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Observational Study

Analysis of short-term prognostic factors of hepatitis B virus-related acute-on-chronic liver failure

Ye *et al*. HBV-related ACLF

Qiaoxia Ye, Jinfa Huang, Zhengju Xu, Yan-Yan Yan, Yan Yan, Liguan Liu

Abstract

BACKGROUND

Acute-on-chronic liver failure (ACLF) refers to a syndrome caused by various triggers on the basis of chronic liver disease.

AIM

To explore the independent predictors of short-term prognosis in patients with hepatitis B virus (HBV)-related acute-on-chronic liver failure (ACLF) and to establish a predictive short-term prognosis model for HBV-related ACLF.

METHODS

From January 2016 to December 2019, 207 patients with HBV-related ACLF attending the 910th Hospital of Chinese People's Liberation Army were continuously included in this retrospective study. According to the survival status in 3 mo after diagnosis patients were divided into survival group and death group (157 patients in the survival group, 50 patients in the death group). The following outcome measures were collected and analyzed. General Information: Gender and age; Coagulation function: Prothrombin time (PT), international normalized ratio (INR); Blood routine: Neutrophil-to-lymphocyte ratio (NLR), platelet count (PLT); Blood biochemistry: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (Tbil), albumin (ALB), cholinesterase (CHE), blood urea nitrogen (BUN), creatinine (Cr), blood glucose (Glu), sodium (Na); Tumor markers: Alpha-fetoprotein (AFP), Golgi protein 73 (GP73); Virological indicators: HBV-DNA, HBsAg, HBeAg,AntiHBe, AntiHBc; Complications: Hepatic encephalopathy, hepatorenal syndrome, spontaneous peritonitis, gastrointestinal bleeding, pulmonary infection.

RESULTS

The results of univariate analysis showed that there were significant differences in age, PLT, TBIL, BUN, NLR, HBsAg, AFP, GP73, INR, stage of liver failure, classification of

liver failure, and incidence of complications (pulmonary infection, hepatic encephalopathy, spontaneous bacterial peritonitis, and upper gastrointestinal bleeding) between the two groups (P<0.05). GP73 (HR: 1.009, 95%Cl: 1.005-1.013, P=0.000), middle stage of liver failure middle (HR: 5.056, 95%Cl: 1.792-14.269, P=0.002), late stage of liver failure middle (HR: 22.335, 95%Cl: 8.544-58.388, P=0.000), pulmonary infection (HR: 2.056, 95%Cl: 1.145-3.690, P=0.016), hepatorenal syndrome (HR: 6.847, 95%Cl: 1.930-24.291, P=0.003), and HBsAg (HR: 0.690, 95%Cl: 0.524-0.908, P=0.008) were independent risk factors of short-term prognosis in patients with HBV-related ACLF. Calculation formula based on binary logistics regression: Calculation formula based on binary logistics regression: Logit(P) = Ln(P/1-P) = 0.013 × (GP73 ng/mL) + 1.907 × (Middle stage of liver failure) + 4.146 × (Late stage of liver failure) + 0.734 × (pulmonary infection) + 22.320 × (hepatorenal syndrome) - 0.529 × (HBsAg) - 5.224. The predictive efficacy of the GP73-ACLF score was significantly better than that of Model for End-Stage Liver Disease (MELD) and MELD-Na score in patients with HBV-related ACLF (P<0.05).

CONCLUSION

GP73, stage, pulmonary infection, hepatorenal syndrome, and HBsAg were independent risk factors of short-term prognosis in patients with HBV-related ACLF. The GP73-ACLF model had a good predictive value for the short-term prognosis of patients with HBV-related ACLF.

Key Words: Hepatitis B virus; Acute-on-chronic liver failure; Golgi protein 73; Short-term prognosis model

Ye Q, Huang J, Xu Z, Yan YY, Yan Y, Liu L. Analysis of short-term prognostic factors of hepatitis B virus-related acute-on-chronic liver failure. *World J Clin Cases* 2022; In press

Core Tip: GP73, stage, pulmonary infection, hepatorenal syndrome, and HBsAg were independent risk factors of short-term prognosis in patients with HBV-related ACLF. And the GP73-ACLF model had a good predictive value for the short-term prognosis of patients with HBV-related ACLF.

