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Predictive Value of the Freiburg Index of Post-TIPS Survival (FIPS) in Cirrhotic Portal Hypertension Treated with TIPS

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Abstract

Aims: To investigate the predictive value of the FIPS in cirrhotic patients with portal hypertension treated with transjugular intrahepatic portosystemic shunt.

Methods: From June 2011 to June 2021, 63 cirrhotic patients with portal hypertension treated by TIPS with complete clinical records were collected, and their clinical data were retrospectively analyzed. The prediction value of FIPS, MELD, MELD-Na, Child-Pugh score and bilirubin-platelet model score on patients' survival was calculated.

Results: By the end of follow-up time, FIPS, MELD, MELD-Na, Child-Pugh scores and bilirubin-platelet model scores of the survival group were significantly lower than those of the death group, with statistical significance between the two groups in each scoring model (P<0.05). With the increase of FIPS score, MELD score, MELD-Na score, Child-Pugh score and bilirubin platelet model score, the survival rate of patients in all models decreased, and the group with the highest score of each model had the lowest survival rate. The area under ROC curve of FIPS was 0.881, which was higher than the other four scoring models (P<0.05).

Conclusion: FIPS score has better predictive value for survival of patients with portal hypertension cirrhosis treated with TIPS.

Keywords: Prognosis; Transjugular Intrahepatic Portosystemic Shunt; Liver cirrhosis; Freiburg index of post-TIPS survival; MELD score

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Introduction

Liver cirrhosis is one of the most important and common causes of portal hypertension, and the main complications of portal hypertension are intractable ascites and variceal bleeding. TIPS is one of the effective methods for the treatment of portal hypertension. Transjugular Intrahepatic Portosystemic Shunt (TIPS) implantation has made remarkable technological progress in the past 30 years. Now, this technique is related to the low incidence of surgery and shunt-related complications. However, patients who need TIPS implantation usually have advanced liver cirrhosis and have previously experienced more than one decompensated episode associated with a poor prognosis. Therefore, it is necessary to select patients who need closer follow-up after TIPS implantation, as they may face a higher risk of complications and are more likely to require liver transplantation. Some predictive models, such as Child-Pugh score [1], MELD score model [2] or their modified MELD-Na score model [3] and bilirubin-platelet model [4], have been proposed to predict the survival of patients after TIPS implantation. However, in the past few years, in addition to improving the techniques of TIPS implantation, such as covered stents and controlled dilatation stents, the patient selection and indications of tips have also changed. Therefore, the proposed prognostic score model is not fully applicable to patients who need TIPS implantation. For the prediction of postoperative survival after TIPS, Bettingerd et al. study [5] included age, bilirubin, albumin and creatinine in a new risk score, which was named the Freiburg Index of Post-TIPS survival (FIPS). FIPS score can identify high-risk patients and help guide clinical decision-making. The study showed that FIPS score showed better prognostic discrimination than Child-Pugh score, MELD score, MELD-Na score and bilirubin-platelet model. However, whether the FIPS model is suitable for the relevant population in China has not been clinically verified. Through retrospective analysis of the data of

patients in our medical unit, this study compared the ability of FIPS score, MELD score, MELD-Na score, Child-Pugh score and bilirubin-platelet model to predict the medium-and short-term survival time of cirrhotic patients with portal hypertension after TIPS, to provide a reference for further clinical research and clinical guidance in the future.

Materials and Methods

Study subjects

A retrospective analysis was made on 63 patients with cirrhotic portal hypertension treated by TIPS in China-Japan Friendship Hospital of Jilin University from June 2011 to June 2021. The exclusion criteria were: (1) primary or metastatic liver cancer; (2) Budd-Chiari syndrome; (3) coagulation disorders; (4) renal insufficiency caused by other causes except for liver cirrhosis. A total of 58 patients finally met the inclusion criteria.

