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ORIGINAL ARTICLE

Predictors and Outcomes of Post-transjugular Intrahepatic Portosystemic Shunt Liver Failure in Patients with Cirrhosis

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Abstract

Background Post-transjugular intrahepatic portosystemic shunt (TIPS) liver failure (PTLF) is a serious complication of TIPS procedure with poor patient prognosis. This study tried to investigate the incidence of PTLF following elective TIPS procedure and evaluated possible predictive factors for the same.

Methods A retrospective analysis of patients who underwent elective TIPS placement between 2012 and 2022 and was conducted to determine development of PTLF (≥ 3-fold bilirubin and/or ≥ 2-fold INR elevation from the baseline) within 30 days following TIPS procedure. Medical record review was done and factors predicting development of PTLF and the 90-day transplant-free survival was determined.

Results Thirty of 352 (8.5%) patients developed PTLF within 30 days of TIPS (mean age 54.2 ± 9.8 years, 83% male). The etiology of cirrhosis was related to non-alcoholic steatohepatitis (NASH) in 50%, alcohol in 33.3%, and hepatitis B/C virus infection in 16.7% of the patients. The mean Child–Turcotte–Pugh (CTP) score was 9.5 ± 1.2 and mean model for end stage liver disease (MELD) score was 14.6 ± 4.5 at the time of admission in patients who developed PTLF. The indication for TIPS was recurrent variceal bleed in 50% (15 of 30) and refractory ascites in 46.7% (14 of 30) patients with PTLF.
Multivariate analysis identified prior HE (OR 6.1; CI 2.57–14.5, $p < 0.0001$) and higher baseline CTP score (OR 1.47; CI 1.07–2.04; $p = 0.018$) as predictors of PTLF. PTLF was associated with significantly lower 90-day transplant-free survival, as compared to patients without PTLF (40% versus 96%, $p < 0.001$).

Conclusion Almost 10% of patients with cirrhosis develop post-TIPS liver failure and is associated with significant early mortality and morbidity. Higher baseline CTP score and prior HE were identified as predictors for PTLF.

Keywords TIPS · Portal hypertension · Cirrhosis · Liver failure · HE

Abbreviations

TIPS	Transjugular intrahepatic portosystemic shunt
PTLF	Post-TIPS liver failure
CTP	Child–Turcotte–Pugh
MELD	Model for end stage liver disease
NASH	Non-alcoholic steatohepatitis
ISGLS	International Study Group of Liver Surgery
HVOTO	Hepatic vein outflow tract obstruction
HE	Hepatic encephalopathy
AKI	Acute kidney injury
INR	International normalization ratio
AST	Aspartate transaminase
ALT	Alanine transaminase
ALP	Alkaline phosphatase
GGT	Gamma-glutamyl transferase
PSG	Portosystemic gradient
PTFE	Polytetrafluoroethylene
SD	Standard deviation
IQR	Interquartile range

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Introduction

Transjugular intrahepatic portosystemic shunt (TIPS) is an extensively studied and a well-established treatment option in the management of portal hypertension and its

complications. Several studies have shown effectiveness of TIPS in preventing variceal bleeding and controlling refractory ascites [1–3]. However, TIPS procedure is not devoid of complications which may severely impact patient prognosis. Post-TIPS liver failure (PTLF) is a rare but significant complication associated with the procedure. It involves acute deterioration of liver function, most likely induced by significant diversion of portal venous blood flow into systemic circulation. At present, there are no consensus guidelines that offer an objective definition of PTLF. Gaba et al. (2016) proposed a simple and objective definition and classification scheme for PTLF [4], which was based on the validated definition for post-hepatectomy liver failure (PHLF) designed by the International Study Group of Liver Surgery (ISGLS) [5]. This study aims to evaluate the incidence of PTLF utilizing the proposed definition and assess predictive factors and outcomes associated with PTLF.

The pathophysiology of acute liver failure after TIPS placement is variable, but involves insult to an already-compromised liver, most importantly due to the markedly decreased portal perfusion [6]. The diversion of intrahepatic portal flow following TIPS results in hepatic hypoperfusion causing hepatic encephalopathy (HE) and deterioration in liver functions [7]. Other proposed mechanisms include technical factors such as compression or occlusion of hepatic artery or portal vein branches by the TIPS stent resulting in hepatic infarction [8, 9] or occlusion of hepatic veins by the covered stent resulting in a hepatic vein outflow tract obstruction (HVOTO) like picture [10].

Bilirubin and INR are recognized surrogate markers of liver function and are widely used in clinical practice for this purpose. Transient rise in bilirubin and INR after TIPS is a common finding and not all such cases have an adverse outcome. However, severe and prolonged rise in their levels may be a sign of hepatic failure [4].

Materials and Methods

The Institutional Review Board at our institution granted approval for this study with a waiver of consent for inclusion. All patients provided written informed consent for TIPS procedures for various indications.