INTRODUCTION

Acute-on-chronic liver failure (ACLF) refers to a syndrome caused by various triggers on the basis of chronic liver disease, with deepening of acute jaundice and coagulopathy as manifestations of liver failure, which can be associated with complications including hepatic encephalopathy, ascites, electrolyte imbalance, infection, hepatorenal syndrome, hepatopulmonary function signs, and extrahepatic organ failure [1]. Although definitions of acute-on-chronic liver failure differ, most address the role of both hepatic and extrahepatic precipitating events and include extrahepatic organ failures [2]. The short-term mortality rate of ACLF can be 50 ~ 90% [3]. Due to the complex complications, rapid changes in the condition, and high mortality of ACLF, early and accurate assessment of the severity and prognosis of ACLF patients is critical, which helps to determine the timing of liver transplantation and can significantly improve the survival rate of ACLF patients.

Recent studies found that age, hepatic encephalopathy, total bilirubin, prothrombin or international normalized ratio, alpha-fetoprotein and other indicators have certain value in the prognostic evaluation of liver failure, which were included in the classical prognostic model of liver failure, such as Child-Turcotte-Pugh (CTP) score, Model for End-Stage Liver Disease (MELD) score, MELD-Na score, King's College Hospital (KCH) criteria [1, 4-7]. Since the classical prognostic model of liver failure faces all types of ACLF, the sensitivity and specificity of the classical prognostic model for ACLF due to a specific cause are lacking. In China, the main cause of cirrhosis in patients with ACLF is hepatitis B virus (HBV) infection.

Kladneyd *et al*[8] found high expression of Golgi 73 in hepatocytes of giant cell hepatitis. Iftikhar found that GP73 is a novel marker for the evaluation of advanced liver disease

and hepatocellular carcinoma (HCC)[9]. Some studies have found that Golgi protein 73 (GP73) levels gradually increase with increasing liver inflammation in patients with HBV [10]. In the meantime, serum GP73 had higher sensitivity and specificity than bilirubin in predicting the short-term prognosis of patients with HBV-related ACLF [11]. Moreover, for patients with HBV-related ACLF, the revised Guidelines for the Prevention and Treatment of Liver Failure in 2018 specified new clinical types and clinical stages [1]. Therefore, the study of mentioned indicators could be helpful to establish a prognostic model for HBV-related ACLF.

The objective of this study was to explore the independent predictors of short-term prognosis in patients with HBV-related ACLF and to establish a predictive short-term prognosis model for HBV-related ACLF.

MATERIALS AND METHODS

Patient population

From January 2016 to December 2019, 207 patients with HBV-related ACLF attending the 910th Hospital of Chinese People's Liberation Army were continuously included in this retrospective study. According to the survival status in 3-month follow-up after diagnosis patients were divided into survival group and death group (157 patients in the survival group, 50 patients in the death group). All patients underwent venous blood and color doppler ultrasound examination and received antiviral therapy within 24 h after admission. The antiviral treatment of choice is entecavir or tenofovir dipivoxil. This study protocol was formulated in accordance with the requirements of the Declaration of Helsinki of the World Medical Association. It was approved by the Ethics Committee of the 910th Hospital of Chinese People's Liberation Army (NO. 32). Written informed consent was obtained from each subject prior to participation.

Inclusion and exclusion criteria

Inclusion criteria: 1. Meet the clinical diagnostic criteria for ACLF [1]; 2. Patients signed informed consent.

Exclusion criteria: 1. Other hepatitis viruses (hepatitis A, C, D,E) infections; 2. Autoimmune liver disease; 3. Drug-induced liver injury; 4. Alcoholic liver disease; 5. Wilson's disease; 6. Malignancy including HBV-related HCC; 7. Obstructive jaundice; 8. History of liver transplantation; 9. Use of anticoagulants.

Diagnostic criteria for HBV-related ACLF

HBsAg positive over 6 mo; 2. Coagulopathy (an international normalized ratio (INR) of ≥ 1.5 or prothrombin activity < 40%); 3. Total bilirubin (Tbil) ≥ 10 upper limit of normal, or total bilirubin increase > 1mg/dL daily [1].

Classification criteria for HBV-related ACLF

Type A: ACLF on the basis of chronic non-cirrhotic liver disease;

Type B: ACLF on the basis of compensatory cirrhosis, usually within 4 wk;

Type C: ACF on the basis of decompensated cirrhosis. [1]

Staging criteria for HBV-related ACLF

Early stage: the prothrombin time activity (PTA) was between 30%-40% or 1.5 ≤ INR < 1.9; There were no complications and other extrahepatic organ failure.

Middle stage: the PTA was between 20%-30% or 1.9 ≤ INR < 2.6; There was 1 complication and/or 1 extrahepatic organ failure.

