model for end-stage liver disease improves short-term prognosis of hepatitis B virus-related acute-on-chronic liver failure. World J Gastroenterol 2017;23:7303-9.
15. Zhang ZQ, He G, Luo ZW, et al. Individual mortality risk predictive system of patients with acute-on-chronic liver failure based on a random survival forest model. Chin Med J (Engl) 2021;134:1701-8.
16. Rui F, Yang H, Guo Z, et al. Derivation and validation of prognostic models for predicting survival outcomes in Acute-on-chronic liver failure patients. J Viral Hepat 2021;28:1719-28.

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