Predictive Value of Blood Ammonia in the Prognosis of Acute Liver Failure Evaluated by Receiver Operating Characteristic Curves

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Abstract

Background: *To investigate the predictive value of blood ammonia (BLA) quantification in the prognosis of acute liver failure (ALF).*

Methods: *Seventy-one patients with ALF were enrolled and BLA concentration was measured in all patients. After following up for 28 days, patients were divided into two groups: the surviving group (n = 21) and the deceased group (n = 50). An independent-samples t-test was used to compare BLA concentrations between the two groups, and receiver operating characteristic curves were used to evaluate the predictive value of BLA in the prognosis of ALF. A fourfold table analysis was performed with the determined BLA cutoff value.*

Results: *The average concentration of BLA in the deceased group was significantly higher compared with the surviving group (144.50 μmol/L vs. 106 μmol/L, respectively; P = .035). The cutoff BLA concentration for a good ALF prognosis was 122.5 μmol/L. The area under the curve was 0.659. Both the sensitivity and specificity were >0.6. The 95% CIs for sensitivity and specificity were 0.452-0.733 and 0.477-0.878, respectively. The fourfold table analysis revealed a positive predictive value of 83.3%, a negative predictive value of 42.9%, a misdiagnosis rate of 28.6%, and an accuracy of 63.4%.*

Conclusion: *With a cutoff BLA concentration of 122.5 μmol/L, the prognosis of ALF could be predicted with high sensitivity and specificity, a positive predictive value, a low misdiagnosis rate, and good accuracy.*

Keywords: *Blood ammonia, acute liver failure, prognosis*

INTRODUCTION

Acute liver failure (ALF) is the acute clinical manifestation of severe liver disease that progresses rapidly and becomes intractable.[1-4] This makes it difficult to predict prognosis for patients with ALF; thus, it is a challenge to conduct related research. Independent of tracking the changes in metabolic liver function in patients with ALF, blood ammonia (BLA) can be used to track the development and progress of hepatic encephalopathy and predict prognosis for patients with ALF.[5] To date, BLA has primarily been applied in cases of hepatic encephalopathy.[6] Although BLA correlates with prognosis after severe hepatitis in some studies, specific details have not been provided.[1] Therefore, the present study aimed to determine the cutoff BLA concentration to predict prognosis for patients with acute ALF using receiver operating characteristic (ROC) curves.

MATERIALS AND METHODS

Clinical Data

From January 2009, 71 patients with confirmed ALF diagnosed according to the diagnostic criteria for ALF were enrolled. Among these patients, 34 patients had drug-induced hepatitis, 18 patients had hepatitis B infection, 6 patients had hepatitis E infection, 5 patients had cytomegalovirus infection, 3 patients had bacterial infection after surgery, and 5 patients had unknown causes. Of the 71 patients, 34 were male and 37 were female with an age range of 3-80 years and an average age of 49.5 years. We followed up with the patients for 28 days (4 weeks) because all patients would either have obvious clinical outcomes, significantly improved risk, or clinical death during this time. The clinicians were familiar with BLA because it is a routine observation item in patients with ALF, but does not affect the management of

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patients. Patients were divided into two groups according to their prognosis: the surviving group (n = 21) and the deceased group (n = 50).

The efficacy criteria were as follows: survival: symptoms were significantly relieved, prothrombin activity was >40%, the decline in serum total bilirubin was >50%, and serum albumin was >30 g/L; death: patients died after disease deterioration. The prevalence of death was determined from the 34 patients who died 12.6 days after the highest concentration of BLA was observed.

The exclusion criteria were tumor (all types of malignant tumor, including liver cancer) and septic shock.

In all patients, the BLA concentration was measured every 2-3 days, and the highest values were taken as the observed values. The reference range of venous BLA was 0-30 μmol/L with a within-batch precision of 5% and a between-batch precision of 7.5%.

