Long-Term Improvement in Liver Function Following Transjugular Intrahepatic Portosystemic Shunt in Patients With Budd–Chiari Syndrome

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Background: **Transjugular intrahepatic portosystemic shunt (TIPS) relieves hepatic venous obstruction in Budd–Chiari syndrome (BCS), but the effect on liver function is unclear, particularly outside the immediate post-treatment period. This study aims to evaluate the long-term impact of TIPS on liver function and outcomes in BCS patients.** ***Methods:*** **Twenty patients with BCS who underwent TIPS from 1999 to 2018 were included. Demographic data and clinical data at the time of TIPS procedure, 6 months, 12 months, 2 years, 5 years, and 10 years post-TIPS were collected.** ***Results:*** **There were 13 (13/20, 65%) women and 7 (7/20, 35%) men with a mean age at the time of TIPS of 42.6 ± 12.8 years. The median time from BCS diagnosis to TIPS was 41 (IQR: 4–165) days. The number of patients with severe ascites decreased significantly from 10/17 (58.8%) at the time of TIPS, to 1/16 (7.7%), 1/13 (7.7%), 2/16 (12.5%), 1/14 (7.1%), and 0/8 (0%) at 6 months, 12 months, 2 years, 5 years and 10 years post-TIPS, respectively. 4/20 (20%) patients developed new hepatic encephalopathy post-TIPS procedure. Child–Pugh score significantly decreased from a score of 9.4 ± 1.8 pre-TIPS to 7.6 ± 1.8 at 6 months, 7.4 ± 1.5 at 12 months, 7.3 ± 1.6 at 2 years, 6.8 ± 1.5 at 5 years, and 6.4 ± 0.7 at 10 years post-TIPS. Fifteen (15/20, 75%) patients required TIPS revision including 4 (4/15, 26.7%) within 30 days, 2 (2/15, 13.3% within 1 month to 1 year, and 9 (9/15, 60%) at more than 1 year. Eight (8/20, 40%) patients underwent liver transplantation (LT) at median time of 7.3 (IQR 3.2–12.9) years after TIPS.** ***Conclusion:*** **TIPS placement for BCS results in sustained resolution of symptoms and improved liver function. Despite the frequent need for revisions, the long-term durability of TIPS can forgo the need for LT in the majority of patients.** **(J Clin Exp Hepatol 2022;12:1474–1479)**

Budd–Chiari syndrome (BCS), or what is commonly now referred to a sinusoidal outflow obstruction, is an uncommon condition characterized by hepatic venous outflow obstruction at the level of the hepatic venules, large hepatic veins, inferior vena cava, or right atrium.[1,2] Increased hepatic sinusoidal pressure and portal hypertension cause hypoxic injury and hepatocyte necrosis which lead to liver dysfunction and, in some cases, cirrhosis.[1] The clinical manifestations of liver dysfunction in BCS depend on the acuity of presentation and may include ascites, variceal bleeding, or acute liver failure (ALF).

The management of BCS involves identification and treatment of precipitating hypercoagulable factors and relieving hepatic outflow obstruction in a stepwise manner.[3] Hepatic vein angioplasty has been described with variable success although many patients with persistent thrombosis require portal system decompression with transjugular intrahepatic portosystemic shunt (TIPS).[4] Liver transplantation (LT) is usually reserved for patients who have failed less invasive approaches but may be considered first-line in patients presenting with ALF due to BCS.

The majority of studies looking at outcomes after TIPS in BCS have focused on stent patency and overall survival. In previous reports, stent patency rates range from 64 to 89% at 1 year to 27–86% at 5 years, while one meta-analysis described 1- and 5-year survival of 88.6% and 72.1%, respectively, following TIPS placement.[5–8] However, there is limited data on improvement of liver function following TIPS for BCS, or outcomes beyond 5 years. Two studies have evaluated changes in liver function after TIPS placement although these investigations did not extend beyond 6 months after TIPS.[6,9]

Data regarding long-term clinical outcomes and liver function are still lacking for patients undergoing TIPS for BCS. The aim of this study is to describe long-term clinical outcomes, including liver function, following TIPS placement in a North American cohort of patients with BCS.