Late stage: the PTA was less than 20% or INR ≥ 2.6; There was 2 complications and/or 2 extrahepatic organ failure. [1]

Observation indicators

General Information: Gender and age.

Coagulation function: Prothrombin time (PT), INR.

Routine blood test and coagulation function were analyzed by Sysmex XN (Sysmex, Kobe, Japan) automatic analyzer with Sysmex kit reagent. The indicators included Neutrophil-to-lymphocyte ratio (NLR) and platelet count (PLT).

Blood biochemistry: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), Tbil, albumin (ALB), cholinesterase (CHE), blood urea nitrogen (BUN), creatinine (Cr), blood glucose (Glu), sodium (Na). The TBA120FR automatic biochemical analyzer

(Toshiba, Japan) was used for analysis. The kit was purchased from Beijing Kangda Taike Medical Technology Co., LTD.

Tumor markers: Alpha-fetoprotein (AFP) was analyzed by Cobas E601 biochemical immunoanalyzer (roche Diagnostics, Germany). The kit was purchased from Roche Diagnostics (Shanghai) Co., LTD. Golgi protein 73 (GP73) was detected by ELISA, which was provided by Beijing Reking Biotechnology Co., LTD.

Virological indicators: HBV DNA was determined by fluorescence quantitative PCR. Taq enzyme, deoxyuracil nucleoside triphosphate and uracil glycosylation enzyme were purchased from Shanghai Huamei Biological Engineering Company. Standard substance, negative and positive control substance and PCR buffer were purchased from Shanghai Fosun Industrial Company. Primer sequences were synthesized by Shanghai Shenyou Co., LTD. Fluorescence quantitative gene amplifiers were produced by Roche Light Cycler Co., LTD. HBV markers were measured by electrochemiluminescence assay using Cobas 6000 biochemical immunoassay [Roche Diagnostics (Shanghai) Co., LTD.] The kit was purchased from Roche Diagnostics (Shanghai) Co., LTD.

Complications: Hepatic encephalopathy, hepatorenal syndrome, spontaneous peritonitis, gastrointestinal bleeding, pulmonary infection.

Other prognostic prediction models

MELD score = 3.78 × ln [bilirubin (mg/dL)] + 11.24 × ln (INR) + 9.57 Ln [creatinine (mg/dL)] + 6.43 [4];

MELD-Na score = MELD + 1.59 × [135-Na (mmol/L)] [5].

Statistical analysis

All the data collected in this study were analyzed using SPSS 19.0 software and MedCalc statistical software. The normality of continuous variables was tested by K-S test. Normally distributed measurement data were expressed as mean±standard deviation (SD), while non-normally distributed measurement data were expressed as median (P25, P75), and the comparisons were examined by Student-t test and Mann-Whitney test (non-parametric distribution). The categorical data were expressed as n

(%), and the differences between the two groups were examined by chi-square analysis or Fisher's Exact Test. The risk factors affecting short-term prognosis of HBV-related ACLF were detected by Cox regression analysis. The establishment of diagnostic model for HBV-related ACLF was based on Logistics analysis. The predictive short-term prognosis model for HBV-related ACLF was evaluated by ROC analysis. Delongs method in MedCalc software was used for ROC curve analysis and comparison of various diagnostic criteria. The statistical significance level was set at 0.05 for a two-sided test.

RESULTS

Demographic and clinical characteristics

A total of 207 patients with HBV-related ACLF were included, including 157 patients in the survival group, with an average of 40 (32, 48) years old, 130 males and 27 females; 50 patients in the death group, with an average of 50 (38.75, 55) years old, 27 males and 23 females. Specific patient demographic and clinical characteristics were shown in **Table 1**.

Univariate analysis of factors affecting short-term prognostic in HBV-related ACLF

The results of univariate analysis showed that there were significant differences in age, PLT, TBIL, BUN, NLR, HBsAg, HBeAg, AFP, GP73, INR, stage of liver failure, classification of liver failure, and incidence of complications (pulmonary infection, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, and upper gastrointestinal bleeding) between the two groups (P<0.05). (**Table 1**)

Cox regression analysis of factors affecting short-term prognostic in HBV-related ACLF

The independent variables, including Age, PLT, TBIL, BUN, NLR, HBsAg,HBeAg, AFP, GP73, INR, stage, classification, and the incidence of complications of factors, were included in collinearity analysis. The tolerance of each variable was greater than 0.1, and variance inflation factor (VIF) was less than 10, showing no obvious multicollinearity relationship. Age, PLT, TBIL, BUN, NLR, HBsAg,HBeAg, AFP, GP73,

INR, stage, classification, and incidence of complications of factors were included in the Cox regression analysis. The results showed that GP73, stage, pulmonary infection, hepatorenal syndrome, and HBsAg were independent risk factors of short-term prognosis in patients with HBV-related ACLF (P<0.05) (**Table 2**).