Methods

The basic data of all patients were collected, including sex, age, operation date, and related biochemical indexes after admission, including Total Bilirubin (TB), INR, Serum Creatinine (Scr), serum Na, platelet, Pre-TIPS PSG, Post-TIPS PSG and so on. The follow-up period was 6 months. The FIPS score, MELD model score, MELD-Na model score, Child-Pugh model score and bilirubin-platelet model score were calculated according to the scoring formula. According to the calculated scores, the survival conditions of patients in different groups were compared within 3 and 6 months after TIPS. The predictive ability of FIPS score, MELD model score, MELD-Na model score, Child-Pugh model score and bilirubin-platelet model score on survival after TIPS was analyzed and compared.

Statistical analyses

SPSS 26.0 software should be used for data analysis. The measurement data in accordance with the normal distribution are expressed by (± s), the independent sample t-test is used for the comparison between groups, the measurement data that do not conform to the normal distribution are expressed by M (P25-P75), and the comparison between groups is expressed by Wilcoxon rank sum test; the grade data is expressed by the number of cases (n), and the comparison between groups is expressed by Wilcoxon rank sum test; the counting data is expressed by n (%), and the comparison between groups is expressed by Chi-square (C^2) test. The diagnostic ability of each index was analyzed by Receiver Operating Characteristic curve (ROC), and the area under ROC curve of each method was compared by Z test. P<0.05 indicates that it is statistically significant.

Results

Baseline characteristics

Among the 63 patients, 5 patients were found to have liver cancer during hospitalization. Finally, 58 patients met the inclusion criteria, including 44 males and 14 females, with a mean age of (52.42 ± 9.02) years. The most common cause of liver cirrhosis was hepatitis B virus (27 cases), followed by alcohol (11 cases), autoimmune (4 cases), hepatitis C virus (4 cases), and 12 cases of liver cirrhosis caused by other causes. During the 6-month follow-up, the mortality rate was 41.3% (24 cases), of which 19 cases were male and 5 cases were female. Among them, 13 patients died of upper gastrointestinal bleeding (including two or more bleeding), 4 patients died of liver failure, 5 patients died of hepatic encephalopathy, 1 patient died of hepatorenal syndrome and 1 patient died of septic shock. According to the collected patient data, the patients were divided into two groups: The survival group and the death group. There were 34 patients in the survival group, including 25 males and 9 females, with an average age of 54.06 ± 8.26 years, and 24 patients in the death group, 19 males and 5 females, with an average age of 54.08 ± 10.27 years. For the clinical data of the patients, there were significant differences in the scores of creatinine, total bilirubin and FIPS between the survival group and the death group and the other four scores (Table 1).

Relationship between different score levels of FIPS score and other four scoring systems and prognosis of patients

The relationship between prognosis and different scores of FIPS and the other four scoring systems was analyzed and the results showed that with the increase in FIPS score, Child-Pugh model score, MELD model score, MELD-Na model score and bilirubin-platelet model score, the survival rate of patients followed up to 3 and 6 months decreased gradually (Table 2).

The survival rate of patients with different models and different scores was further analyzed during the 3- and 6-month follow-up. After 3 months of follow-up, the survival rate of patients with FIPS score < -0.92 was 100%, which was significantly higher than that of patients with > -0.92 (63.6%), P<0.05. In MELD score, the survival rate of <13 group was 81.1%, which was higher than that of >13 group (57.1%), P<0.05; In MELD-NA score, the survival rate of <15 was 81.1%, which was higher than that of >15 group (57.1%), P<0.05. The survival rate of grade I bilirubin-platelet model was 91.3%, significantly higher than that of grade II (60%), P<0.05 (Table 3).

After 6 months of follow-up, the survival rate of patients with different models and different scores was analyzed. The results showed that the survival rate of patients with FIPS score < -0.92 was 92.9%, which was higher than that of patients with > -0.92 (47.7%), P<0.05; the survival rate of grade I bilirubin-platelet model was 78.3%, higher than that of grade II (45.7%), P<0.05 (Table 3).