Eligibility Criteria

All patients with cirrhosis (diagnosed based on biopsy or imaging) who underwent TIPS placement for the following indications were included in the study: control of acute or recurrent bleeding from esophageal or gastric varices, refractory ascites, and refractory hepatic hydrothorax. Patients who were excluded from the study were those with inadequate follow-up (adequate follow-up being defined as approximately two values during the first week and two subsequent values within the first month after TIPS), patients who underwent salvage TIPS procedure within 24 h of failed medical and endoscopic therapy, patients with established acute-on-chronic liver failure, patients with HVOTO and those having hepatocellular carcinoma or any other extrahepatic malignancy.

Study Population

The study was a retrospective analysis of all patients with cirrhosis who underwent technically successful elective TIPS placement between May 2012 and June 2022 at a single tertiary care center. A total of 608 patients who underwent TIPS placement for various indications were identified through a review of our hospital database. Two-hundred fifty-six patients were excluded for the following reasons: HVOTO ($n=149$), salvage TIPS ($n=66$), inadequate post-procedural follow-up ($n=20$), established acute-on-chronic liver failure ($n=17$), and the presence of hepatocellular carcinoma or extrahepatic malignancy ($n=4$). A total of 352 patients were eligible for analysis. The study design is depicted in Fig. 1.

Data Collection

The medical records of the patients were reviewed, and demographic and clinical data that included age, sex, indication for TIPS placement, cause of cirrhosis, history of prior hepatic encephalopathy (HE), prior variceal bleed, history of acute kidney injury (AKI) and the presence of co-morbidities, were collected. Laboratory values including hemoglobin, platelet count, International Normalization Ratio (INR), bilirubin, Aspartate transaminase (AST), Alanine transaminase (ALT), Alkaline phosphatase (ALP), Gamma-glutamyl transferase (GGT), creatinine, urea, and sodium levels were collected as close to the procedure as available. Composite scores including Child–Turcotte–Pugh (CTP) score and model for end-stage liver disease (MELD) score, MELD-Na score, and ALBI score were calculated in accordance with previously published formulas. Procedure-related data, including type of stent placed, diameter of the stent, the portosystemic gradient (PSG) before TIPS placement, and the PSG after TIPS placement, were also collected.

Baseline (within 24 h of TIPS creation) and peak (highest value within 30-days post-procedure) bilirubin and INR levels were collected for each case. If there was no peak value higher than baseline during the 30 days after TIPS creation, the baseline value was used as the peak value. Review of medical records was performed to collect information on post-procedural clinical outcomes.

