Dynamic changes in liver function after transjugular intrahepatic portosystemic shunt in patients with cirrhosis

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ABSTRACT
Purpose: To evaluate the dynamic changes in liver function after transjugular intrahepatic portosystemic shunt (TIPS) creation in patients with cirrhosis and to explore its association with clinical outcomes.

Methods: This retrospective study included patients who underwent TIPS between August 2016 and December 2020. Liver function was primarily evaluated using the model for end-stage liver disease (MELD) score, which was analyzed at baseline, 1 week, 1 month, 3 months, 6 months, and 12 months using one-way repeated measures ANOVA. The Kaplan-Meier method, log-rank test, and multivariate analysis were used as appropriate.

Results: In total, 235 patients were included in this study. The MELD score was significantly higher at 1 week (11.8 ± 3.1 vs 13.5 ± 3.5, p < 0.05) and 1 month (11.8 ± 3.1 vs 13.2 ± 4.6, p < 0.05) than the baseline level and recovered at 3 months (11.8 ± 3.1 vs 11.9 ± 3.9, p > 0.05). At 12 months, the MELD score was higher than the baseline level (11.8 ± 3.1 vs 12.4 ± 3.2, p < 0.05). Patients with a recovery of the MELD score (n = 151) at 3 months had a lower probability of overt and severe HE (log-rank p = 0.015 and p = 0.027, respectively) than those without recovery (n = 84). Logistic regression analysis revealed that albumin (odds ratio [OR], 0.926; 95% confidence interval [CI], 0.863–0.992; p = 0.029) and platelet count (OR, 0.993; 95% CI, 0.987–0.999; p = 0.033) were independent predictive factors for non-recovery of the MELD score at 3 months.

Conclusions: Liver function after TIPS creation showed a trend of deterioration at first, followed by recovery. Recovery of liver function at three months was associated with reduced overt and severe HE.

1. Introduction

Transjugular intrahepatic portosystemic shunt (TIPS) has been widely used for treating variceal bleeding and refractory ascites in patients with cirrhosis and is associated with a significant decrease in mortality.1–3 Despite its minimally invasive approach, TIPS creation causes unavoidable stress in the liver through mechanical parenchymal injury and reduced intrahepatic portal venous perfusion, which are closely related to hepatic encephalopathy (HE) and liver failure.4,5 Whether liver function can recover to the baseline level and how long it takes have not been adequately investigated. Therefore, a clear understanding of the dynamic changes in liver function after TIPS creation can help clinicians assess prognosis and conduct rational treatment.

In this study, we aimed to evaluate dynamic changes in liver function after TIPS creation in patients with cirrhosis and explore their association with clinical outcomes.

2. Materials and methods

2.1. Patients

Data were extracted from electronic charts of consecutive patients...
treated with TIPS at our hospital between August 2016 and December 2020. The inclusion criteria were as follows: liver cirrhosis diagnosed by clinical, laboratory, and imaging findings and/or liver biopsy; Child-Pugh score ≤ 13; and variceal bleeding and refractory ascites as indications for TIPS. The exclusion criteria were as follows: liver cancer or other malignancies, previous TIPS, previous liver transplantation, survival time < 3 months, and incomplete medical records. A patient selection flowchart is presented in Fig. 1.

The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. Written informed consent was obtained from all patients, and the study protocol was approved by the Ethics Review Committee of Wuhan Union Hospital.

### 2.2. TIPS protocol

All TIPS procedures were performed according to previously described protocols. Briefly, hepatic vein catheterization was performed through the right internal jugular vein using a transjugular liver access set (RUPS-100; Cook Medical). When the portal vein was punctured by the TIPS needle, a hydrophilic guidewire (Terumo) was gradually advanced to the portal, splenic, or superior mesenteric vein. The Viatorr stent (Gore, Inc.) was in short supply in our center, and an 8-mm expanded polytetrafluoroethylene-covered stent (Fluency; Bard, Inc.; or Viabahn; Gore, Inc.) was placed in the intrahepatic tract after dilation with a balloon catheter. The portal pressure gradient (PPG) was measured in every patient before and after TIPS creation, and the target PPG was 12 mmHg or less. A technical success was defined as successful creation of a shunt between the hepatic and intrahepatic branches of the portal vein.

