A model to predict early hepatic encephalopathy in patients undergoing transjugular intrahepatic portosystemic shunt

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ABSTRACT

Background/Aims: *Early hepatic encephalopathy (HE) is one of the most common complications developed after undergoing transjugular intrahepatic portosystemic shunt (TIPS). Hence, its early prevention and treatment are important. This study aimed at establishing a model to predict early post-TIPS HE.*

Materials and Methods: *Clinical data of 262 patients who underwent TIPS procedure was analyzed retrospectively. Patients were divided into early post-TIPS HE and non-early post-TIPS HE groups, based on the presence of HE within 3 months after TIPS. About 70% of the patients were randomly selected as the model group to establish a prediction model, and the remaining 30% were used as the validation group to test the model. The independent risk factors for early HE post-TIPS were identified and selected using single factor analysis and multi-factor logistic regression analysis. Subsequently the prediction model was established and validated.*

Results: *Age, Child-Pugh classification, and fibrinogen were found to be the independent risk factors for early post-TIPS HE., The logistic regression model was established based on these factors and their regression coefficients: p=1/{1+exp[4.829–1.975*age–1.110*(Child-Pugh classification)+1.724*loge (fibrinogen in g/L)]}. Finally, the model was validated among a set of 79 patients from the validation group.*

Conclusion: *The logistic regression model based on age, Child-Pugh classification, and fibrinogen for early post-TIPS HE can effectively predict the risk of early HE after TIPS.*

Keywords: *Early hepatic encephalopathy, transjugular intrahepatic portosystemic shunt, prediction model*

INTRODUCTION

The first successful transjugular intrahepatic portosystemic shunt (TIPS) in humans was performed in Germany in 1989 by Richter. This procedure has significant advantages compared to the previous techniques such as less trauma, reduced the pressure of the portal vein effectively, and reliable short-term efficacy. TIPS is mainly used in the clinical treatment of portal hypertension-induced esophageal and gastric variceal bleeding and refractory ascites. However, this established procedure has two major complications which have limited its broad applications, namely, post-TIPS shunt occlusion and hepatic encephalopathy (HE). With the advent of covered stents in the last years, the long-term shunt patency rate has greatly improved, but post-TIPS HE remains unsuccessfully addressed. The median cumulative incidence of post-TIPS HE at 1 year was reported to range from 10% to 50% (1), and in most cases, HE occurs within 3 months after TIPS (2,3). Therefore, it is of great clinical significance to identify the risk factors of early post-TIPS HE for targeted prevention and treatment. In this study, we conducted a retrospective analysis of clinical data from TIPS patients at a single center, with the purpose of establishing a model for predicting early post-TIPS HE. Such a model can help clinicians predict the incidence of post-TIPS HE, thereby reducing the occurrence of HE and improving the clinical application of TIPS.

MATERIALS AND METHODS

Case selection

Data were collected from inpatients who underwent TIPS for cirrhosis and portal hypertension at the Southern Medical University Hospital, from January 2013 to June 2016. The inclusion criteria were cirrhotic patients who underwent TIPS to treat at least one episode of gastrointestinal bleeding and patients who underwent the TIPS procedure for refractory ascites. Refractory ascites is defined as ascites that is unresponsive to a sodium-restricted diet and intensive diuretic therapy requiring control by paracentesis more frequently than every 2 weeks, which is consistent with the consensus statement (4). The exclusion criteria were as follows: 1) primary or secondary liver cancer and 2) severe heart, lung, or kidney disease. A

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total of 262 patients were included in the study, and their basic information is listed in Table 1. We selected 70% of the patients as the model group to establish a prediction model, and the remaining 30% were used as the validation group to test the model. The case selection was performed randomly using the IBM SPSS Statistics version 21. The study was approved by the hospital's ethics review committee, obtaining an informed consent form from each patient before TIPS confirming their voluntary participation.

Endpoint indicators

Early post-TIPS HE is defined as HE that occurred within 3 months after TIPS procedure. The diagnosis of HE was based on the definition in the final report presented at the 11th World Congress of Gastroenterology (5). This study excluded subclinical HE and all patients had clinically symptomatic HE, grade ≥1, based on the West Haven Criteria—the most frequently used for grading HE.