Keywords: Budd–Chiari syndrome, TIPS, liver function, liver transplant, long-term
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Abbreviations: ALF: Acute liver failure; BCS: Budd–Chiari syndrome; HE: hepatic encephalopathy; IQR: interquartile range; LT: liver transplant; MELD: Model of end-stage liver disease; TIPS: transjugular intrahepatic portosystemic shunt
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METHODS

Study Design

After receiving institutional review board approval, a retrospective chart review of electronic health record data at a tertiary referral academic medical center from January 1999 to December 2019 was performed. ICD-9, ICD-10 and CPT codes were used to identify patients with primary BCS (ICD-9453.0; IC-10 I82.0) who underwent TIPS (ICD-9 39.1; ICD-10 Z95.828; CPT 37182, 37183). Patients were excluded if they were under 18 years or age or if they were lost to follow-up.

Demographic data, comorbidities, BCS diagnosis date, BCS etiology, TIPS date, TIPS success, type of stent used, LT date (where applicable), death date and cause of death were recorded. Clinical and laboratory data were collected at pre-procedure, 6 months, 12 months, 2 years, 5 years, and 10 years post-procedure. Ascites and hepatic encephalopathy (HE) were graded according to the Child–Pugh score. Using available imaging, ascites was classified as either absent, mild to moderate (diuretic responsive), or severe (diuretic refractory). Using physical examination findings, HE was classified as absent, grade 1–2 ("confused" to "somnolent"), and grade 3–4 ("markedly confused/stupor" to "comatose"). TIPS revision in this study was defined as TIPS venogram followed by intervention with dilation. Laboratory data included basic metabolic panel, complete blood count, liver function tests (including direct bilirubin), total protein and albumin in addition to imaging and procedure reports. Clinical severity scores including Child–Pugh score, model of end-stage liver disease (MELD) and MELD-Na scores were calculated. Finally, procedural data such as stent size and portosystemic gradient were collected.

Statistical Methods

Data were compared between the pre-TIPS and post-procedure periods and reported as percentages for categorical variables and either mean ± standard deviation or median (interquartile range [IQR]) for continuous variables. Continuous data were compared using the student t-test. Categorical data were compared using the $\chi 2$ or Fisher's exact test. Follow-up was censored at death, LT or loss to follow-up. All analyses were performed using JMP version 10 software (SAS Institute Inc., Cary, NC). $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 20 patients who underwent TIPS procedure for BCS were included. There were 13 (13/20, 65%) women and 7 (7/20, 35%) men. Nineteen patients were non-Hispanic White (19/20, 95%), and one patient was Asian (1/20, 5%). Demographic data is presented in Table 1. Mean age at the time of TIPS procedure was 42.6 ± 12.8 years. One patient (1/20, 5%) had type II diabetes mellitus.

A total of 16 (16/20, 80%) patients had underlying hypercoagulable state: 12 (12/20, 60%) patients had a JAK-2 mutation; 4 (4/20, 20%) patients had antiphospholipid syndrome; and 2 (2/20, 10%) patients were homozygous for factor V Leiden mutation. Of these, one patient had both JAK-2 mutation and antiphospholipid syndrome; and one patient had both JAK-2 mutation and homozygous factor V Leiden mutation. Eighteen (18/20, 90%) patients were on anticoagulation at the time of TIPS placement. Two (2/20, 10%) patients were not on anticoagulation due to history of gastrointestinal bleeding or intra-abdominal bleeding. During the follow-up period, one patient was initially lost to follow-up, did not take the prescribed anticoagulation and later presented with TIPS occlusion requiring TIPS revision.