### 2.3. Follow-up and outcomes

Patients underwent liver, renal function, and Doppler ultrasonography during outpatient or inpatient (for emergency) follow-up visits at 1, 3, 6, and 12 months after TIPS creation and then yearly thereafter.

The primary outcome was to evaluate dynamic changes in liver function, mainly reflected by the MELD score over time after TIPS creation. Secondary outcomes included clinical outcomes and predictive factors for changes in liver function. Liver function was primarily reflected by the MELD score, which was calculated using the following equation: MELD = 3.78 × ln [serum bilirubin (mg/dL)] + 11.2 × ln [INR] + 9.57 × ln [serum creatinine (mg/dL)] + 6.43. ΔMELD was defined as the difference between the baseline and subsequent MELD score (ΔMELD = subsequent MELD score – baseline MELD score). HE was diagnosed and graded according to the West Haven criteria, in which grades II, III, and IV were defined as overt HE (OHE), and grades III and IV HE were categorized as severe. Clinical relapse was defined as the recurrence of clinically significant bleeding or ascites requiring paracentesis. Shunt dysfunction was suspected based on Doppler ultrasound (maximum shunt flow velocity ≤ 50 or ≥ 250 cm/s) or clinical findings (recurrent bleeding or ascites) and confirmed by portography (shunt stenosis > 50%).

### 2.4. Statistical analysis

Categorical variables are expressed as n (%), and differences were compared using the chi-square test or Fisher’s exact test. Continuous variables were expressed as mean ± standard deviation, and differences were compared using the unpaired t-test. One-way repeated measures ANOVA was used to investigate changes in liver function over time.

The cumulative probability of OHE, clinical relapse, and shunt dysfunction was evaluated using the Kaplan-Meier method, and the differences were tested using a log-rank test. Pearson's correlation analysis was used to estimate the correlation between the baseline and ΔMELD scores. Logistic regression analysis was used to explore predictive factors that were independently associated with ΔMELD > 0 at 3 months. Factors with substantial effects (p < 0.1) in the univariate analysis were included in the multivariate analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated and reported. All statistical analyses were performed using SPSS (version 22.0; IBM, Inc., Chicago, IL, USA). Statistical significance was set at p < 0.05.
3. Results

3.1. Patient characteristics

Among 352 patients treated with TIPS between August 2016 and December 2020, 235 were included. The baseline characteristics of the patients are shown in Table 1. In total, 158 (67.2%) patients were male, and the mean age was 53.8 ± 11.1 years old. The baseline MELD and Child-Pugh score were 11.8 ± 3.1 and 7.6 ± 1.5, respectively. The technical success rate of TIPS creation was 100%, including the Fluency stent used in 101 patients and Viabahn stent used in 134 patients. The PPG decreased from 26.5 ± 4.6 mm Hg to 10.7 ± 2.5 mm Hg. In particular, the PPG in 212 patients decreased to less than 12 mmHg, and in the remaining 23 patients, the PPG also reached a 50% or more reduction. Overall, the PPG in all patients achieved a reduction target. The median follow-up time was 32 months (range 12–62 months).

3.2. Changes in liver function after TIPS

The MELD score showed a trend of increase followed by a decrease and a final increase. The MELD score was significantly higher at 1 week – baseline MELD score; PPG, portal pressure gradient.

Table 1. Baseline characteristics of patients.