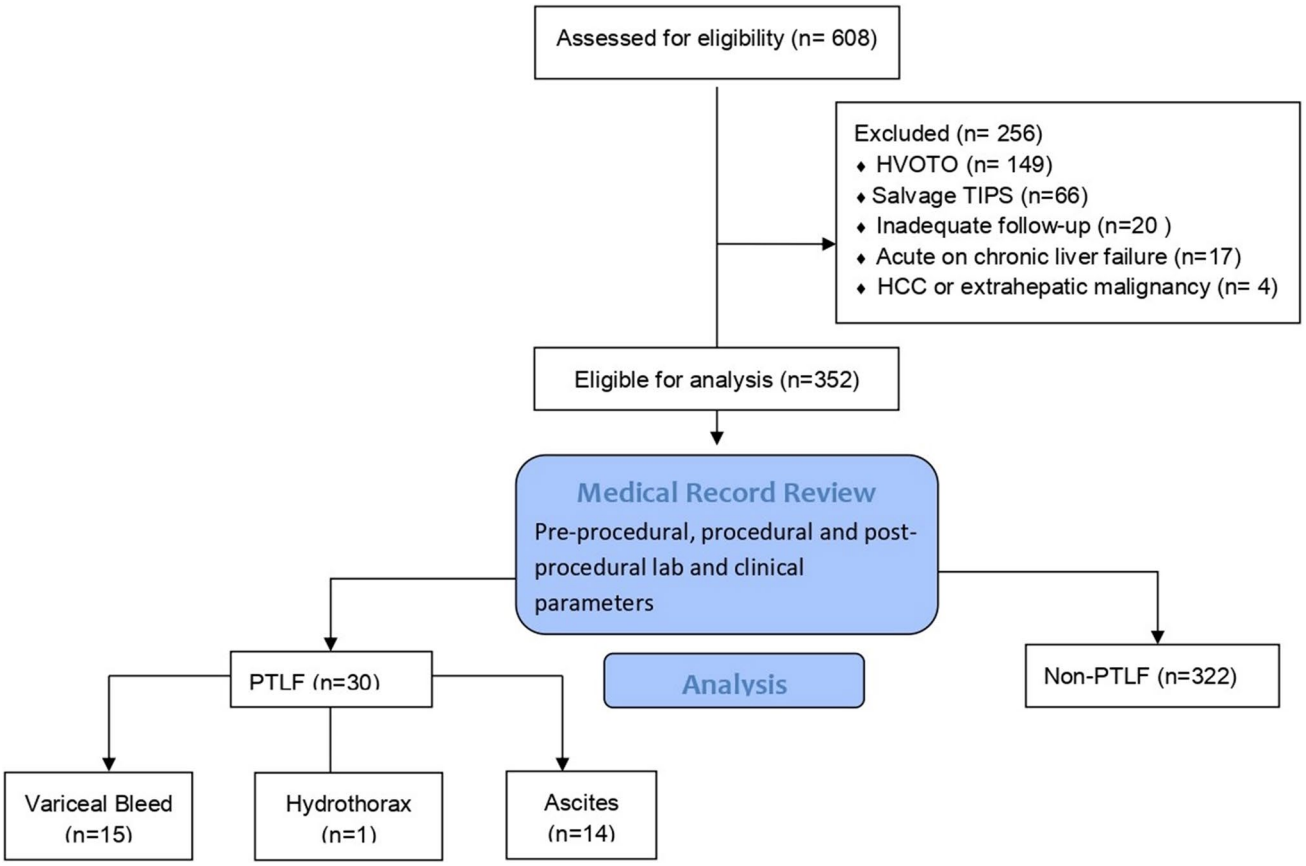

Fig. 1 Flowchart of patients treated with TIPS between May 2012 and July 2022 in a specialty center (*HVOTO* hepatic venous outflow tract obstruction, *TIPS* transjugular intrahepatic portosystemic shunt, *HCC* hepatocellular carcinoma, *PTLF* post-TIPS liver failure)

Transjugular Intrahepatic Portosystemic Shunt Procedure

TIPS creation was performed according to previously described methods using moderate sedation in the interventional radiology suite. A 8 mm polytetrafluoroethylene (PTFE)-covered stent (Fluency plus, BARD, NJ, USA) was used in all patients after January 2018, while 10 mm stent was used in patients who underwent TIPS from May 2012 to December 2017. A bare metal stent was placed in an overlapping manner such that it protruded about 2 cm into the portal vein. After TIPS procedure, patients underwent inpatient monitoring for at least 48–72 h with daily acquisition of liver function tests and INR. Patients were then followed up in an outpatient hepatology clinic at 1 week and subsequently within 1 month of the procedure.

Definition of PTLF

PTLF was defined as the presence of essential lab criteria combined with an escalation of clinical care or liver-specific adverse clinical outcome within 30 days of TIPS [4]. Abnormal lab elevation criteria are a 3-fold or greater increase in bilirubin and/or a 2-fold or greater increase in INR (based on peak laboratory values) compared to baseline within 30 days of TIPS, excluding other identifiable causes such as biliary obstruction or suspected biliary vascular fistula. Adverse clinical outcomes include prolonged hospitalization (defined as continued admission post day 5 of TIPS in the absence of other clinical outcome criteria), development of new onset hepatic encephalopathy, TIPS reduction, liver transplantation, or death within 30 days of TIPS.

Patients fulfilling the predefined criteria of abnormal lab elevation associated with adverse clinical outcomes were classified as having PTLF. The study population was divided into two cohorts—PTLF and non-PTLF groups. Table 1 summarizes the PTLF definition.

Measured Outcomes

The outcome measures of this study were the incidence of PTLF based on predefined criteria and transplant-free

Table 1 PTLF definition

PTLF	
Essential lab criteria	> 3 × Bilirubin and/or > 2 × INR compared to baseline
Associated with any of the following	
Liver specific adverse clinical outcome, or	• Coagulopathy • New onset/worsening HE • Death within 30 days
Escalation of clinical care	• Prolonged hospital stay • Invasive management with TIPS reduction or liver transplant due to liver failure within 30 days

survival of patients with PTLF at 90 days following TIPS creation.

Statistical Analysis

Descriptive statistics were used to characterize patient demographics. Data were presented as mean ± standard deviation or median with interquartile range for numerical variables and as a percentage for categorical variables. Comparisons for categoric data were performed using the Pearson χ^2 test or Fisher exact test. Comparisons for continuous nonparametric datasets were performed using the Mann–Whitney *U* test. All variables were assessed using univariate logistic regression. Those significant at $p < 0.05$ were analyzed using a multivariate logistic regression model. Variables significant at $p < 0.05$ in multivariate logistic regression analysis were then selected as independent predictors for PTLF. The transplant-free survival rate was assessed for both groups and *p* value was calculated using Log Rank test for categorical variables. Kaplan–Meier survival curves were then created.

Results

Patient Characteristics

The study cohort comprised 352 patients with cirrhosis who underwent elective TIPS placement. Patient demographics, liver disease characteristics, baseline laboratory parameters, and procedural parameters of the study cohort are summarized in Table 2.

TIPS Procedure

All 352 patients underwent covered stent-graft TIPS, with stent diameter of 10 mm in 294 (83.5%) patients and 8 mm in 58 (16.5%) patients. TIPS hemodynamic success [defined as an absolute post-procedural portosystemic pressure gradient (PSG) of less than or equal to 12 mm] was achieved in 303/352 (86.1%) procedures, with a mean PSG reduction of 15 ± 6 mmHg.