Establishment of prognostic models (GP73-ACLF)

Calculation formula based on binary logistics regression: Logit(P) = Ln(P/1-P) = 0.013 × (GP73 ng/mL) + 1.907 × (Middle stage of liver failure) + 4.146 × (Late stage of liver failure) + 0.734 × (pulmonary infection) + 22.320 × (hepatorenal syndrome) - 0.529 × (HBsAg) - 5.224.

P represents the survival probability of patients after 3 mo. For the meanings of stage, pulmonary infection, and hepatorenal syndrome in the formula, 1 indicates that this condition exists and 0 to indicate the others.

Hosmer-lemeshow test found that this multi-factor model fit the real data well (*P* = 0.467).

ROC Curve analysis of the GP73-ACLF prognostic model

The GP73-ACLF prognostic model was compared with the prediction effects of the two models, MELD and MELD-Na, and ROC curves were plotted (**Figure 1**). The specific ROC curve analysis values are shown in Table 3. The predictive efficacy of the GP73-ACLF score was significantly better than that of MELD and MELD-Na score in patients with HBV-related ACLF (*P*<0.05) (**Table 4**).

DISCUSSION

At present, the treatment of HBV-related ACLF mainly includes medical comprehensive treatment, artificial liver support therapy and liver transplantation, of which liver transplantation is the only treatment that can effectively improve the condition of HBV-related ACLF [1]. In China, the scarcity of liver donors, complex surgical complications and continuous postoperative immunotherapy all limit the application of liver transplantation to varying degrees. Early and accurate judgment of

the severity and prognosis of HBV-related ACLF patients is essential for the development of a reasonable clinical treatment plan.

The development of HBV-related ACLF involves a variety of cytokines, and the study of these cytokines is helpful to understand the pathogenesis of HBV-related ACLF. This univariate analysis showed that age, PLT, TBIL, BUN, NLR, HBsAg, HBeAg,AFP, GP73, INR, stage of liver failure, classification of liver failure, and incidence of complications were associated with survival outcomes at 3-month follow-up. TBIL and INR have been recognized as prognostic indicators of viral hepatitis - associated liver failure [12]. As liver damage worsens, the liver's ability to clear endotoxins decreases. The accumulation of endotoxin in turn induces platelet aggregation, activation and damage, resulting in a decrease in platelet count. On the other hand, hypersplenism secondary to cirrhosis can also cause a decrease in platelet count. Therefore, platelet level can reflect liver function and degree of cirrhosis to a certain extent. The results of this study suggest that platelets may play a role in predicting the prognosis of chronic subacute liver failure.

Similar findings were found in studies on NLR, which was significantly higher in ACLF patients than that in patients with chronic hepatitis B at admission, and NLR was associated with the severity of the disease and 3-month mortality [13]. The increase in NLR in patients in the death group was mainly due to a decrease in the number of lymphocytes. NLR reflected the severity of inflammation, and in patients with malignancies, NLR was markedly increased in peripheral blood and significantly decreased after receiving treatment [14]. In patients with HBV-related ACLF, changes in NLR during treatment may be used as an indicator to determine the prognosis of patients.

This study showed that age and hepatic encephalopathy were independent predictors of short-term prognosis in patients with HBV-related ACLF, consistent with previous studies [15, 16]. GP73 is expressed in hilar bile duct epithelial cells, with little or no expression in normal liver cells, and increased in autoimmune hepatitis or hepatitis B or C virus infection [17]. Iftikhar found that GP73 was mainly derived from

hepatocytes and activated hepatic stellate cells, suggesting that serum GP73 could better reflect the pathological changes of liver [9]. An increasing number of current studies have confirmed that GP73, as a liver cancer marker, has increased cellular expression levels in acute or chronic liver disease, and that serum GP73 Levels gradually increased in patients with aggravated inflammation [18]. In current study, GP73 was also confirmed as an independent predictor of short-term prognosis in HBV-related ACLF. High GP73 expression by hepatocytes was associated with liver inflammation resulting from an HBV-induced immune response [19], however this association coexisted in viral and non-viral liver diseases [20]. In patients with chronic hepatitis B, serum GP73 Levels were not associated with HBeAg status or HBV-DNA levels [18]. Although the exact mechanism of GP73 on liver injury is not clear, studies have shown that GP73-deficient mice are more likely to develop severe liver cell injury, suggesting that GP73 Levels have a certain role in predicting the severity of liver injury[21].