Methods

Treatment

Based on the principles described in the 2006 edition of the Guideline for Diagnosis and Treatment of Liver Failure, patients enrolled in the study received comprehensive medical treatment, including general supportive therapy, specific treatment against causes and pathogenesis, prevention and treatment of complications, and treatment with artificial liver.[7]

Instruments and Reagents

BLA concentrations were measured in the clinical laboratory at our hospital using a Vitros® 350 System (Johnson & Johnson, USA) using the multilayer film dry chemical technique. The heparinized vacuum tubes used in this study were purchased from BD (USA).

Specimen Processing Methods

A total volume of 3 mL of morning fasting blood was collected from each patient. Blood was sent to the clinical laboratory using the pneumatic tube system and immediately centrifuged after collection. The whole procedure was performed within 30 min.[8,9]

Statistical Analysis

Measurement data are presented as median, and the independent-samples t-test was used to compare BLA concentrations between the two groups. A bilateral P value of <.05 was considered statistically significant. SPSS 16.0 software was applied to establish ROC curves, calculate the area under the curve (AUC), and conduct the fourfold table analysis with the optimal cutoff value.

RESULTS

Comparison of BLA Concentrations Between the Surviving Group and the Deceased Group

The results are shown in Table 1. The BLA concentration in the surviving group was significantly lower compared with the deceased group. Furthermore, the BLA concentrations of the four patients in the surviving group were within the normal range, while BLA concentrations were elevated in the remaining patients (94.4%).

Methodological Evaluation of BLA Quantification to Predict ALF Prognosis

An ROC curve was drawn using BLA as the test variable and the different groups as the state variables. The value of the state variable was 1. The ROC curve revealed that the AUC (0.659) was greatest when the cutoff BLA value was 122.50 μmol/L, suggesting that patients with ALF with a BLA concentration of >122.50 μmol/L have a poor prognosis and a higher probability of death (Table 2 and Figure 1).

The AUC (0.659) was greatest when the cutoff value was 122.50 μmol/L, and the standard error of the AUC was 0.070. It had a sensitivity of 60.00% and a specificity of 71.40%. The 95% CIs for sensitivity and specificity were 0.452-0.733 and 0.477-0.878, respectively. A P value equal to .035 was considered statistically significant.

Table 1. Comparison of Blood Albumin Concentrations Between the Surviving Group and the Deceased Group

	BLA (Minimum to Maximum, Median)	Z	*P*
Surviving group (n = 21)	40-355 106	–2.104	.035
Dead group (n = 50)	29-355 144.5		

BLA: blood ammonia.

Table 2. Methodological Evaluation of Blood Albumin Concentration (μmol/L) to Predict Prognosis in Patients With Acute Liver Failure

Cutoff Value	Sensitivity (95% CI)	Specificity (95% CI)	Standard Error of AUC	AUC
122.5	0.60 (0.452-0.733)	0.714 (0.477-0.878)	0.070	0.659

AUC: area under the curve.

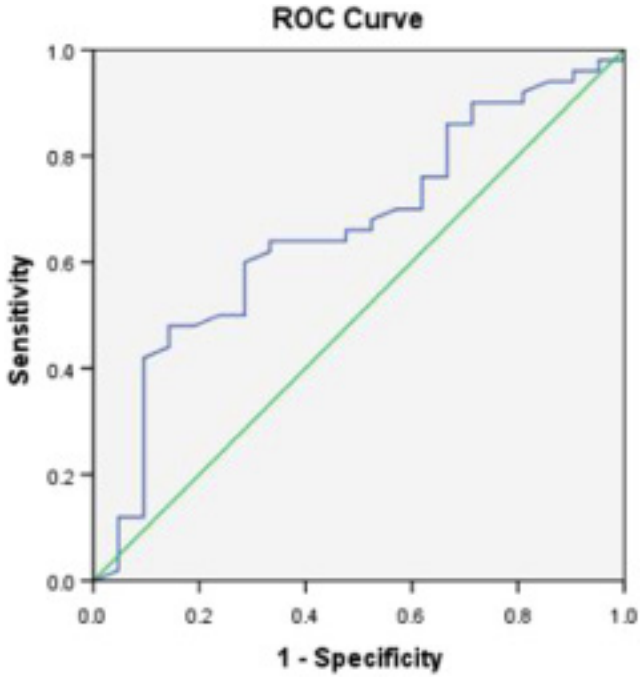

Figure 1. Receiver operating characteristic curve for blood albumin detection to predict prognosis in patients with acute liver failure.

