High-density lipoprotein cholesterol is a predictor of survival in cirrhotic patients with acute gastrointestinal bleeding: a retrospective study

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Abstract

Background: Lipid profiles are declined in patients with viral liver cirrhosis and correlated with severity of liver disease. Hepatitis B virus (HBV) is the leading cause of liver cirrhosis in China. Our primary aim was to investigate whether serum lipids and lipoproteins associate with survival in patients with HBV-related cirrhosis and acute gastrointestinal bleeding, and develop a 6-week mortality risk score that incorporates it.

Methods: From January 2008 to December 2015, consecutive cirrhotic patients with acute gastrointestinal bleeding admitted to our hospital were evaluated and divided into the derivation (n=593) and validation (n=350) cohorts. A logistic regression model was established to confirm the association between lipoprotein cholesterol and mortality. Accuracy to predict mortality were assessed by area under the receiver operating characteristic curves (AUROCs) and compared using the Hanley and McNeil test.

Results: Among study subjects, the 6-week mortality rate was 10.6%. High-density lipoprotein cholesterol (HDL-C) level was found to correlate most strongly with prognostic scores. On ROC analysis, HDL-C showed excellent diagnostic accuracy for 6-week mortality. Logistic regression analysis provided a simple algorithm based on the combined use of 4 variables (serum sodium (Na), HDL-C, presence of hepatocellular carcinoma (HCC) and QT interval prolongation), allowing accurate early discrimination of 3 distinct prognostic subgroups with 1.7% (low risk), 10.6% (intermediate risk), and 55.6% (high risk) mortality. Its accuracy was similar to the D'Amico score and significantly better than that of Child–Pugh, the model of end-stage liver disease (MELD), albumin-bilirubin (ALBI), and Augustin score. Baseline HDL-C values ≤ 0.57mmol/L were associated with markedly lower 6-week survival. Comparable results were found in the validation set.

Conclusion: HDL-C is a potential indicator for the prognosis of patients with cirrhosis and acute gastrointestinal bleeding. The new algorithm based on HDL-C allowed an accurate predictive assessment of 6-week mortality after bleeding attack.

Introduction

Liver cirrhosis is an important cause of morbidity and mortality as a consequence of continuous liver injuries\(^1\). Acute gastrointestinal bleeding is a serious complication and critical clinical event in cirrhotic patients\(^2\). Despite the significant improvements in general therapeutic management of critically ill patients and in specific haemostatic therapy, the mortality rate remains high, ranging from 6% to 20% in different studies\(^3\). The factors associated with the striking difference in life expectancy may include the severity of complications and the degree of liver failure\(^4,5\). Conventional prognostic scores such as Child-Pugh\(^6\), the model of end-stage liver disease (MELD)\(^7\), and albumin-bilirubin score (ALBI)\(^8\) have been useful for assessing the prognosis of general patients with liver cirrhosis, but their predictive performances remain suboptimal for the estimation of outcomes after an episode of acute gastrointestinal bleeding in patients with cirrhosis. D'Amico score\(^9\) and Augustin score\(^10\) were designed
especially for acute variceal bleeding and complicated to calculate. Therefore, identification of objective indicator obtained from routine examinations that can provide a predictive value is warranted.

Since the liver plays a crucial role in cholesterol homeostasis, hypocholesterolemia often occurs in patients with chronic liver diseases. The decrease in serum levels of lipids and lipoproteins is highly prevalent in cirrhotic patients, with a prevalence that increases in parallel with the disease severity. Previous studies have shown that high-density lipoprotein cholesterol (HDL-C) was an independent predictor of mortality in cirrhotic patients and associated with the severity of sepsis. However, studies regarding the effects of liver disease on lipid profiles have reached conflicting conclusions. The reason for the discrepancy could be the different etiology. Chronic hepatitis B is the leading cause of liver cirrhosis in China. To eliminate the influence of the etiology, the present study was focus on hepatitis B virus (HBV)-related cirrhotic patients. We aimed to investigate the prognostic value of lipid profiles in cirrhosis and acute gastrointestinal bleeding, and develop a simple and practical risk model to better predict 6-week mortality incorporates it.