| Overall patients (n = 235) | Patients with ΔMELD<0 (n = 151) | Patients with ΔMELD >0 (n = 84) | P value |
|---------------------------|---------------------------------|---------------------------------|--------|
| Sex, male                 | 158 (67.2)                      | 104 (68.9)                      | 0.473  |
| Age, years                | 53.8 ± 11.1                     | 52.5 ± 10.9                     | 0.023  |
| Cause of cirrhosis        |                                 |                                 | 0.484  |
| Hepatitis B virus         | 125 (53.2)                      | 82 (54.3)                       | 0.512  |
| Hepatitis C virus         | 31 (13.2)                       | 17 (11.3)                       | 0.167  |
| Alcoholic liver disease   | 18 (7.7)                        | 10 (6.6)                        | 0.951  |
| Others                    | 61 (25.9)                       | 42 (27.8)                       | 0.328  |
| Indication for TIPS       |                                 |                                 |        |
| Variceal bleeding         | 206 (87.7)                      | 130 (86.1)                      | 0.905  |
| Refractory ascites        | 29 (12.3)                       | 21 (13.9)                       | 0.951  |
| SPSS                      | 43 (18.3)                       | 30 (19.9)                       | 0.040  |
| Emergent TIPS             | 68 (28.9)                       | 46 (30.5)                       | 0.489  |
| Laboratory tests          |                                 |                                 |        |
| Total bilirubin, μmol/L   | 28.9 ± 12.6                     | 29.2 ± 11.2                     | 0.642  |
| Albumin, g/L              | 31.5 ± 4.2                      | 32.0 ± 4.1                      | 0.014  |
| Creatinine, μmol/L        | 65.9 ± 18.4                     | 66.6 ± 19.2                     | 0.402  |
| PT, seconds               | 16.5 ± 1.8                      | 16.5 ± 1.7                      | 0.679  |
| Platelet count, 10^9/L    | 82.6 ± 49.8                     | 88.1 ± 52.7                     | 0.024  |
| Hemoglobin, g/L           | 78.8 ± 15.6                     | 77.9 ± 15.3                     | 0.223  |
| WBC, 10^3/L               | 4.6 ± 2.1                       | 4.6 ± 2.1                       | 0.400  |
| MELD score                | 11.8 ± 3.1                      | 12.1 ± 3.0                      | 0.054  |
| Child-Pugh score          | 7.6 ± 1.5                       | 7.8 ± 1.4                       | 0.042  |
| Child-Pugh class          |                                 |                                 | 0.001  |

Data are presented as n (%) or mean ± standard deviation. TIPS, transjugular intrahepatic portosystemic shunt; MELD, model for end-stage liver disease; ΔMELD = MELD score at three months – baseline MELD score; SPSS, spontaneous portosystemic shunt; PT, prothrombin time; WBC, white blood cell; PPG, portal pressure gradient.

3.3. Association of ΔMELD at 3 months and the clinical outcome

According to the changing trend of the MELD score, the patients were classified into the recovery group (ΔMELD < 0, n = 151) and the non-recovery group (ΔMELD > 0, n = 84). The baseline characteristics of the patients are shown in Table 1. There were significant differences in age (52.5 ± 10.9 vs 55.9 ± 11.6, p = 0.023), albumin (32.0 ± 4.1 vs 30.6 ± 4.3, p = 0.014), platelet count (88.1 ± 52.7 vs 72.8 ± 42.5, p = 0.024), and Child-Pugh score (7.8 ± 1.4 vs 7.4 ± 1.5, p = 0.042) between the two groups.

During follow-up, OHE occurred in 40 (17.1%) patients, including 19 (12.6%) patients in the recovery group and 21 (25%) patients in the non-recovery group. The cumulative probabilities of OHE at 1, 3, and 12 months were 3.3%, 8.6%, and 11.9%, respectively, in the recovery group and 5.9%, 15.5%, and 21.4%, respectively, in the non-recovery group (log-rank p = 0.015, Fig. 3A). Furthermore, the rate of severe HE was lower in the recovery group than that in the non-recovery group (5.3% vs. 14.2%, p = 0.027, Fig. 3B). Additionally, clinical relapse occurred in 25 (10.6%) patients (20 with variceal rebleeding and 5 with recurrence of ascites), including 16 (10.6%) in the recovery group and 9 (10.7%) in the non-recovery group. Shunt dysfunction was identified in 21 (13.9%) and 13 (15.5%) patients in the two groups. There was no significant difference in the cumulative probability of clinical relapse (log-rank p = 0.963, Fig. 3C) and shunt dysfunction (log-rank p = 0.724, Fig. 3D) between the two groups.

In addition, we investigated the correlation of ΔMELD with baseline MELD and Child-Pugh scores. There was a significant yet weak association between ΔMELD and the baseline MELD score (r = −0.208, p = 0.001; Fig. 4A), but no significant association was observed between ΔMELD and the baseline Child-Pugh score (r = −0.089, p = 0.174; Fig. 4B).

3.4. Predictive factors for ΔMELD >0 at 3 months

Logistic regression analysis revealed that albumin level (OR, 0.926; 95% CI, 0.863–0.992; p = 0.029) and platelet count (OR, 0.993; 95% CI, 0.987–0.999; p = 0.033) were independent predictive factors associated with a ΔMELD >0 at 3 months (Table 2).