PTLF

Incidence

Out of 352 patients, 30 (8.5%) patients had abnormal lab elevation associated with adverse clinical outcomes within 30 days of TIPS procedure, fulfilling the criteria for PTLF.

Lab Criteria

Out of 30 patients fulfilling criteria for PTLF, 6 (20%) had 2-fold or greater increase in INR, and 18 (60%) had 3-fold or greater increase of bilirubin as compared to baseline, while 6 (20%) had both 2-fold or greater increase in INR and 3-fold or greater increase in bilirubin.

Clinical Outcomes

The incidence of post-TIPS HE was significantly higher in PTLF patients as compared to non-PTLF cohort ($p < 0.001$). Sixteen (53.3%) patients with PTLF developed HE within 30 days of TIPS as compared to 36 (11.2%) patients in non-PTLF group ($p < 0.001$). TIPS reduction was undertaken in 3 (10%) patients in PTLF cohort. Early mortality within 30 days of TIPS was also significantly higher in the PTLF cohort. Of 30 patients with PTLF, 15 (50%) died within 30 days, with mortality being attributed to liver failure or associated complications, while only 8 of 322 (2.5%) patients in the non-PTLF group had early mortality ($p < 0.001$). The findings are summarized in Table 3.

Predictive Factors for PTLF

Univariate analysis showed that indication for TIPS ($p = 0.05$), prior HE ($p < 0.0001$), prior variceal bleed ($p = 0.024$), pre-procedural higher serum creatinine level ($p = 0.039$), lower hemoglobin level ($p = 0.017$), higher MELD score ($p = 0.008$), and higher Child–Pugh score ($p = 0.001$) had statistically significant association with PTLF. Other factors including patient age, gender, etiology, serum bilirubin, AST, ALT, ALP, GGT, albumin, blood urea, serum sodium, MELD-Na, and ALBI score were not

Table 2 Patient characteristics and procedural parameters—PTLF vs. non-PTLF

Parameter	Study population ($n=352$) Mean ± SD|| frequency (%)	PTLF ($n=30$) Mean ± SD|| frequency (%)	Non-PTLF ($n=322$) Mean ± SD|| frequency (%)	p value***
Age (years)	54.57 ± 10.27	54.23 ± 9.89	54.61 ± 10.31	0.845
< 40	33 (9.4%)	1 (3.3%)	32 (9.9%)	
40–60	215 (61.1%)	21 (70.0%)	194 (60.2%)	
> 60	104 (29.5%)	8 (26.7%)	96 (29.8%)	
Gender				0.796
Male	297 (84.4%)	25 (83.3%)	272 (84.5%)	
Female	55 (15.6%)	5 (16.7%)	50 (15.5%)	
Etiology				0.316
NASH	163 (46.3%)	15 (50.0%)	148 (46.0%)	
Ethanol	114 (32.4%)	10 (33.3%)	104 (32.3%)	
HBV/HCV	37 (10.5%)	5 (16.7%)	32 (9.9%)	
Cryptogenic	30 (8.5%)	0 (0.0%)	30 (9.3%)	
Others	8 (2.3%)	0 (0.0%)	8 (2.5%)	
Indication				**0.05**
Ascites	232 (65.9%)	14 (46.7%)	218 (67.7%)	
Variceal bleed	110 (31.3%)	15 (50.0%)	95 (29.5%)	
Hydrothorax	10 (2.8%)	1 (3.3%)	9 (2.8%)	
Past history				
Prior HE	41 (11.6%)	13 (43.3%)	28 (8.7%)	**< 0.001**
Prior AKI	80 (22.7%)	10 (33.3%)	70 (21.7%)	0.242
Prior bleed	195 (55.4%)	23 (76.7%)	172 (53.4%)	**0.024**
Comorbidities				
Diabetes mellitus	188 (53.4%	19 (63.3%)	169 (52.5%)	0.343
Hypertension	83 (23.5%)	11 (36.7%)	72 (22.4%)	0.112
Hypothyroidism	50 (14.2%)	4 (13.3%)	46 (14.3%)	> 0.999
Lab parameters				
Hemoglobin (g/dL)	8.89 ± 1.62	8.11 ± 1.54	8.97 ± 1.61	**0.017**
Platelet count (/mm^3)	99.60 ± 65.13	109.20 ± 86.19	98.70 ± 62.91	0.781
INR	1.41 ± 0.26	1.56 ± 0.41	1.40 ± 0.24	0.056
Total bilirubin (mg/dL)	1.44 ± 0.84	1.71 ± 1.01	1.42 ± 0.82	0.106
AST (U/L)	53.88 ± 57.26	81.98 ± 143.11	51.26 ± 40.67	0.190
ALT (U/L)	32.88 ± 42.20	44.89 ± 73.40	31.76 ± 38.02	0.395
ALP (U/L)	106.39 ± 61.40	116.60 ± 57.43	105.4 ± 61.75	0.194
GGT (U/L)	50.74 ± 54.79	53.77 ± 56.18	50.46 ± 54.74	0.717
S. albumin (g/dL)	2.89 ± 0.55	2.86 ± 0.64	2.89 ± 0.54	0.866
S. creatinine (mg/dL)	1.01 ± 0.50	1.16 ± 0.47	0.99 ± 0.50	**0.039**
Blood urea (mg/dL)	51.92 ± 31.33	62.60 ± 43.00	50.93 ± 29.90	0.178
S. sodium (mEq/L)	132.72 ± 5.16	133.06 ± 5.71	132.69 ± 5.11	0.607
Composite scores				
CTP score	8.74 ± 1.33	9.53 ± 1.20	8.66 ± 1.32	**0.001**
CP class				**0.016**
A	17 (4.8%)	0 (0.0%)	17 (5.3%)	
B	253 (71.9%)	17 (56.7%)	236 (73.3%)	
C	82 (23.3%)	13 (43.3%)	69 (21.4%)	
MELD	12.62 ± 3.69	14.67 ± 4.51	12.43 ± 3.55	**0.008**
MELD-Na	16.60 ± 5.11	18.27 ± 5.78	16.45 ± 5.02	0.105
ALBI score	− 1.58 ± 0.48	− 1.51 ± 0.59	− 1.59 ± 0.47	0.391
Procedural parameters				
Stent diameter (mm)				0.701