Comparison of the predictive value of different scoring systems for postoperative survival

The comparison of the predictive value of different scoring systems on postoperative survival of patients was analyzed, and the area under the ROC curve during the 6-month follow-up was calculated. The results showed that: The areas of FIPS score, Child-Pugh model score, MELD model score, MELD-Na model score, and bilirubin-platelet model score under ROC curve were 0.881, 0.685, 0.686, 0.669 and 0.661, respectively. The optimal cut-off points of FIPS score, MELD,

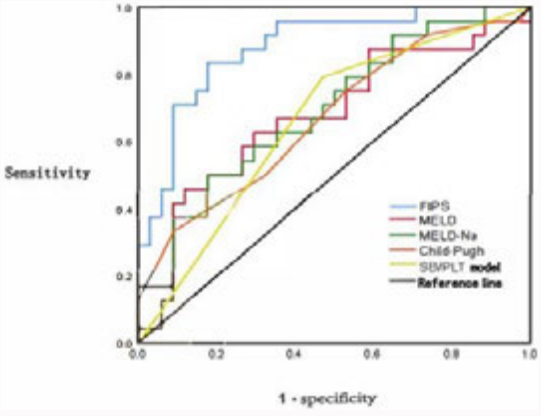

Figure 1: FIPS score versus Child-Pugh, MELD, MELD-Na score and 6-month ROC curve of bilirubin-platelet model.

Table 1: Clinical characteristics and score results of 58 patients.

		Survival group (n=34)	Death group (n=24)	X^2/Z/t values	p values
Gender (cases, %)	Male	25 (73.5)	19 (79.2)	0.244	0.621
	Female	9 (26.5)	5 (20.8)		
age		54.06 ± 8.26	54.08 ± 10.27	0.01	0.992
Pre-TIPS PSG, mmHg		41.13 ± 8.03	42.21 ± 7.59	0.514	0.609
Post-TIPS PSG, mmHg		27.38 ± 6.78	28 ± 5.76	0.363	0.718
Albumin (g/L)		29.22 ± 4.69	29.37 ± 7.48	0.094	0.925
TBiL (mg/dl)		1.26 (0.84, 1.74)	2.02 (1.08, 2.92)	-2.1	0.036
PLT × 10^9		76.5 (55, 87.5)	58.5 (45.5, 83.75)	-1.555	0.12
INR		1.38 (1.26, 1.55)	1.4 (1.25, 1.56)	-0.008	0.994
Creatinine (md/dl)		0.77 (0.66, 0.87)	0.96 (0.89, 1.26)	-4.8	<0.001
Serum sodium (mmol/l)		136.46 ± 6.72	133.82 ± 5.52	-1.578	0.12
FIPS score		0.82 ± 0.65	0.11 ± 0.6	5.572	<0.001
MELD score		11.53 ± 2.19	14.48 ± 5.85	2.356	0.026
MELD-Na score		12.37 (9.62, 15.79)	16.54 (12.19, 24.07)	2.4	0.016
Child-Pugh score		8.76 ± 1.83	9.96 ± 2.14	2.285	0.026
Bilirubin -	I grade	18	5	2.441	0.015
platelet model	II grade	16	19		

Table 2: Survival rate of different models at different follow-up time points (%).

Scoring model		Follow-up time		
		1 month	3 months	6 months
FIPS score	< -0.92 (n=14)	100	100	92.9
	> -0.92 (n=44)	100	63.6	47.7
MELD score	<13 (n=37)	100	81.1	67.6
	>13 (n=21)	100	57.1	42.9
MELD-Na score	<15 (n=37)	100	81.1	67.6
	>15 (n=21)	100	57.1	42.9
Child-Pugh score	≤ 6 (n=4)	100	100	75
	6~9 (n=31)	100	74.2	64.5
	≥10 (n=23)	100	65.2	47.8
Bilirubin–platelet model	I degree (n=23)	100	91.3	78.3
	II degree (n=35)	100	60	45.7

MELD-Na and Child-Pugh score were -0.32, 13.66, 17.58 and 11.50, respectively. The bilirubin-platelet model was grade data, and there was no optimal cut-off point, as shown in Figure 1 and Table 4.

Further comparison of the area under ROC curve between FIPS score and the other four models showed that FIPS score and the other four models could accurately evaluate the short- and medium-term prognosis of TIPS patients until the end of follow-up of this study. FIPS score showed better predictive value compared with child-Pugh model score, MELD model score, MELD-Na model score and bilirubin-platelet model score, as shown in Table 5.