Four (4/20, 25%) patients had a liver biopsy at the time of TIPS placement. There was no evidence of cirrhosis in any of these biopsies. Two (2/20, 10%) patients presented with ALF; 10 (10/20, 50%) patients presented with abdominal pain; three (3/20, 15%) patients presented with gastrointestinal bleeding; and two (2/20, 10%) patients presented with new onset ascites. The level of occlusion was at the hepatic vein in fourteen (14/20, 70%) patients, and at

Table 1 Baseline Characteristics of Patients With Budd–Chiari Syndrome Who Underwent TIPS Placement.

n = 20	n (%)
Female	13 (65%)
Race	
Non-Hispanic White	19 (95%)
Asian	1 (5%)
Age (mean ± SD)	42.6 ± 12.8 years
Hypercoagulation disorder	
Jak-2 mutation	12 (60%)
Antiphospholipid syndrome	4 (20%)
Homozygous factor V Leiden mutation	2 (10%)
On anticoagulation	18 (90%)
Level of occlusion	
Hepatic vein	14 (70%)
Hepatic vein and inferior vena cava	3 (15%)
Stent type	
PTFE-covered stent	16 (80%)
Unknown	4 (20%)
Portosystemic gradient (mean ± SD)	
Pre-TIPS (n = 10)	20.3 ± 8.4 mmHg
Post-TIPS (n = 13)	8.3 ± 3.5 mmHg

PTFE = polytetrafluoroethylene, TIPS = transjugular intrahepatic portosystemic shunt.

combined hepatic vein and inferior vena cava in three (3/20, 15%) patients. Three (3/20, 15%) patients did not have information available regarding level of occlusion.

TIPS Procedure

The median time (IQR) from first symptom to BCS diagnosis was 164 (IQR: 74–291) days. The median time from BCS diagnosis to TIPS procedure was 41 (IQR: 4–165) days.

Sixteen (16/20, 85%) patients received a polytetrafluoroethylene-covered stent. Of the sixteen patients, fourteen (14/16, 87.5%) patients received a 10-mm diameter stent, one (1/16, 6.25%) patient received a 8-mm diameter stent, and one (1/16, 6.25%) patient received both 10- and 12-mm diameter stents. Regarding stent length, seven (7/16, 43.75%) patients received a 8-cm stent, two (2/16, 12.5%) patients received a 7-cm stent, three (3/16, 18.75%) patients received a 6-cm stent, three (3/16, 18.75%) patients received a 5-cm stent, and one (1/16, 6.25%) received a 4-cm stent. There was no stent data for four patients who underwent stent placement prior to 2004: these were presumed to be uncovered stents. The mean ± SD of portal pressure gradient pre- and post-TIPS procedure were 20.3 ± 8.4 mmHg and 8.5 ± 3.3 mmHg, respectively ($P < 0.001$).

Six (6/20, 30%) patients had immediate complications related to the TIPS procedure. One (1/20, 5%) patient had intraperitoneal bleeding requiring vasopressors and intensive care unit admission, and also required TIPS recanalization on the same day of initial placement. Two (2/20, 10%) patients developed ALF with one requiring an urgent LT. One (1/20, 5%) patient had worsening HE, treated with medical therapy. One (1/20, 5%) patient had acute portal vein thrombosis treated with heparin, and 1 (1/20, 5%) patient had internal jugular vein thrombosis.

Fifteen (15/20, 75%) patients required TIPS revision: four (4/15, 26.7%) patients required revision within 30-days of TIPS placement; two (2/15, 13.3%) patients required TIPS revision between 1 month and 1 year, and nine (9/15, 60%) patients after 1 year (Figure 1). Five (5/15, 33.3%) patients required a single TIPS revision; three (3/15, 20%) patients required two revisions; one (1/15, 6.7%) patient required three revisions; one (1/15, 6.7%) patient required four revisions, and five (5/15, 33.3%) patients required five or more revisions. The indication for revision was TIPS stenosis in six (6/15, 40%) patients, thrombosis in five (5/15, 33%) patients, intimal hyperplasia in one (1/15, 6.7%) patient and was not documented in three (3/15, 20%) patients. Of the 15 TIPS revisions, nine (9/15, 60%) patients had balloon angioplasty, two (2/15, 13.3%) patients had an additional covered stent placed, one (1/15, 6.7%) patient had catheter-mediated thrombolysis, and three (3/15, 20%) patients underwent a combined procedure of balloon angioplasty and other techniques including thrombectomy, additional stent placement, and thrombolysis.