4. Discussion

In this study, changes in liver function were monitored in patients with cirrhosis who underwent TIPS implantation. To our knowledge, this is the first study that evaluates this topic. The MELD score significantly increased at 1 week (11.8 ± 3.1 vs 13.5 ± 3.5, p < 0.05) and 1 month (11.8 ± 3.1 vs 13.2 ± 4.6, p < 0.05), and then recovered to the baseline level at 3 months (11.8 ± 3.1 vs 11.9 ± 3.9, p > 0.05). The changes in total bilirubin and PT were consistent with the MELD score, which revealed that liver function showed a trend of...
deterioration at first and then recovery.

The deterioration of liver function can be explained by an acute reduction in portal vein perfusion after TIPS creation. A proportion of the blood provides no nutritive function, as it bypasses the sinusoids through intrahepatic shunt and contributes to the occurrence of HE. The recovery of liver function may be due to a compensatory hepatic arterial...
The MELD score increased again at 12 months, which may have contributed to liver blood distribution to hepatic artery in patients with hepatic artery hypersplenism. The results agreed with those reported by Bureau et al., who mainly have alcoholic cirrhosis. Bilirubin is a redox-active molecule, plays an important role in hepatic metabolism. Bilirubin is bound and exclusively transported by albumin to hepatocytes for conjugation with glucuronic acid and elimination via the biliary-intestinal system. Thus, high albumin levels may promote the recovery of liver function. The platelet count also has an important prognostic value for non-recovered MELD, and it may reflect the severity of hemodynamic abnormalities correlated with portal hypertension and hypersplenism. The results agreed with those reported by Bureau et al., which showed that bilirubin level and platelet count were the two most important determinants of mortality in patients treated with TIPS.

Our study had several limitations. First, it was designed retrospectively and was dependent on previously collected data. Second, bare stents combined with covered stents were used rather than Viatorr stents. However, some researchers have confirmed that double stents are a reasonable alternative when the availability of Viatorr stents is limited. Finally, the patients primarily had hepatitis B virus-induced cirrhosis (53.2%) and only 18 (7.7%) had alcoholic cirrhosis. Therefore, the results may not represent findings for European or American patients who mainly have alcoholic cirrhosis.

In conclusion, liver function after TIPS creation showed a trend of deterioration at first, followed by recovery. Recovery of liver function at three months was associated with reduced overt and severe HE.
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Authors' contributions

Conceptualization: Bin Xiong; Methodology: Chaoyang Wang and Jiacheng Liu; Data collection: Jinghong Yao, Shuguang Ju; Data analysis and interpretation: Chongtu Yang; Software: Chongtu Yang and Yaowei Bai; Writing original draft: Chaoyang Wang; Writing review and editing: Huanzhang Niu and Bin Xiong.

Declaration of competing interest

The authors of this manuscript declare that they have no conflict of interest.