**Patients And Methods**

1. **Patients**

From January 2008 to December 2015, this retrospective study included 943 patients with HBV-related cirrhosis and acute gastrointestinal bleeding who were admitted to Peking University First Hospital. Liver cirrhosis was confirmed either by liver biopsy or by clinical presentations, routine liver function tests and medical imaging techniques. Acute upper gastrointestinal bleeding was considered in patients presenting with hematemesis, melena, and/or nasogastric aspirate of fresh or dark blood drained by a nasogastric tube. The exclusion criteria were as follows: (1) other causes of chronic liver disease; (2) the use of lipid-regulating drugs within half a year; (3) terminal illness involving the major organs, such as severe heart failure, chronic obstructive pulmonary disease, and malignancy other than hepatocellular carcinoma (HCC); (4) lack of complete medical records; (5) previous liver transplantation; (6) pregnancy. The study was performed in line with the 1975 Declaration of Helsinki and was approved by the Ethics Committee of Peking University First Hospital, Beijing, China.

Patients received standard management at our institution that included continuous proton pump inhibitor infusion, vasoactive drugs for 5 days, and prophylactic parenteral antibiotics upon admission. The use of packed red blood cell transfusion was determined by the admitting physician. Unless contraindications to endoscopy existed, all patients with upper gastrointestinal bleeding underwent endoscopic therapy performed by an experienced endoscopist as soon as safely possible. Sclerotherapy or ligation choice was left to the endoscopist's discretion according to recommended standards. Transjugular intrahepatic portosystemic shunt (TIPS) was used for variceal bleeding that could not be controlled by endoscopy. Treatment of nonvariceal bleeding was left to the discretion of the endoscopist.

2. **Clinical data collection and Prognostic Scores**
The parameters collected at admission included demographic data, medical comorbidities, medication use, vital signs, laboratory tests and electrocardiogram (ECG). Endoscopy findings and outcomes were recorded. Routine biochemical tests were performed in our hospital laboratory.

QT length was assessed by an observer blinded to patients. The QT interval was corrected for heart rate according to the ‘cirrhosis-specific’ formula\(^{15}\) (QTc = QT/RR\(^{1/3.02}\)) in cirrhotic patients. The prolongation of the QTc interval was defined as a length >450 ms in men and >470 ms in women.

Prognostic scores including the Child-Pugh\(^{6}\), MELD\(^{7}\), ALBI\(^{8}\), D'Amico score\(^{9}\), and Augustin score\(^{10}\) were calculated and graded at admission using the formulas from the original article (Table 1).

3. Statistical Analysis

Data were analyzed using SPSS (version 20.0, IBM, USA) and MedCalc software (version 18.2.1, Ostend, Belgium). Statistically significant differences were indicated by a two-sided P-value < 0.05 for all analyses. Continuous variables are expressed as the mean ± standard deviation (SD). Categorical variables are expressed as frequencies (percentages). Differences between derivation and validation cohorts were compared by the independent samples t-test for continuous variables and the \(\chi^2\) test for categorical variables. The correlation was evaluated by Pearson test. The predicting performance for mortality was assessed by area under the receiver operating characteristic curve (AUROC) and compared using the Hanley and McNeil test\(^{16}\). Cut-off values were obtained with the maximal Youden index (sensitivity + specificity-1)\(^{17}\). Univariate logistic regression was performed to assess the association between potential risk factors and mortality. Variables with P values<0.05 in univariate analysis were used for multiple logistic regression analysis. The Hosmer–Lemeshow goodness-of-fit statistic\(^{18}\) was used to test the reliability of the model. Variables that maintained P<0.05 in multiple logistic regression analysis of the derivation cohort were weighted according to the odds ratio (OR) and 95% confidence intervals (CI) to develop a scoring system for predicting mortality. Survival and death risk analyses were performed using the Kaplan–Meier method and differences between groups were assessed by the log-rank test. In the present study, the threshold to define high risk was set at a mortality rate of 20%\(^{10}\), and low risk was set at 10%\(^{19}\).

Results

1. Patient characteristics

A total of 943 HBV-related cirrhosis and acute gastrointestinal bleeding were included in the final analysis, of which 593 and 350 patients were randomly enrolled into the derivation and validation cohorts, respectively. Table 1 compares demographic, clinical, and laboratory characteristics between the two cohorts of patients. The two cohorts were not entirely matched: in the derivation cohort, the prevalence of hepatocellular carcinoma (HCC), the percentage of males and QTc interval prolongation were significantly lower than those among the patients in the validation cohort (Table 3).
2. Lipid profiles correlate with liver disease severity

Lipid profiles include triglyceride, cholesterol, HDL-C and low-density lipoprotein cholesterol (LDL-C). In the derivation and validation cohorts, the association of individual lipid fractions with prognostic models (Child-Pugh, MELD, and ALBI) was assessed by Pearson correlation, as shown in Table 3. HDL-C was found to have strongest correlation with liver function score.