All four (4/15, 26.7%) patients with presumed bare metal stents required TIPS revision. Of these four patients, three (3/4, 75%) patients required ≥5 TIPS revision, and one (1/4, 25%) patient required one TIPS revision.

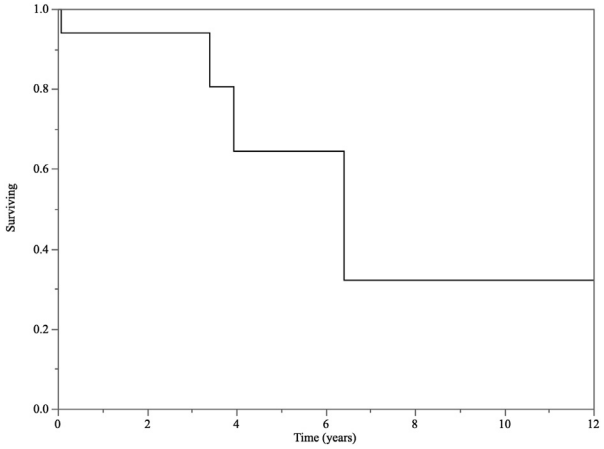

Figure 1 TIPS revision-free survival in patients with Budd-Chiari syndrome.

Pre- and Post-TIPS Comparison

During the follow-up period of 6 months, 12 months, 2 years, 5 years, and 10 years, there were 16, 13, 16, 14, and 8 patients with available data, respectively.

Clinical Symptoms

Severe ascites decreased significantly at 6 months, 12 months, 2 years, 5 years, and 10 years compared with pre-TIPS, $P < 0.05$ for all. The number of patients with severe ascites at pre-TIPS, 6 months, 12 months, 2 years, 5 years, and 10 years post-TIPS were 10/17 (58.8%), 1/16 (7.7%), 1/13 (7.7%), 2/16 (12.5%), 1/14 (7.1%), and 0/8 (0%), respectively (Table 2).

Prior to TIPS procedure, two (2/20, 10%) patients had grade 2 HE. Four (4/20, 20%) patients developed new onset HE following TIPS placement: one patient developed HE secondary to post-TIPS ALF and required urgent LT. Two patients with post-TIPS HE required hospital admission for HE at 3 and 6 months post-TIPS, respectively. With regard to management, three patients were managed chronically with lactulose alone, and two patients were managed with long-term lactulose and rifaximin.

Liver Function

Laboratory data are shown in Table 3. Serum albumin significantly improved from pre-TIPS (3.0 ± 0.6 g/dL) through 6 months (3.5 ± 0.7 g/dL), 12 months (3.7 ± 0.6 g/dL), 2 years (3.6 ± 0.6 g/dL), 5 years (3.9 ± 0.5 g/dL), and 10 years (4.0 ± 0.6 g/dL), follow-up ($P < 0.05$ all). Similarly, total protein significantly improved from pre-TIPS (6.4 ± 1.4 g/dL) through 6 months (7.3 ± 1.0 g/dL), 12 months (6.8 ± 0.9), 2 years

Table 2 Clinical Symptoms of Patients Pre- and Post-TIPS Procedure.

	Pre-TIPS	6 months	12 months	2 years	5 years	10 years
Severe ascites	10/17 (58.8%)	1/16 (7.7%)$^{+}$	1/13 (7.7%)$^{+}$	2/16 (12.5%)$^{+}$	1/14* (7.1%)$^{+}$	0/8 (0%)
Presence of hepatic encephalopathy	2/16 (12.5%)	2/16 (12.5%)	2/16 (12.5%)	1/18 (6.3%)	1/15 (7.1%)	0/13 (0%)

P-value *<0.05, $^{\#}$<0.01, $^{+}$<0.001.
TIPS = transjugular intrahepatic porto-systemic shunt.