Study methods

Preoperative data collection from the patients included relevant examination results within 7 days before TIPS. Patients were followed up at 1 month, 3 months, 6 months, and 1 year after TIPS, and subsequent follow-up performed once a year. Patient follow-up methods included telephone and outpatient or hospital visits at the time of medical events. Follow-up ended on March 1, 2017. Patients were divided into early post-TIPS HE and non-early post-TIPS HE groups based on the presence of HE within 3 months after TIPS procedure. Eighteen indicators were used for statistical analysis and model establishment and validation. These indicators were as follows: the patient's gender, age, etiology, surgical indications (gastrointestinal hemorrhage and refractory ascites), serum creatinine, serum sodium concentration, international normalized ratio (INR), total bilirubin, plasma fibrinogen, albumin, and prothrombin time, preoperative Child-Pugh classification, punctured branch of the portal vein (left branch, right branch, bifurcation, or trunk), presence of variceal embolization, preoperative and postoperative portal venous pressure, portal pressure difference between preoperative and postoperative venous pressure, and shunt stent size.

Statistical analysis

Statistical analysis was carried out using the IBM SPSS Statistics version 21. To reduce the influence of extreme laboratory values, we transformed the quantitative variables to their natural logarithms. Measured data are presented as the mean±standard deviation. Student's t-test and the χ^2 test were used to compare the sample means and the rates, respectively. Multivariate logistic regression analysis included the preoperative clinical features of the patients showing statistically significant differences. Sample means were considered statistically significant at $p<0.05$. Receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic values and determine the model cutoff values. The area under ROC curves was compared using a normal Z test.

RESULTS

General information

Data from a total of 262 patients were collected in the study, consisting of 210 males and 52 females, aged 51.1±11.9 years (range, 19-80 years). We randomly selected 183 patients as the model group to establish a prediction model and the remaining 79 as the validation group. The average follow-up time was 1.8 years (range, 0.1-3.9 years). During follow-ups, 91 (34.7%) patients presented with post-TIPS HE, 73 (27.8%) of whom developed early HE within 3 months after TIPS. Eighteen of these patients who had early HE within 3 months after TIPS died and overall 33 (12.6%) patients died. The cumulative survival rates at 1, 2, and 3 years were 84%, 73%, and 59%, respectively. Conversely the cumulative survival rates at 1, 2, and 3 years for patients who had no HE within 3 months after TIPS were 97%, 91%, and 85%, respectively. A significant difference was detected in the survival time between the two groups of patients using the Kaplan-Meier analysis (χ^2: 14.8, $p<0.05$).

Model construction

For the patients in the model group, the occurrence of HE within 3 months after TIPS was used as the endpoint. Seven indicators that had a significant difference between groups ($p<0.05$) were selected employing a univariate analysis, and these indicators are age, Child-Pugh classification, INR, total bilirubin, albumin, fibrinogen, and prothrombin time. A multivariate forward stepwise logistic regression analysis was then conducted to identify the independent risk factors for early post-TIPS HE that showed statistical significance. These factors are age, Child-Pugh class, and fibrinogen (Table 2). Child-Pugh classification and age have positive regression coefficients, indicating that the likelihood of developing early post-TIPS HE increased with increasing Child-Pugh classification and age. Conversely, fibrinogen has negative regression coefficients, indicating that the likelihood of developing early post-TIPS HE decreased with an increasing fibrinogen level.

Table 1. Patients' basic information.