3. Derivation cohort: predictors of 6-week mortality

On ROC analysis, HDL-C showed excellent diagnostic accuracy for 6-week mortality, with an AUROC of 0.841 (95% CI 0.809-0.870). The best cut-off value of HDL-C was 0.57mmol/L, with a sensitivity of 71.7% and specificity of 84.4%.

We performed univariate and multivariate analyses to assess the independent predictors of 6-week mortality. Variables included in the univariate analysis are shown in Table 4. The variables significantly associated with 6-week mortality in the univariate analysis were as follows: ascites, hepatic encephalopathy, HCC, heart rate, hemoglobin (HGB), total leukocyte count (WBC), alanine aminotransferase (ALT), serum sodium (Na), total bilirubin (TBIL), albumin (ALB), QTc interval prolongation, cholesterol, HDL-C, LDL-C, prothrombin time (PT), international normalized ratio (INR), fibrinogen (FIB), Child-Pugh, MELD, and ALBI (Table 4). Multivariate logistic regression analyses showed that HDL-C, Na, HCC, and QTc interval prolongation were independently associated with 6-week death. Based on the multivariate regression coefficients, we calculated a new prognostic model for HBV-related cirrhotic patients with acute GIB named N-CGIB according to the following formula: 12.654 - 0.095 × Na + 1.041 × QTc prolongation (yes=1, no=0) − 3.846 × HDL (mmol/L) + 0.856×HCC (yes=1, no=0). The N-CGIB model showed an excellent discrimination for 6-week death prediction, with an AUROC of 0.880 (95% CI 0.832-0.928). Hosmer and Lemeshow analysis confirmed goodness-of-fit for the model (P=0.904).

The developed model showed an excellent predictive accuracy, with AUROCs significantly better than that of Child-Pugh, MELD, ALBI, and Augustin scores (Table 5, Fig. 1A). Comparison with D’Amico score shows that N-CGIB is a more accurate predictor than the D’Amico score for outcome, although the differences failed to reach statistical significance for mortality. (Table 5, Fig. 1A)

4. Mortality in external validation cohort

HDL-C was an excellent predictor of 6-week mortality (AUROC 0.838, 95% CI 0.763-0.912) in the validation cohort.

Hosmer and Lemeshow analysis confirmed the goodness-of-fit of the N-CGIB model (P=0.531). The diagnostic accuracy of the N-CGIB model (AUROC 0.882; 95% CI 0.822-0.942) was similar to D’Amico model (AUROC 0.832; 95% CI 0.789-0.870), significantly better than that of the other models, including Child–Pugh (AUROC 0.794; 95% CI 0.748-0.835), ALBI (AUROC 0.803; 95% CI 0.758-0.844), MELD (AUROC
Survival

In the derivation cohort, 60 of the 593 (10.1%) patients died during study observation, with early death rate (12 of 60, 20%) occurring within the first five days. In the test set, 40 of the 350 (11.4%) patients died during study observation, with early death rate (11 of 40, 27.5%) occurring within the first five days.

Mortality increased with increasing N-CGIB score. The final selected cutoff value accurately discriminated patients in 3 subgroups with distinct prognosis: a low-risk group (N-CGIB score below -3), whose in-hospital mortality was 1.7%; an intermediate-risk group (N-CGIB score range from -3 to -1), with a 10.6% mortality; and a high-risk group (N-CGIB score more than -1) associated with a 55.6% or greater predicted risk. Comparable results were found in the validation set with a significant decrease in 6-week probability of survival: 98%, 89.8%, and 41.9%, respectively. (Fig. 2A.2B)

On Kaplan-Meier analysis, baseline HDL-C values ≤ 0.57mmol/L were associated with markedly lower 6-week survival in the derivation cohorts (Fig. 3A), and validation cohorts (Fig. 3B).