Table 2 (continued)

Parameter	Study population ($n=352$) Mean ± SD|| frequency (%)	PTLF ($n=30$) Mean ± SD|| frequency (%)	Non-PTLF ($n=322$) Mean ± SD|| frequency (%)	p value***
8	58 (16.5%)	6 (20%)	52 (16.1%)	
10	294 (83.5%)	24 (80%)	267 (82.9%)	
PSG (pre-intervention) (mmHg)	23.80 ± 5.7	23.20 ± 3.94	23.85 ± 5.88	0.664
PSG (post) (mmHg)	8.92 ± 3.60	7.90 ± 3.56	9.02 ± 3.61	0.091
PSG reduction (mmHg)	14.88 ± 5.61	15.3 ± 4.34	14.83 ± 5.75	0.475
PSG reduction (%)	61.5 ± 15	65.9% ± 14.7	61.2 ± 15	0.082
Hemodynamic success	303 (86.1%)	27 (90%)	276 (85.7%)	0.782

Bold signifies P value <0.05

***Significant at $p<0.05$

Table 3 Clinical outcome—PTLF vs. non-PTLF

Clinical outcome	PTLF		p value
	No	Yes	
Prolonged hospital stay	71 (22.0%)	9 (30.0%)	0.362
New onset HE	36 (11.2%)	16 (53.3%)	**< 0.001**
TIPS reduction	0 (0.0%)	3 (10.0%)	**< 0.001**
Liver transplantation	0 (0%)	0 (0%)	
Death within 30 days	8 (2.5%)	15 (50.0%)	**< 0.001**

Bold significant p value <0.05

associated with PTLF. There were no statistically significant differences in procedure technical outcomes among the study groups. Hemodynamic success was achieved in 276 of 322 (85.7%) patients in non-PTLF group and in 27 of 30 (90%) in PTLF group ($p=0.782$), with median portosystemic pressure gradient reduction of approximately 15 mmHg in both groups ($p=0.475$). The results of univariate analysis are summarized in Table 2.

For multivariate logistic regression analysis, TIPS indication, history of prior HE, baseline MELD, and Child–Pugh score, which showed significant association on univariate analysis, were chosen as explanatory variables. On multivariate analysis (Table 4), the study identified two significant independent predictors of PTLF: prior HE (OR = 6.1, CI 2.57–14.5, $p<0.0001$) and baseline Child–Pugh score (OR = 1.47, CI 1.07–2.04, $p=0.0189$), while baseline MELD score (OR 1.08, CI 0.98–1.19, $p=0.132$) and TIPS indication failed to show statistical significance.

Using AUROC analysis (Table 5; Fig. 2), Child–Pugh score of > 9 (AUROC = 0.685) showed a sensitivity of 83.3% and specificity of 43.2% in predicting PTLF. MELD score of > 14 (AUROC 0.646) showed a sensitivity of 60.0% and specificity of 66.5% in predicting PTLF. There was no significant difference in the diagnostic performance of CTP Score and MELD ($p=0.533$).