Fourfold Table Analysis of the Cutoff BLA Concentration

According to the ROC curve, the optimal cutoff BLA concentration was 122.50 μmol/L. Therefore, BLA concentrations >122.50 μmol/L were considered positive, while BLA concentrations <122.50 μmol/L were considered negative. After grouping based on clinical prognosis, the disease group in the diagnostic test was equivalent to the deceased group, and the disease-free group was equivalent to the surviving group. The sensitivity, specificity, rate of misdiagnosis, rate of missed diagnosis, positive predictive value, negative predictive value, and accuracy were calculated to predict the prognosis for patients with ALF with 122.50 μmol/L as the cutoff BLA concentration (Tables 3 and 4).

DISCUSSION

There are great challenges in the diagnosis and treatment of ALF.[10] In the present study, in spite of active treatment, the mortality of patients with ALF was 70.40%, 28 days after admission to the intensive care unit. This result was unpredictable. These patients died due to ALF or due to complications of ALF. Patients who died due to other accidents (e.g., cardiac arrest, liver cancer rupture, and bleeding) were not included in the study. BLA concentrations increased to 94.40% in all patients. In the majority of patients with ALF, disease progressed rapidly even after active treatment. Clinical manifestations included hepatic coma, bleeding, jaundice, severe edema, hydrothorax, and ascites.[11] Hence, it is of great significance to ascertain quantitative indicators in the blood of patients with ALF that could be used to conveniently predict the prognosis of ALF quickly, economically, and relatively accurately.

Table 3. Fourfold Table Diagnostic Test for Blood Albumin Concentration to Predict Prognosis for Patients With Acute Liver Failure

	Clinical Prognosis		
BLA	Dead Group	Surviving Group	Total
Positive	30	6	36
Negative	20	15	35
Total	50	21	71

The results also revealed that the death rate of the observation group was 70.4% in this study.
BLA: blood ammonia.

In this study, 122.5 μmol/L was used as the cutoff BLA concentration for a good prognosis in ALF. In accordance with our results, Niranjan-Azadi et al. reported that a higher mortality rate in patients with ALF could be observed when the concentration of BLA is >120 μmol/L (P = .026; odds ratio = 7.188; 95% CI 1.3326-38.952).[12] Bhatia et al. also reported that a BLA concentration of >124 μmol/L could be used as a predictor of mortality of ALB.[13]

BLA is produced by the decomposition and metabolism of amino acids in various tissues of the body and is absorbed by the intestinal tract.[14] Hepatic encephalopathy is the most severe and common complication in patients with ALF.[15] It is considered that this complication of ALF is caused by ammonia metabolism.[16] However, there is

Table 4. Diagnostic Test Parameters for Blood Albumin Concentration to Predict Prognosis for Patients with Acute Liver Failure

BLA Level	Sensitivity	Specificity	Rate of Misdiagnosis	Rate of Missed Diagnosis	Positive Predictive Value	Negative Predictive Value	Accuracy Rate
>122.5	60%	71.4%	28.6%	40%	83.3%	42.9%	63.4%

BLA, blood ammonia.

no evidence that BLA can directly or indirectly damage the liver. In the past, quantitative detection of BLA has received some attention in the evaluation of the development of hepatic encephalopathy, as well as in the prediction of disease prognosis. However, most studies focused on predicting the prognosis of patients with chronic severe hepatitis.[2] Recently, the definition of ALF was corrected, and the course from jaundice to hepatic encephalopathy was limited to 12 weeks (<1 week: hyperacute; 1-4 weeks: acute; 4-12 weeks: subacute).[15] Furthermore, studies that consider the prognosis of ALF are rare; thus, this area requires further exploration.