Table 3 Laboratory Values of Patients Pre- and Post-TIPS Procedure.

	Pre-TIPS	6 months post-TIPS	12 months	2 years	5 years	10 years
Albumin (g/dL)	3.0 ± 0.6	3.5 ± 0.7*	3.7 ± 0.6$^{\#}$	3.6 ± 0.6*	3.9 ± 0.5^{+}	4.0 ± 0.6^{+}
Total protein (g/dL)	6.4 ± 1.4	7.3 ± 1.0*	6.8 ± 0.9	6.6 ± 1.5	7.3 ± 0.6*	7.6 ± 0.8*
Total bilirubin (mg/dL)	3.2 ± 2.6	2.6 ± 3.7	1.6 ± 0.9	2.0 ± 2.4	1.2 ± 0.5*	1.2 ± 0.8
Aspartate transaminase	388.1 ± 843.0	47.2 ± 23.2*	57.9 ± 31.2	60.2 ± 64.7	44.3 ± 21.2	44.3 ± 21.2
Alanine aminotransferase	272.6 ± 405.0	40.0 ± 17.0*	39.8 ± 10.9*	42.1 ± 32.3*	33.5 ± 14.3*	33.3 ± 12.6*
Alkaline phosphatase	177.4 ± 131.9	237.2 ± 244.6	216.8 ± 160.9	221.3 ± 221.4	226.5 ± 214.7	189.4 ± 124.7
White blood cell	11.8 ± 7.0	6.8 ± 3.9*	7.2 ± 3.0*	6.7 ± 2.4$^{\#}$	6.7 ± 2.2$^{\#}$	6.8 ± 2.5*
Platelet	182.1 ± 120.7	168.8 ± 98.9	157.8 ± 83.4	186.5 ± 99.3	241.6 ± 134.9	232.5 ± 131.2
Hemoglobin	13.4 ± 3.4	12.5 ± 2.4	14.5 ± 1.9	13.5 ± 2.9	13.1 ± 1.9	13.4 ± 2.3
Sodium	136.3 ± 4.5	140.2 ± 2.6	140.1 ± 3.0	138.9 ± 2.7*	140.5 ± 2.1$^{\#}$	139.5 ± 2.3*
Potassium	4.3 ± 0.5	4.0 ± 0.5*	4.1 ± 0.6	4.0 ± 0.4*	3.9 ± 0.4*	4.1 ± 0.8
Blood urea nitrogen	15.9 ± 12.5	7.6 ± 1.8$^{\#}$	10.9 ± 4.3	11.8 ± 4.5	12.1 ± 3.0	13.3 ± 3.3
Creatinine	1.1 ± 1.3	0.8 ± 0.3	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2
INR	1.8 ± 1.1	1.8 ± 0.7	2.0 ± 0.9	1.8 ± 0.6	2.1 ± 0.9	2.5 ± 1.7

P-value *<0.05, $^{\#}$<0.01, $^{+}$<0.001.
TIPS = transjugular intrahepatic porto-systemic shunt, INR = international normalized ratio.

(6.6 ± 1.5 g/dL), 5 years (7.3 ± 0.6 g/dL), and 10 years (7.6 ± 0.8) follow-up (P < 0.05 for all).

Clinical severity scores of patients pre- and post-TIPS procedure are shown in Table 4. Child–Pugh score significantly decreased with a score of 9.4 ± 1.8 pre-TIPS, compared with 7.6 ± 1.8 at 6 months, 7.4 ± 1.5 at 12 months, 7.3 ± 1.6 at 2 years, 6.8 ± 1.5 at 5 years, and 6.4 ± 0.7 at 10 years post-TIPS (P < 0.05 all). MELD and MELD-Na score were not significantly changed pre- and post-TIPS procedure.