90-Day Transplant-Free Survival: PTLF vs. Non-PTLF

Among the 352 patients evaluated, 31 patients died within 90 days of TIPS, and no patient underwent transplant. Of the 30 patients in PTLF cohort, 18 patients died within 90 days of TIPS, with majority dying within 30 days (15 of 18). In the non-PTLF cohort, 13 of 322 patients died within 90 days of TIPS. Causes of death among patients with PTLF included liver failure and associated complications such as multiorgan dysfunction ($n=5$), sepsis ($n=4$), gastrointestinal bleed ($n=3$) and were undetermined in the rest ($n=6$). The 90-day transplant-free

Table 4 Results of multiple logistic regression analysis to assess predictors of PTLF

Predictors	PTLF		OR (95% CI, p value)
	No	Yes	
Indication			
Ascites (reference)	218 (67.7%)	14 (46.7%)	
Bleed	95 (29.5%)	15 (50%)	2.07 (0.89–4.76, $p=0.088$)
Hydrothorax	9 (2.8%)	1 (3.3%)	1.67 (0.18–15.32, $p=0.649$)
Prior HE	28 (8.7%)	13 (43.3%)	**6.1 (2.57–14.5, $p<0.0001$)**
CTP	8.7 ± 1.33	9.53 ± 1.20	**1.47 (1.07–2.04, $p=0.018$)**
MELD	12.4 ± 3.5	14.7 ± 4.5	1.08 (0.97–1.19, $p=0.132$)

Bold signifies P value <0.05

Table 5 ROC curve analysis showing diagnostic performance of CTP and MELD score in predicting PTLF

Parameter	Value (95% CI)	
	CTP score	MELD score
Cutoff (p value)	≥9 (0.001)	≥14 (0.008)
AUROC	0.685 (0.594–0.776)	0.646 (0.531–0.762)
Sensitivity	83.3% (65–94)	60.0% (41–77)
Specificity	43.2% (38–49)	66.5% (61–72)
Positive predictive value	12.0% (8–17)	14.3% (9–22)
Negative predictive value	96.5% (92–99)	94.7% (91–97)
Diagnostic accuracy	46.6% (41–52)	65.9% (61–71)
Diagnostic odds ratio	3.8 (1.42–10.17)	2.97 (1.38–6.39)

survival rate was 40% (12 of 30) in the PTLF group, as compared to 96% (309 of 322) in the non-PTLF group (OR 0.032, CI 0.013–0.08, $p < 0.001$). Increased mortality associated with PTLF was seen in the early post-procedural period, and there was no significant difference between proportions of mortality at 30 days and 90 days ($p = 0.604$). The Kaplan–Meier survival curves at 90 days based on the presence or absence of PTLF are illustrated in Fig. 3.

Discussion

TIPS creation is associated with some degree of liver injury, mainly by the decreased antegrade intrahepatic portal perfusion and to a lesser extent by direct mechanical injury to liver parenchyma [11]. This injury may at times manifest as PTLF which is associated with grave prognosis for the patient. Acute liver failure post-TIPS or PTLF is a relatively unexplored area with only few studies specifically evaluating it. Gaba et al. (2016) proposed a definition and classification scheme of PTLF [4] that has been employed in this study.

Our study shows that incidence of PTLF is not uncommon after elective TIPS and occurs in 8.5% patients. Rouillard et al. (1998) reported that 19 of 354 (5.4%) patients developed severe hyperbilirubinemia within 1 month of TIPS creation [12]. The overall incidence of PTLF reported by Gaba et al. was 20% [4] where the baseline MELD score of the study cohort was higher as compared to our study (MELD score 17 ± 7 vs. 12.6 ± 3.7). Luca et al. (2016) reported an incidence of 9.2% for early liver failure after TIPS in cirrhosis in patients with a baseline MELD score of 12 or less [13], which is similar to the incidence reported in our study. A recent retrospective study by Yao et al. who evaluated 93 patients who underwent TIPS placement for gastroesophageal variceal bleeding reported a liver failure rate of 30.11% [14].

Many studies have evaluated predictors of survival after TIPS [15–17]; however, specific predictive factors for PTLF have not been extensively studied. This study attempted