References

1. García-Pagán JC, Caca K, Bureau C, et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. N Engl J Med. 2010;362:2370–2379.
2. Lv Y, Yang Z, Liu L, et al. Early TIPS with covered stents versus standard treatment for acute variceal bleeding in patients with advanced cirrhosis: a randomised controlled trial. Lancet Gastroenterol Hepatol. 2019;4:587–598.
3. Bureau C, Thabut D, Oberi F, et al. Transjugular intrahepatic portosystemic shunts with covered stents increase transplant-free survival of patients with cirrhosis and recurrent ascites. Gastroenterology. 2017;152:157–163.
4. García-Pagán JC, Di Pascoli M, Caca K, et al. Use of early-TIPS for high-risk variceal bleeding: results of a post-RCT surveillance study. J Hepatol. 2013;58:45–50.
5. Bettigeri D, Schultheiss M, Boettler T, et al. Procedural and shunt-related complications and mortality of the transjugular intrahepatic portosystemic shunt (TIPS). Aliment Pharmacol Ther. 2016;44:1051–1061.
6. Luca A, Miraglia R, Maruzelli L, et al. Early liver failure after transjugular intrahepatic portosystemic shunt in patients with cirrhosis for model for end-stage liver disease score of 12 or less: incidence, outcome, and prognostic factors. Radiology. 2016;280:622–629.
7. Liu J, Ma J, Yang C, et al. Impact of TIPS on splenic volume and thrombocytopenia. AJR Am J Roentgenol. 2021;216:698–703.
8. Tripathi D, Stanley AJ, Hayes PC, et al. Transjugular intrahepatic portosystemic stent-shunt in the management of portal hypertension. Gut. 2020;69:1173–1192.
9. Liu J, Ma J, Yang C, et al. Sarcopenia in patients with cirrhosis after transjugular intrahepatic portosystemic shunt placement. Radiology. 2022;303:711–719.
10. Yip TC, Chan HL, Tse YK, et al. On-treatment improvement of MELD score reduces death and hepatic events in patients with hepatitis B-related cirrhosis. Am J Gastroenterol. 2018;113:1629–1638.
11. Reverter E, Tandon P, Augustin S, et al. A MELD-based model to determine risk of mortality among patients with acute variceal bleeding. Gastroenterology. 2014;146:412–419.
12. Vilstrup H, Amiodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American association for the study of liver diseases and the European association for the study of the liver. Hepatology. 2014;60:715–735.
13. Lv Y, He C, Wang Z, et al. Association of nonmalignant portal vein thrombosis and outcomes after transjugular intrahepatic portosystemic shunt in patients with cirrhosis. Radiology. 2017;285:999–1010.
14. Gilberg V, Haag K, Rosele M, et al. Hepatic arterial buffer response in patients with advanced cirrhosis. Hepatology. 2002;35:630–634.
15. Walter EM, Dela PR, Villanueva-Meyer J, et al. Hepatic perfusion before and after the transjugular intrahepatic portosystemic shunt procedure: impact on survival. J Vasc Interv Radiol. 2006;11:913–918.
16. Giota S, Merli M, Nardelli S, et al. The modification of quantity and quality of muscle mass improves the cognitive impairment after TIPS. Liver Int. 2019;39:871–877.
17. Cheung K, Lee SS, Raman M. Prevalence and mechanisms of malnutrition in patients with advanced liver disease, and nutrition management strategies. Clin Gastroenterol Hepatol. 2012;10:117–125.
18. Trotter JF, Suhocki PV, Rockey DC. Transjugular intrahepatic portosystemic shunt (TIPS) in patients with refractory ascites: effect on body weight and Child-Pugh score. Am J Gastroenterol. 1998;93:1891, 1894.
19. Salerno F, Merli M, Cazzaniga M, et al. MELD score is better than Child-Pugh score in predicting 3-month survival of patients undergoing transjugular intrahepatic portosystemic shunt. J Hepatol. 2002;36:494–500.
20. Huo TI, Wu JC, Lin HC, et al. Evaluation of the increase in model for end-stage liver disease (DeltaMELD) score over time as a prognostic predictor in patients with advanced cirrhosis: risk factor analysis and comparison with initial MELD and Child-Turcotte-Pugh score. J Hepatol. 2005;42:826–832.
21. Bernardi M, Angeli P, Claria J, et al. Albumin in decompensated cirrhosis: new concepts and perspectives. Gut. 2020;69:1127–1138.
22. Spinella R, Sawhney R, Jani R. Albumin in chronic liver disease: structure, functions and therapeutic implications. Hepatol Int. 2016;10:124–132.
23. Peck-Radosavljevic M. Thrombocytopenia in chronic liver disease. J Hepatol. 2014;60:793–800.
24. Bureau C, Mérivier S, D’Amico M, et al. Serum bilirubin and platelet count: a simple predictive model for survival in patients with refractory ascites treated by TIPS. J Hepatol. 2011;54:901–907.
25. Yang Z, Han G, Wu Q, et al. Patency and clinical outcomes of transjugular intrahepatic portosystemic shunt with polytetrafluoroethylene-covered stents versus bare stents: a meta-analysis. J Gastroenterol Hepatol. 2010;25:1718–1725.
26. Saad WE, Darwish WM, Davies MG, et al. Stent-grafts for transjugular intrahepatic portosystemic shunt creation: specialized TIPS stent-graft versus generic stent-graft/bare stent combination. J Vasc Interv Radiol. 2010;21:1512–1520.
27. Kashani A, Salehi B, Angheson D, et al. Spleen size in cirrhosis of different etiologies. J Ultrasound Med. 2015;34:233–238.