Long-term Outcomes

Three (3/20, 15%) patients died at 3.6, 13.5, and 21.0 years following TIPS placement from septic shock, pulmonary embolism during LT and diverticular perforation.

Eight (8/20, 40%) patients underwent LT at median time of 7.3 (IQR 3.2–12.9) years after TIPS (Figure 2). Five (5/8, 62.5%) of the eight explants showed cirrhosis; the transplant was performed 1, 5, 10, 12, and 13 years post-TIPS. Transplant-free survival at 10 years was 75% (15/20) (Figure 2). The indication for LT was recurrent TIPS occlusion requiring frequent revision in six (6/8, 75%) patients, recurrent pyogenic cholangitis in one (1/8, 12.5%) patient, and hepatocellular carcinoma in one (1/8, 12.5%) patient. None of the patients required re-transplantation. Two (2/8, 25%) of the LT patients died: one (1/8, 12.5%) patient died of a massive pulmonary embolism during the LT operation, and one (1/8, 12.5%) patient died from a diverticular perforation 9 years after the LT date.

Table 4 Clinical Severity Scores of Patients Pre- and Post-TIPS Procedure.

	Pre-TIPS	6 months post-TIPS	12 months	2 years	5 years	10 years
Child–Pugh score	9.4 ± 1.8	7.6 ± 1.8$^{\#}$	7.4 ± 1.5$^{\#}$	7.3 ± 1.6$^{\#}$	6.8 ± 1.5^{+}	6.4 ± 0.7^{+}
MELD	16.1 ± 8.7	14.9 ± 5.3	15.6 ± 4.9	14.8 ± 4.6	15.0 ± 5.1	16.1 ± 6.7
MELD-Na	18.8 ± 8.0	15.5 ± 5.3	16.1 ± 5.0	15.4 ± 4.4	15.0 ± 5.1	16.8 ± 7.1

P-value $^{\#}$<0.01, $^{+}$<0.001.
TIPS = transjugular intrahepatic porto-systemic shunt, MELD = model of end-stage liver disease.

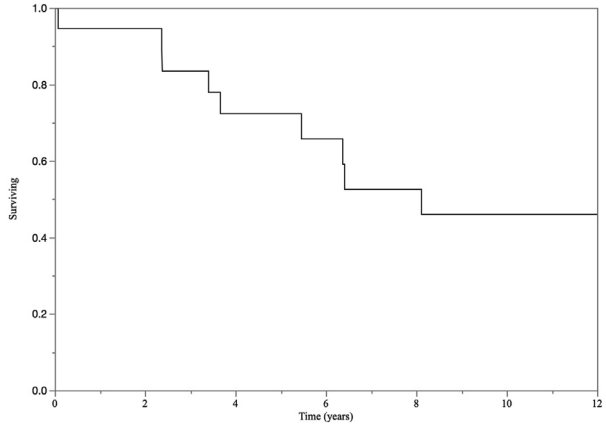

Figure 2 Transplant-free survival in patients with Budd-Chiari syndrome.

The 10-year, long-term outcomes of 16 patients, excluding four patients who underwent LT within 10 years of TIPS placement, were analyzed for ascites, HE, laboratory values, Child–Pugh score, MELD, and MELD-Na (Supplementary Data 1, 2, 3).

DISCUSSION

The results from our study show that TIPS can achieve good long-term control of symptoms for patients with BCS, as well as a sustained improvement in liver function. Consequently, TIPS placement can prevent or delay the need for LT in a large proportion of this population.