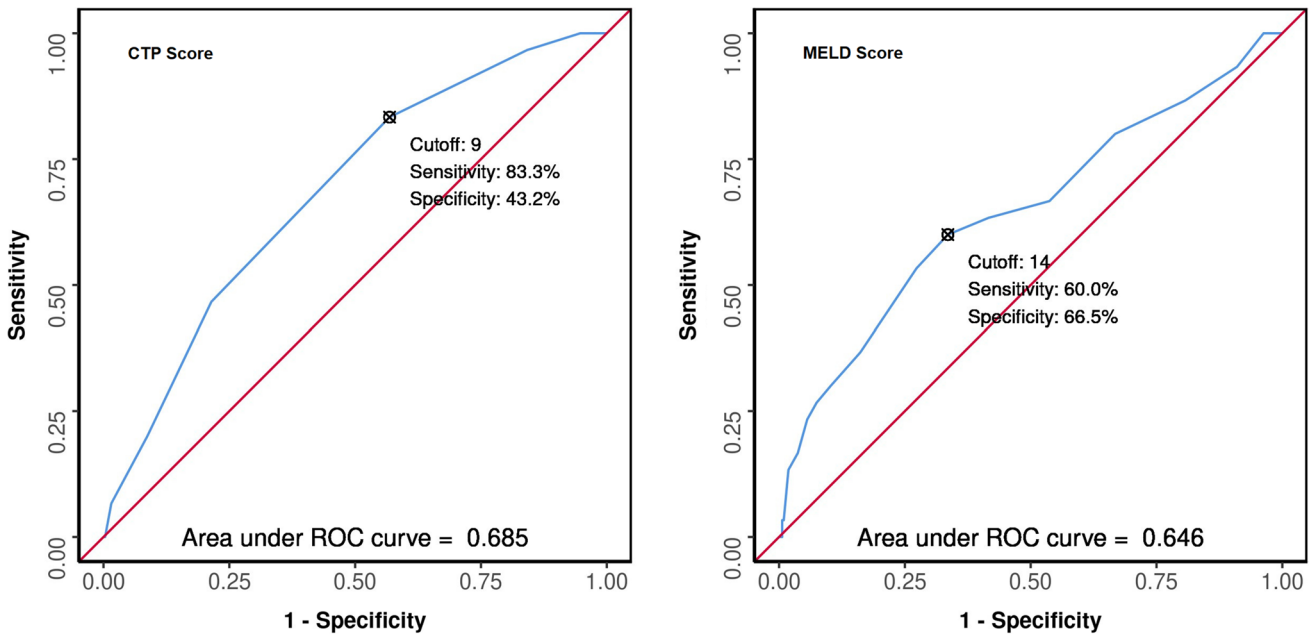

Fig. 2 ROC curve analysis for CTP score and MELD score

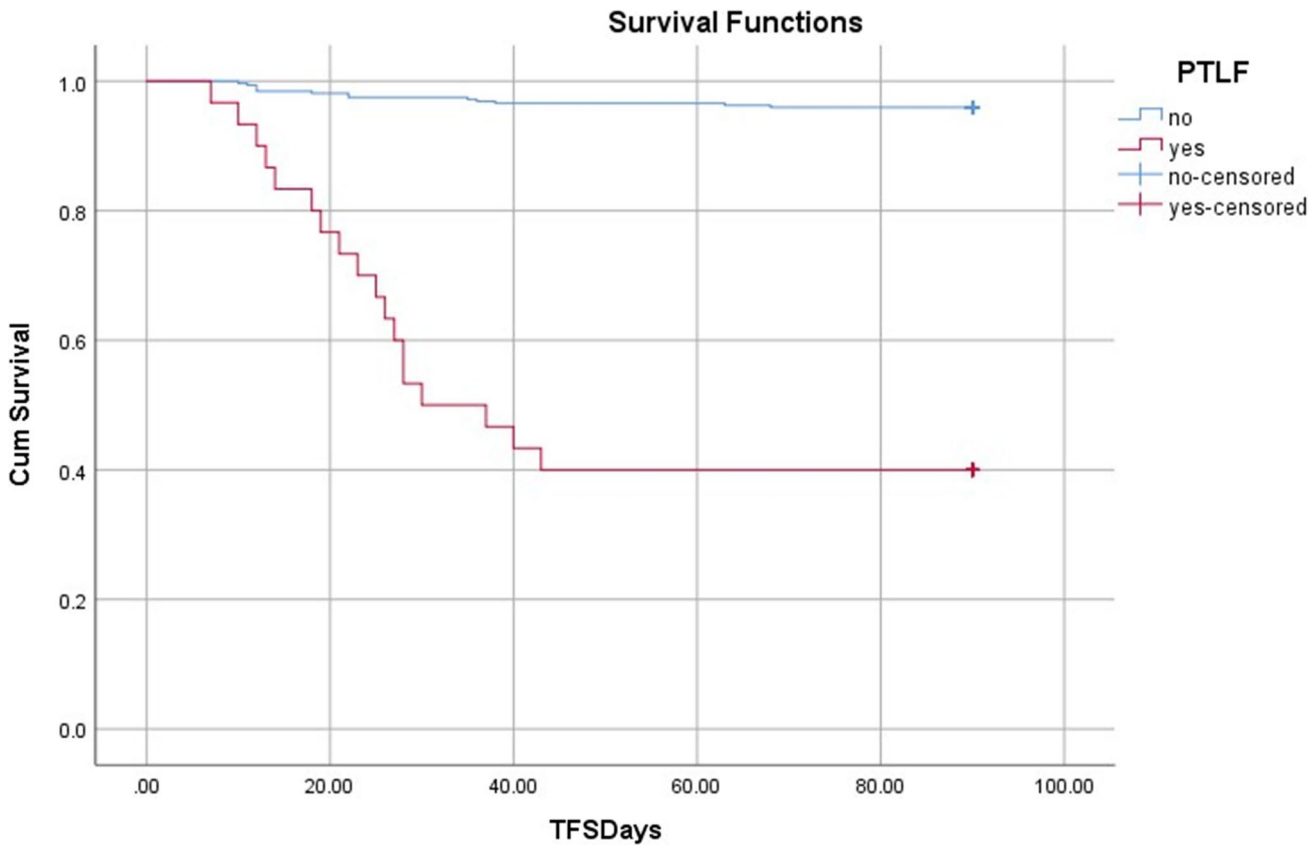

Fig. 3 Kaplan–Meier survival curve of patients with and without PTLF

to identify predictive factors for PTLF from pre and peri-procedural parameters. Univariate logistic regression revealed that the following pre-TIPS clinical or laboratory factors were associated with PTLF: indication for TIPS, prior HE, baseline higher serum creatinine, low hemoglobin levels, higher baseline MELD score, higher baseline Child–Pugh score, and Child–Pugh class. On multivariate analysis, history of prior HE (OR 6.1, CI 2.57–14.5, p <0.0001) and higher baseline Child–Pugh score (OR 1.47, CI 1.07–2.04, p=0.018) were identified as significant predictors of PTLF. Prior HE has been shown to be a robust predictor for development of post-TIPS HE in a 2011 meta-analyses by Bai et al. [18]. However, its association with PTLF has not been brought out in literature to the best of our knowledge. Pathogenesis of HE in advanced liver disease is characterized by a reversible metabolic encephalopathy most commonly attributed to circulating gut neurotoxins. Various other factors have been implicated in development of HE, including infections and liver necrosis [19]. HE is associated with poor survival and a high risk of recurrence. The higher incidence of PTLF in patients with prior HE may be due to the higher degree of liver dysfunction in these patients exacerbated by the reduction in portal perfusion following TIPS.

The study also identified CTP score as an independent predictor of PTLF. Understandably, higher CTP score/Child–Pugh class which implies worse liver function is significantly associated with development of PTLF. On AUROC analysis, a cutoff of 9 was seen to predict increased occurrence of PTLF with sensitivity of 83.3%. Higher baseline MELD score showed significant association with PTLF in univariate analysis; however, on multivariate analysis failed to show statistical significance (p=0.059). Rouillard et al. reported that Child–Pugh class C (OR 3.0, CI 0.96 to 9.4) predicted the development of severe hyperbilirubinemia within 30 days post-TIPS [12]. Luca et al. reported preoperative MELD score, low hemoglobin level, and platelet count as predictors of early liver failure after TIPS in patients with refractory ascites [13].

Higher incidence of PTLF was observed in patients with variceal hemorrhage as indication for TIPS as compared to ascites. The phenomenon of "hepatic arterial buffer response (HABR)" by which a decrease in portal venous blood flow results in an increase in hepatic arterial flow [20] has been said to occur instantly after TIPS creation [21]. Several studies have shown increased hepatic arterial resistance in advanced cirrhosis which was related to the degree of portal hypertension and portal resistance [22].