Discussion

Previous studies showed that chronic liver diseases strongly impair the lipid metabolism with the hypercholesterolemia and hyperlipidemia as a common finding in viral hepatitis. Additionally, in patients with viral liver cirrhosis, total serum cholesterol, LDL, and HDL-cholesterol were lower than that in patients with chronic active hepatitis. In this retrospective study, we showed that HDL-C level, cholesterol and LDL-C level, as measured by routine automated laboratory methods, are correlated with validated prognostic indexs (Child–Pugh, ALBI, MELD scores). Among them, HDL-C was the most remarkable indicator. On ROC analysis, HDL-C shows excellent diagnostic accuracies for 6-week mortality in patients with HBV-related cirrhosis and acute gastrointestinal hemorrhage, with AUROCs similar to the conventional liver function scores and models for acute variceal bleeding. Using a large patient cohort, we confirmed that HDL-C level was evidently lower in HBV-related cirrhotic patients who died than in survivors. In multivariate analysis, HDL-C is confirmed as an independent indicator of prognosis. Then we finally formulated a risk scoring system named N-CGIB to predict 6-week mortality for HBV-related cirrhotic patients admitted with acute UGIB. For predicting death, the N-CGIB model performed significantly better than the conventional scoring models. HDL levels less than 0.57 mmol/L were associated with an 11-fold increase in the hazard ratio for 6-week death.

Acute gastrointestinal bleeding is common in cirrhosis and account for significant mortality. The most consistently reported risk indicators of death are the degree of liver failure and the severity of complications. HDL-C was confirmed as a risk factor of 6-week mortality in the present study. A complex number of factors may contribute to this phenomenon, first, serum HDL-C is considered as a marker of liver function, which further decreased due to hepatocyte ischemia provoked by anemia,
tachycardia and arterial hypotension; second, HDL-C has been discovered as a modulator of both intrinsic and extrinsic coagulation cascades in vitro experiments.\textsuperscript{22}

Our second aim was to devise and validate a prognostic system predicting 6-week mortality risk of bleeding patients. Therefore, our analyses excluded prognostic variables that cannot be available at the initial patient evaluation, such as the source of bleeding, transfusion needs, portal vein thrombosis, and bleeding-induced bacterial infections. Our choice was to develop a simple and practical model based on HDL-C, integrated by 3 other predictors (QT interval prolongation, presence of HCC, and serum Na) by logistic regression analysis. The presence of HCC has been reported to be an independent predictor of death and rebleeding in patients with cirrhosis and gastrointestinal bleeding.\textsuperscript{9, 23} QTc interval prolongation has been reported to be a prognostic criterion for cirrhosis and is worsened by acute gastrointestinal bleeding in patients with cirrhosis.\textsuperscript{24} For predicting 6-week mortality, the developed model performed significantly better than the previously described models. The Hosmer–Lemeshow test indicated a good prediction performance.

We categorized N-CGIB based on -3 and −1 thresholds and yielded 3 groups. These cut-off values divided patients into groups with low, medium, and high risk of mortality. Importantly, this stratification confirmed its strength in the validation set. N-CGIB can easily distinguish patients at low risk from those at high risk and allow clinicians to begin assessment of a patient’s mortality risk upon admission to the hospital and allow for appropriate management.

The limitations of this study should be acknowledged. First, this study was a single-center retrospective study. Inevitably, bias could arise from missing data and selection criteria. Thus, the results should be validated in prospective multicenter studies using larger sample sizes. Second, a proportion of patients did not receive the current standard of care. This is mainly due to the long inclusion period and the fact that not all patients were managed in wards experienced in hepatology. Third, the result was confirmed in patients with HBV infection, which needs further validation for other etiology.

**Conclusion**

The present study confirmed HDL-C as an independent predictor of 6-week mortality in HBV-associated cirrhosis patients with acute upper gastrointestinal bleeding. The developed model predicts 6-week mortality with higher accuracy than the existing prognostic models. Moreover, it succeeded in stratifying patients into different risk groups, providing a basic assessment method to identify patients at high risk of death, making it possible to select those who should be managed in a more intensive way. Thus, further studies are warranted to validate its effectiveness as a predictor of bleeding in cirrhotic patients.

**Declarations**

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**Conflict of interest statement:**

There are no conflicts of interest to report.

**Author contributions:**

Ran Cheng: concept and design, data acquisition, data analysis, writing of manuscript; Ning Tan, Qian Kang, Hao Luo, Hongyu Chen, Jiali Pan Yifan Han and Yuqing Yang: data acquisition; Xiaoyuan Xu edited, reviewed and approved the final article.

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**Figures**

**Figure 1**

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**Figure 2**

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Figure 3

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