As expected, ascites significantly improved following TIPS placement in this cohort. Importantly, rates of HE did not significantly worsen after TIPS. HE can lead to significant morbidity and utilization of health care resources, particularly hospital readmissions.[10] In prior studies evaluating TIPS placement in patients with BCS, the development of HE was less common compared with patients undergoing TIPS for complications of cirrhosis.[4,5,7,9,11,12] This discrepancy is likely related to the relatively preserved liver function in patients with BCS compared with the diffuse hepatic parenchymal disease that characterizes cirrhosis.[13]

Repeat interventions for TIPS dysfunction were required in the majority of patients, particularly in the early follow-up period. The primary unassisted stent patency rates at 1, 2, and 5 years in this study were 65%, 40%, and 10%, respectively, comparable with stent patency rates in other studies looking at TIPS for BCS.[5,11,14,15] While most of the patients in this cohort received covered stents, the data here emphasizes the need for both close short- and long-term clinical follow-up in this patient population.[5,11,14,15] Weber *et al.* showed that stent patency slowly decreases from 2 years in all patients who receive a covered TIPS.[15] In patients with TIPS placement for BCS, maintaining stent patency remains a challenge, regardless of stent type, due to underlying hypercoagulable disease present in most patients.[5,7,16]

This is one of the only studies to evaluate long-term changes in liver function in patients with BCS who undergo TIPS placement. Older studies have shown significant improvements in liver function tests in the early stages after TIPS placement.[6,9] In this study, total bilirubin and alanine aminotransferase markers of liver injury-significantly improved soon after TIPS placement and remained in the normal range to the end of the follow-up period. Total protein and albumin markers of liver synthetic function also showed a sustained improvement from TIPS placement for the entire duration of the study. Similarly, the Child–Pugh score-a clinical scoring system with prognostic value in BCS- significantly improved soon after TIPS placement which persisted through the end of the study period. No improvements were seen in the MELD or MELD-Na scores following TIPS in this cohort. This is probably attributable to elevations in INR secondary related therapeutic anticoagulation after TIPS placement. Furthermore, serum creatinine is a heavily weighted component of the MELD and MELD-Na scores but is not directly affected by TIPS.[17]

A large proportion of patients in this study did not undergo LT. The longer follow-up time likely accounts for the higher degree of patients requiring a LT when compared with prior studies.[5,7,9] TIPS is the modality of choice in the treatment of patients with BCS, even in early cases of ALF.[3] However, LT may be required for patients with BCS who develop recurrent TIPS dysfunction which is no longer amenable to TIPS revision. The median time of 7.3 years from TIPS placement to LT demonstrates the ability of TIPS to substantially delay the need for LT in patients with BCS. This is particularly important as the demand for liver allografts continues to outstrip supply in the United States, and to minimize the long-term complications of immunosuppression in a younger patient population.[18,19]

The limitations of this study include its retrospective nature. Given the low prevalence of BCS, the number of patients included is relatively small. A small proportion of patients received uncovered stents, which has been clearly shown to affect stent patency outcomes.[20] This cohort of patients is also comprised entirely of patients from the United States whereas the characteristics of BCS can vary with geography.[21] Furthermore, this study is an observational study with no comparison of TIPS against other interventions, including other venoplasty modalities, while TIPS techniques themselves have also evolved over the long study period. Finally, the study was conducted at a quaternary referral center and the outcomes achieved may not be applicable to all institutions.

In conclusion, TIPS placement can result in a sustained improvement in both clinical symptoms and liver function in patients with BCS. Due to the frequent need for TIPS

revision in this patient population, close short- and long-term follow-up is advised. Nonetheless, TIPS for BCS has good long-term durability and can delay the need for LT in the majority of patients. Prospective studies should focus on optimizing techniques or other interventions to promote stent patency in BCS patients who undergo TIPS placement.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Nicha Wongjarupong: Conceptualization, Data curation, writing—original draft preparation; Shamar Young**:** Conceptualization, Methodology, Software, Writing- Reviewing and Editing; Richie K Huynh**:** Writing—Reviewing and Editing; John Lake: Supervision, Writing—Reviewing and Editing; Nicholas Lim: Conceptualization, Supervision, Writing—Reviewing and Editing. All authors had reviewed and revised the manuscript and had approved the final version of the manuscript.

CONFLICTS OF INTEREST

The authors have none to declare.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jceh.2022.07.251.