Current prognostic evaluation models for liver failure include CTP score, MELD score, MELD-Na score, and KCH criteria. The evaluation of ascites and hepatic encephalopathy in CTP score was subjective, and the prognosis of patients in the same grade varied greatly, which limit its application in the prognosis prediction of patients with liver failure [22]. The MELD score was first used for the short-term prognostic assessment of patients undergoing transjugular portosystemic shunts and was modified to rely on objective experimental parameters to distinguish the severity of the patient's condition [23]. In recent years, MELD score has been widely used to predict the mortality of patients with end-stage liver disease, and many studies have used it to assess the prognosis evaluation of HBV-related ACLF [24]. However, MELD score did not take liver failure-related complications into account, such as hepatic encephalopathy and gastrointestinal bleeding. At present, the most widely used prognostic model of liver failure, KCH criteria, had the strongest predictive power, high specificity, and can also be used to evaluate patients undergoing liver transplantation, but the sensitivity was relatively poor [6]. In this study, the area under the ROC curve of the GP73-ACLF model

for prognostic prediction of HBV-related ACLF patients reached 0.916, with a sensitivity of 81%, a specificity of 60%, a positive predictive value of 39%, and a negative predictive value of 91%, which was higher than that of the MELD score and MELD-Na score. It was able to accurately determine whether patients with HBV-related ACLF require liver transplantation treatment in the short term, while it can be reassessed based on disease progression.

One of the limitations was that this single-center retrospective study with small sample size may weaken the generalisability of the results. Another limitation was that the specificity of GP73-ACLF model was poor, with a specificity of 60%, which may affect the predictive power. Notably, the specificity of the GP73-ACLF model was significantly improved by combining the KCH criteria.

CONCLUSION

GP73, stage, pulmonary infection, hepatorenal syndrome, and lgHBsAg were independent risk factors of short-term prognosis in patients with HBV-related ACLF. And the GP73-ACLF model had a good predictive value for the short-term prognosis of patients with HBV-related ACLF.

ARTICLE HIGHLIGHTS

Research background

Acute-on-chronic liver failure (ACLF) refers to a syndrome caused by various triggers on the basis of chronic liver disease, with deepening of acute jaundice and coagulopathy as manifestations of liver failure. The short-term mortality rate of ACLF can be 50 ~ 90%.

Research motivation

Early and accurate assessment of disease severity and short-term prognosis in patients with ACLF can help determine the timing of liver transplantation, which can significantly improve the survival rate of patients with ACLF.

Research objectives

To explore the independent predictors of short-term prognosis in patients with HBV-related ACLF and to establish a predictive short-term prognosis model for HBV-related ACLF.

Research methods

Patients were divided into survival group and death group according to their survival 3 mo after diagnosis (157 cases in survival group and 50 cases in death group), and the data of relevant observation indicators of patients were retrospectively collected and analyzed. After determining the influencing factors of short-term prognosis, a prognostic model was established based on binary logistics regression, and the prediction effectiveness of this model was tested by comparing with the classical prognostic model.

Research results

The univariate analysis showed that there were significant differences in age, PLT, TBIL, BUN, NLR, lgHBsAg, AFP, GP73, INR, stage of liver failure, classification of liver failure, and incidence of complications between the two groups. GP73, stage, pulmonary infection, hepatorenal syndrome, and lgHBsAg were independent risk factors of short-term prognosis in patients with HBV-related ACLF. The predictive efficacy of the GP73-ACLF score prognostic model was significantly better than that of Model for End-Stage Liver Disease (MELD) and MELD-Na score in patients with HBV-related ACLF.

Research conclusions

GP73, stage, pulmonary infection, hepatorenal syndrome, and lgHBsAg were independent risk factors of short-term prognosis in patients with HBV-related ACLF.

The GP73-ACLF model had a good predictive value for the short-term prognosis of patients with HBV-related ACLF.

Research perspectives

Combined with King's College Hospital (KCH) Criteria, the weak specificity of GP73-ACLF prognostic model can be greatly enhanced, which is worth verifying in subsequent studies.

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