Thus, an inadequate arterial compensation response may contribute to exacerbation of hepatic ischemia brought on by sudden decrease in portal perfusion after TIPS. Variceal hemorrhage is proven to occur at higher PSG with increasing risk of rebleeding associated at higher pressures [23–25]. It is postulated that the rapid reduction in PSG from higher baseline values may result in greater degree of hepatic perfusion compromise and resultant hepatic ischemia. However, drawing definitive conclusions in this regard will require further investigation.

Patients with PTLF have significantly poor prognosis with high early mortality as compared to patients with an uncomplicated post-procedural course. Approximately, 60% patients with PTLF progressed to death within 90 days. It is also associated with higher incidence of new onset HE seen in 53% of patients as compared to 11% in non-PTLF group. The transplant-free survival rate in the PTLF group at 90 days was 40%, while in the non-PTLF group it was 96%. These findings are keeping in line with the results of Luca et al. who showed that patients with early liver failure after TIPS had a significantly lower transplant-free survival rate as compared to patients without liver failure at 6 months and 12 months (37% vs. 95% at 6 months and 24% vs. 86% at 12 months). Rouillard et al. reported that 95% of patients with severe hyperbilirubinemia either died or required liver transplantation within 90 days of TIPS [12]. Yao et al. reported a mortality rate of 17.86% among patients with variceal hemorrhage who developed liver failure post-TIPS [14].

The key strengths of this study were the large patient population available for evaluation and the high rate of follow-up. However, there were some limitations of our study. Firstly, it is a single institution, retrospective study and was dependent on medical record documentation. Second, heterogeneity in post-procedural lab follow-up was present owing to the long time period covered by the study. Third, the relatively small sample size of patients with PTLF limited the number of variables that could be assessed simultaneously in a multiple logistic regression model. Lastly, as patients in this study spanned over a long time period, technical differences in TIPS procedure and clinical care during the study period may have contributed to different clinical outcomes over time.

In summary, our data suggested that PTLF within 30 days of uneventful TIPS placement is not an uncommon complication and is associated with significant mortality and morbidity. Higher baseline CTP score, i.e., worse baseline liver function, and prior HE were identified as predictors for PTLF. PTLF was associated with significant early mortality as compared to patients with an uneventful post-procedural course. Clinical situations may necessitate that TIPS be undertaken even in patients with significant risk. However, such patients should be carefully evaluated so that the benefit provided by the procedure is not outweighed by the risk of post-TIPS liver failure.

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Declarations

Conflict of interest No conflict of interest. Authors disclosures None; Financial disclosures None.

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