	All patients (n=262)	Model group (n=183)	Validation group (n=79)
Demographic			
Gender (%)			
Male	80.2	81.4	77.2
Female	19.8	18.6	22.8
Age (yr) (mean±SD)	51.1±11.9	50.4±12.2	52.6±10.9
Cause of cirrhosis (%)			
HBV	73.3	74.3	70.9
HCV	3.1	1.6	6.3
Alcoholic	11.1	10.4	12.7
Others†	12.6	13.7	10.1
Biochemical (mean ± SD)			
Albumin (g/dL)	3.4±0.5	3.3±0.6	3.4±0.5
Serum bilirubin (mg/dL)	1.4±1.3	1.5±1.4	1.2±0.9
Serum creatinine (mg/dL)	0.9±0.3	0.9±0.2	0.9±0.3
Serum sodium (mEq/L)	139.7±2.9	139.7±3.1	139.8±2.5
Prothrombin time(s)	15.6±2.3	15.7±2.3	15.4±2.4
Plasma fibrinogen (g/L)	1.6±0.7	1.7±0.7	1.5±0.6
INR	1.4±0.2	1.4±0.2	1.4±0.2
Child–Pugh classification (%)			
A	26.0	25.7	26.6
B	61.1	62.3	58.2
C	13.0	12.0	15.2
Score* (mean±SD)	7.5±1.7	7.5±1.7	7.5±1.9
Hepatic hemodynamics(mean±SD)			
Pre-TIPS gradient, mm Hg	29.6±4.9	29.5±5.2	29.6±4.2
Post-TIPS gradient, mm Hg	18.9±4.3	18.8±4.2	18.5±4.2
Early HE after TIPS§ (%)			
Stage I	69.9	65.5	86.7
Stage II	24.7	27.6	13.3
Stage III	2.7	3.4	0.0
Stage IV	2.7	3.4	0.0

†Others: Includes Wilson's disease, autoimmune disease, and cryptogenic cirrhosis.
*Score: Based on hepatic encephalopathy, ascites, bilirubin, albumin, and prothrombin time (seconds).
§Early HE after TIPS: Hepatic encephalopathy that occurred within 3 months after TIPS.

Table 2. The results of multivariate logistic regression analysis of the model group.

Variable	Regression coefficient	Regression coefficient Standard effort	p
Age	1.975	0.536	<0.01
Child–Pugh classification	1.110	0.358	<0.01
Fibrinogen (loge value)	−1.724	0.480	<0.01
INR (loge value)	−7.697	6.916	0.27
Total bilirubin (loge value)	0.356	0.330	0.28
Albumin (loge value)	−1.035	1.171	0.38
Prothrombin time (loge value)	8.892	7.147	0.21

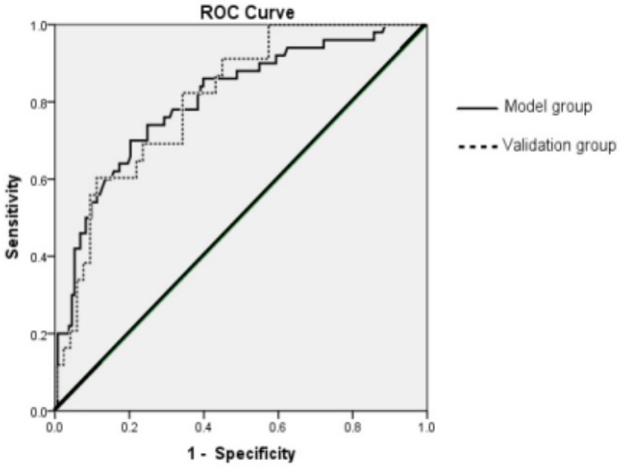

Figure 1. ROC curve showing the AUCs for model and validation groups.

A multiple regression equation of the prediction model was established based on the independent risk factors and their regression coefficients. p represents the probability that early post-TIPS HE will occur, and it is within the range of 0-1. The logistic regression model was established as follows: p=1/{1+exp[4.829−1.975*age-1.110*(Child-Pugh classification)+1.724*$\log_e$ (fibrinogen in g/L)]}. In this formula, age <65 years is defined as 1, age ≥65 years is defined as 2, and Child-Pugh class A is defined as 1, class B is defined as 2, and class C is defined as 3.

Validation of the prediction model for early post-TIPS HE

A ROC curve of the p value was established. As shown in the ROC curve analysis of the model group, the area under the curve (AUC) of the prediction probability was 0.805 (95% confidence interval, 0.732-0.877). The cutoff P value, based on the Youden index equation, was determined using the combination of maximum sensitivity and specificity as a criterion. The cutoff was 0.29, with a diagnostic sensitivity of 70.0% and specificity of 79.7% for the model group. The same cutoff value was applied to the validation group with the same criteria, and it showed an AUC of 0.816 (95% confidence interval, 0.719-0.913) to predict the endpoint with a diagnostic sensitivity of 69.6% and specificity of 71.4%. The positive predictive value was 66.7% and the negative predictive value was 84.5%. The AUC of the two groups (model and validation groups) was shown in Figure 1. There was no significant difference found between the validation and model groups (Z, 0.83; p>0.05). However, the diagnostic efficiency was similar in these groups, indicating that the model had good repeatability.