In most previous studies on BLA in ALF carried out in China, patients with ALF, sub-AL, and acute-on-chronic liver failure were combined as the study objects, without conducting a more rigorous and in-depth analysis. Wang et al. 2013[17] highlighted the importance of detection and analysis of BLA concentrations in patients with severe hepatitis. Yun et al. 2012[18] reported that the proportion of patients with elevated BLA concentrations and the mean BLA concentrations were 63.16% and 51.16 μmol/L in chronic viral hepatitis, 73.33% and 84.80 μmol/L in decompensated liver cirrhosis, 80.00% and 94.60 μmol/L in severe hepatitis, 83.33% and 97.66 μmol/L in hepatic encephalopathy, and 52.78% and 56.80 μmol/L in upper gastrointestinal bleeding, respectively.

The accuracy of BLA detection is influenced by many factors, including sample storage time and detection method.[9,15] Rahman et al. 2015[19] conducted research on hepatic encephalopathy and other complications of severe hepatitis, as well as some blood test indicators for prognosis prediction. In other studies, statistical analyses were conducted on the prognosis of ALF caused by hepatitis B.[20]

In domestic research, BLA was proposed as a risk factor for prognosis, but no cutoff value was provided.[2,15,17] Furthermore, there are certain limitations in the use of average values in statistical analyses, and the use of medians is a better choice.

The correlation between high BLA concentrations and poor prognosis has been reported in many studies.[19] However, since none of these provided a cutoff BLA concentration, this relied on the experience of doctors in predicting the prognosis of patients with ALF in the clinic. Most domestic and international studies on BLA in the context of ALF were conducted in specific populations.[20-22] For example, in one study on patients with ALF who underwent liver transplantation, more than a dozen patients with acute and sub-acute liver failure[23] suffered from chronic severe hepatitis,[24] which was statistically unscientific. Since there were 71 cases of ALF in the present study, our findings are convincing due to the large sample size.

As a comprehensive and scientific statistical method for evaluating test items, ROC curves are not affected by disease prevalence and can therefore be used to determine the diagnostic cutoff value based on the balance of sensitivity and specificity.[25] In the present study, BLA quantification as a diagnostic test revealed the surviving group as the positive group and the deceased group as the negative group, and a cutoff value was identified. Hence, it was innovative to use ROC curves to analyze the relationship between BLA concentrations and ALF prognosis. When 122.50 μmol/L was used as the cutoff BLA concentration to predict prognosis for patients with ALF, the AUC was 0.659, and both the sensitivity and specificity were >0.6 and were statistically significant. The four-fold table analysis revealed a positive predictive value of 83.3%, a negative predictive value of 42.9%, a misdiagnosis rate of 28.6%, a missed diagnosis rate of 40%, and an accuracy of 63.4%. It could be inferred that in patients with ALF with BLA concentrations >122.50 μmol/L, prognosis is relatively poor. Determination of the cutoff BLA concentration to predict prognosis for patients with ALF would undoubtedly be beneficial for treatment and doctor-patient communication. Therefore, whether in community hospitals or hospitals at higher levels, doctors should exercise caution on poor prognosis when BLA concentrations are greater than the cutoff value in the clinic. Since diagnostic tests were used as statistical methods, the results of the present study could be used as a reference for the group method in subsequent studies examining the prognosis of ALF.

In summary, a BLA cutoff concentration of 122.50 μmol/L can predict prognosis for patients with ALF with high sensitivity and specificity, a positive predictive value, a good accuracy rate, and a low false-positive rate.

Ethics Committee Approval: This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Fifth Medical Center of Chinese PLA Hospital. Written informed consent was obtained from the participants or their guardians.

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

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