Discussion

Cirrhosis is widely prevalent worldwide; about 1 million people die of cirrhosis every year. Cirrhosis is the third leading cause of death among people aged 45 to 64, together with liver cancer, accounting for 3.5% of all deaths worldwide [6]. The most common complication of cirrhosis is ascites due to portal hypertension [7]. The progression of ascites was associated with a poor prognosis [8]. The second most common complication of cirrhosis with portal hypertension is gastrointestinal bleeding. Varicose bleeding is the most common cause of bleeding. Despite improvements in treatment, variceal bleeding has a mortality rate of about 20% after 6 weeks of onset [8]. Primary prevention of variceal bleeding and secondary prevention are crucial for improving the prognosis of patients with cirrhosis [9].

TIPS, one of the effective treatments for portal hypertension, was first described by Josef Rosch in 1968 and first performed on patients by Ronald Colapinto in 1982 [10]. Palmaz and Rossle et al. introduced balloon dilation stents in 1985, and the clinical application of TIPS was first introduced in 1989 [11]. Over the past 30 years, there have been significant technical advances in TIPS implantation. Patients requiring TIPS implants typically present with advanced cirrhosis and have previously experienced ≥ 1 decompensated episode associated with a poor prognosis. Therefore, it is necessary to select patients who require closer follow-up after TIPS implantation

Table 3: Comparison of survival rates in different models with different scores at 3 months and 6 months follow-up.

Follow-up	Scoring model	Stratify	Survival	Death	c2 value	P value
3 months						
	FIPS score	< -0.92	14 (100)	0 (0)	5.328	0.021
		> -0.92	28 (63.6)	16 (36.4)		
	MELD score	< 13	30 (81.1)	7 (18.9)	3.843	0.0495
		> 13	12 (57.1)	9 (42.9)		
	MELD-Na score	< 15	30 (81.1)	7 (18.9)	3.843	0.0495
		> 15	12 (57.1)	9 (42.9)		
	Child-Pugh Score	≤ 6	4 (100.0)	0 (0.0)	1.708	0.434
		6~9	23 (74.2)	8 (25.8)		
		≥ 10	15 (65.2)	8 (34.8)		
	Bilirubin– platelet model	I degree	21 (91.3)	2 (8.7)	6.809	0.009
		II degree	21 (60)	14 (40)		
6 months						
	FIPS score	< -0.92	13 (92.9)	1 (7.1)	8.918	0.003
		> -0.92	21 (47.7)	23 (52.3)		
	MELD score	< 13	25 (67.6)	12 (32.4)	3.372	0.066
		> 13	9 (42.9)	12 (57.1)		
	MELD-Na score	< 15	25 (67.6)	12 (32.4)	3.372	0.066
		> 15	9 (42.9)	12 (57.1)		
	Child-Pugh score	≤ 6	3 (75.0)	1 (25.0.0)	1.928	0.449
		6~9	20 (64.5)	11 (35.5)		
		≥ 10	11 (47.8)	12 (52.2)		
	Bilirubin– platelet model	I degree	18 (78.3)	5 (21.7)	6.061	0.014
		II degree	16 (45.7)	19 (54.3)		

Table 4: FIPS score and Child-Pugh, MELD, MELD-NA score and bilirubin-platelet model score for prognosis.

Scoring mode	Boundary value	Sensitivity	Specificity	Youden index	AUC (95%CI)	SE	P value
FIPS score	-0.32	83.30%	82.40%	0.657	0.881 (0.793, 0.969)	0.045	<0.001
MELD score	13.66	45.80%	88.20%	0.34	0.685 (0.541, 0.829)	0.073	0.017
MELD-Na score	17.58	50.00%	82.40%	0.324	0.686 (0.548, 0.824)	0.07	0.016
Child-Pugh score	11.5	33.30%	91.20%	0.245	0.669 (0.527, 0.811)	0.073	0.029
SB/PLT model	——	79.20%	52.90%	0.321	0.661 (0.519, 0.802)	0.072	0.039

Table 5: Comparison of the area under the curve between FIPS score and other four scores.