DISCUSSION

This study showed that the model constructed using the risk factors as patient's age, Child-Pugh classification, and fibrinogen before TIPS can accurately predict the incidence of early post-TIPS HE, which is highly beneficial for clinicians for better prevention and treatment of post-TIPS HE.

Previous reports revealed that patients with HE had their first HE episodes within 3 months after TIPS (2,3). The TIPS procedure allows a portion of the portal venous blood to directly enter the inferior vena cava, which reduces portal venous pressure and thereby prevents severe complications caused by portal hypertension. However, the portal venous shunt increases the incidence of HE after procedure, especially within the first 3 months after TIPS. On the one hand, the liver is supplied with blood mainly by the portal vein. Following TIPS, a reduction in portal venous blood flow leads to a marked decrease in the blood supply to hepatocytes, which damages hepatocytes or even causes ischemic necrosis. The increase in blood ammonia concentration is a consequence of impaired liver function, which thereby induces HE. On the other hand, cerebral blood flow increases after a portal venous shunt is created, leading to the entry of blood ammonia into the brain tissue and a subsequent decline in the brain function. Due to the sudden change in the cerebral blood flow in a short period of time, HE is a potential complication shortly after TIPS. When the

brain has gradually adapted 3 months after procedure, the cerebral blood flow has also slowly decreased to preoperative levels and the blood ammonia level decreased, without increasing the incidence of HE (6). In the present study, post-TIPS HE was observed during follow-ups in 34.7% of the patients. The majority (27.8%) of patients with post-TIPS HE had their first episodes of HE within 3 months after TIPS, which was consistent with the previous reports.

We selected the occurrence of HE within 3 months as the endpoint to establish the clinical prediction model. This allows us to determine the long-term prognosis of the patients in a timely manner based on their manifestations after TIPS. The survival analysis clearly showed that the long-term survival rate in patients who had HE within 3 months after TIPS was worse than that in patients who did not have HE within 3 months after the procedure. To date, the relationship between postoperative HE and patient survival has been rarely reported. Some researchers believe that there is no relationship between postoperative HE and long-term patient prognosis (7). However, others also believe that HE can predict the long-term survival of patients (8). In the present study, our analysis revealed that the cumulative survival rate in patients who had HE within 3 months after TIPS was lower compared with those who did not have HE within 3 months after procedure. We maintain that, although post-TIPS HE can be cured in most cases, the pathogenic process has impaired the patient's systemic organ function. HE is a disease that cannot be completely reversed, and impaired consciousness in patients remains even after the clinical symptoms of HE disappear (9). Therefore, active prevention of post-TIPS HE may to some degree prolong patient survival and further increase the benefits of TIPS for patients undergoing this procedure.

Our model used preoperative data including the patient's age, Child-Pugh classification, and fibrinogen to predict the incidence of early post-TIPS HE. Existing reports have shown that the major risk factors for the occurrence of HE following TIPS were age >65 years, HE before procedure, and Child-Pugh classification C (10-12). Age was an independent predictor of HE occurrence after TIPS. This is because older patients have a relatively poor liver detoxification function and often have constipation, which are commonly caused by HE. Thus, older patients have a higher risk of developing HE after TIPS than younger patients. Additionally, they are more likely to develop HE because their brain cells are more susceptible to the toxic effects of increased blood ammonia after TIPS (13). Plasma fibrinogen is synthesized by the liver. Therefore, the fibrinogen concentration partially reflects the synthesis function of the liver and also indicates the state of liver function in cirrhotic patients. Several studies have shown that the patient's liver function before TIPS is a predictor of HE after procedure. This suggests further that the lower the fibrinogen level before TIPS procedure, the more likely HE will occur after procedure.

The prediction model for early post-TIPS HE constructed in this study thereby showed good preliminary predictive ability and stability. However, this model was established based on the data from patients at a single center. As the technical difficulties of TIPS and the clinical features of the patients vary across different medical centers, the predictive ability of the model requires validation using a multi-center study.

Ethics Committee Approval: Ethics committee approval was received for this study from the Southern Medical University Hospital.

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

Peer-review: Externally peer-reviewed.

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