	FIPS score	MELD	MELD-Na	Child-Pugh score	SB/PLT model
AUC (95% CI)	0.881 (0.793, 0.969)	0.685 (0.541, 0.829)	0.686 (0.548, 0.824)	0.669 (0.527, 0.811)	0.661 (0.519, 0.802)
Z value	——	2.286	2.343	2.472	2.591
P value (*vs.* FIPS score)	——	0.022	0.019	0.013	0.01

because they may face a higher risk of complications and are more likely to require a liver transplant. Several scores, particularly the Child-Pugh score, End-stage Liver Disease (MELD) score model or its modifications, such as the MELD-Na score and bilirubin-platelet model, have been proposed to predict survival in TIPS patients. However, in addition to improving the technical aspects of TIPS implantation, patient selection and indications for TIPS implantation have changed significantly over the past few years. Thus, established prognostic scores cannot be fully applicable to other cohorts of patients different from those currently assigned to TIPS implants. Therefore, an alternative model is needed to accurately predict the survival rate of patients with TIPS for secondary prevention of ascites or variceal bleeding. An observational study by Dominik Bettinger [5], conducted between 2000 and 2018, in 7 German centers with extensive expertise in TIPS implants were retrospectively recruited for secondary prevention due to intractable ascites or varicose bleeding of 2,161 patients who received TIPS implantation, another prognostic model was developed by statistical analysis for those who received TIPS for secondary prevention of refractory ascites and/or variceal bleeding, including scoring prognostic model with four influencing factors including age before TIPS, bilirubin, albumin and creatinine. It's called the Freiburg Index of Post-TIPS Survival (FIPS).

In this study, patients who received TIPS implants for secondary prevention of refractory ascites or variceal bleeding at a single medical center during the 10-year period from June 2011 to June 2020 were collected. A retrospective study was conducted to analyze and compare the value of FIPS, MELD, MELD-Na, Child-Pugh score, and bilirubin-platelet model in predicting the survival of patients after TIPS surgery, and to verify whether FIPS score is suitable for predicting the survival of patients receiving TIPS implantation in our medical center. In terms of predictive value, the areas under the ROC curve of FIPS score, MELD, MELD-Na, Child-Pugh score and bilirubin-platelet model were 0.881, 0.685, 0.686, 0.669 and 0.661, respectively, after statistical analysis. By comparing the scores of FIPS with the other four models, the results showed that, by the end of follow-up of this study, FIPS model score showed better prognostic differentiation compared with child-Pugh model score, MELD model score, MELD-Na model score and bilirubin-platelet model score. FIPS model score is applicable to the survival prediction of patients receiving TIPS implantation in our hospital, which has certain clinical guiding significance.

However, due to the lack of domestic multi-center, large-sample clinical trial verification, FIPS scoring system in domestic hospital clinical work to be recognized and widely used, there is still a long way to go. The five scoring models used in this study were mostly based on the clinical data of patients with cirrhosis in Western and European countries, the main causes of cirrhosis were alcoholic liver disease and HCV. While China is a large country with hepatitis B, the main cause of cirrhosis is viral hepatitis B. Whether all the indicators in the FIPS scoring formula show good value for the assessment of liver function in advanced hepatitis B cirrhosis, whether the weighting ratio given in the formula is appropriate, and whether other factors significantly affect the prognosis of the disease, cannot be easily concluded. Secondly, the calculation formulas of FIPS and MELD model scores and MELD-Na model scores are complicated. Whether the calculation formulas of the above models can be simplified to make them more convenient and simpler to use in clinical work is also a problem that needs continuous improvement and refinement in future clinical trial studies. In addition to the above-mentioned problems, although TIPS is an effective and safe method for the treatment of gastrointestinal bleeding and intractable ascites, which are complications of portal hypertension in cirrhosis, there are many and complex prognostic factors that need to be considered by clinicians because of the principles and characteristics of TIPS itself.

Conclusion

FIPS scores showed better prognostic differentiation than Child-Pugh scores, MELD model scores, MELD-Na scores and bilirubin-platelet model scores. Nevertheless, the FIPS score for the survival prediction of domestic cirrhotic patients after TIPS still needs a large number of clinical validations, so as to further clarify the value and accuracy of FIPS for the survival prediction of domestic patients, which requires the joint efforts of medical researchers from different medical centers in China.

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