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REVIEW ARTICLE

Transjugular intrahepatic portosystemic shunt in liver transplant recipients: indications, feasibility, and outcomes

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Abstract The role of transjugular intrahepatic portosystemic shunt (TIPS) for treating complications of portal hypertension after orthotopic liver transplantation (OLT) is unclear. In this review of 13 retrospective studies and 8 case reports comprising 213 patients, we assessed the indications, technical success, and clinical outcomes of TIPS procedures performed in patients who had undergone OLT. Indications for TIPS were refractory ascites ($n = 168$), variceal hemorrhage ($n = 36$), and hydrothorax ($n = 9$). Technical success was reported in 98 % of cases. Five procedures failed because of portal vein thrombosis, caval tear, technical inability, patient instability, and unknown reasons (one each). Clinical success of TIPS after OLT was 57 % in patients with refractory ascites, 69 % in those with variceal hemorrhage, and 56 % in those with hydrothorax. TIPS revision was required in 16 % of cases, while 19 % of patients underwent subsequent retransplantation. Postprocedural or worsening encephalopathy occurred in 33 % of patients. Survival analysis based on 122 cases with data available revealed a 30-day mortality rate of 11 %, a 1-year cumulative survival rate of 53 %, and a 1-year cumulative retransplantation-free survival rate of 41 %. Given the complexity of post-OLT cases with complications of recurrent portal hypertension, it is not surprising that the overall clinical success rate of TIPS was relatively low. Nevertheless, TIPS may remain a viable choice for the treatment of patients who have undergone OLT with recurrent portal hypertensive complications when medical therapy is unsuccessful.

Keywords Transjugular intrahepatic portosystemic shunt · Portal hypertension · Orthotopic liver transplantation

Abbreviations

ESLD	End-stage liver disease
IVC	Inferior vena cava
OLT	Orthotopic liver transplantation
SAE	Splenic artery embolization
TIPS	Transjugular intrahepatic portosystemic shunt

Introduction

Liver transplantation is considered an effective therapy for end-stage liver disease (ESLD). However, portal hypertension can develop in the transplanted liver due to

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recurrence of the original diseases, vascular disorders, rejection, or small-for-size syndrome after partial liver transplantation [1, 2]. In patients who receive a liver transplant, the complications of portal hypertension, such as variceal bleeding, refractory ascites, or hydrothorax, can be similar to the complications seen in patients with native cirrhotic portal hypertension; however, patients who have received a transplant have the additional burden of chronic immunosuppression, which can complicate medical management of recurrent portal hypertension. Previous studies have demonstrated the efficacy of transjugular intrahepatic portosystemic shunt (TIPS) placement in managing complications of portal hypertension in patients with native cirrhosis [3, 4]. TIPS has also been used as a bridge to liver transplantation in patients with ESLD [5–7]. However, the role of TIPS in patients who have already undergone orthotopic liver transplantation (OLT) is still largely unknown.

This purpose of this review was to analyze the literature to evaluate the indications, technical success, and outcomes of TIPS procedures performed after patients had undergone OLT with complications of portal hypertension.

Materials and methods

Literature search

To identify all studies related to TIPS performed after liver transplantation, we searched the electronic databases of Pubmed and Embase using the following terms: "transjugular intrahepatic portosystemic shunt*" or "TIPS" and "liver transplantation" or "liver transplant." All studies identified through this search were included in this analysis, including prospective and retrospective studies, case-controlled studies, case series, and case reports. The bibliographies of all identified relevant studies were used to perform a recursive search of the literature.

Data extraction

The following information was extracted for each study: location of study, study design, number of patients in each study, age and sex of patients, results of liver biopsy before TIPS placement, indication for TIPS procedure, time from liver transplantation to TIPS placement, technical success or failure of the TIPS procedure, number of cases requiring TIPS revision, occurrence of procedure-related complications (including hepatic encephalopathy), clinical improvement of underlying indication for TIPS, and number of retransplantations and deaths.

Statistical analysis

The quality of clinical studies and case reports was assessed with the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) approach, with study and report quality categorized as high, moderate, low, or very low [8]. Survival analysis was performed for studies with the necessary data available. Cumulative survival was determined with the Kaplan–Meier method, and the survival difference between patients with variceal bleeding and those with refractory ascites was determined with a log-rank test. Logistical regression analysis was used to identify possible factors influencing survival, including age, sex, and time interval from OLT to TIPS. SPSS 17.1 software (SPSS, Chicago, IL, USA) was used for all analyses.

Results

The literature search revealed a total of 21 reports that met the criteria; these reports were published from 1999 to 2013 and included 13 retrospective studies [7, 9–20] and 8 case reports [21–28], involving a total of 213 patients. According to the GRADE system, the quality of evidence of the included studies was as follows: 13 low and 8 very low. The median duration from transplantation to TIPS procedure was 18 months (range = 0.3–192 months), based on data available for 72 cases. The indications for liver transplantation among the 213 patients were hepatitis C (55 %; $n = 116$), alcoholic cirrhosis (8 %; $n = 18$), primary biliary cirrhosis (7 %; $n = 16$), hepatitis B (3 %; $n = 7$), and other indications (27 %; $n = 56$). The indications for TIPS among the 213 study patients were refractory ascites (79 %; $n = 168$), variceal bleeding (17 %; $n = 36$), and hydrothorax (4 %; $n = 9$) (Table 1). Three different stent types were reported in the studies, including Wallstent (32 cases), Viatorr Gore stents (26 cases), combined Wallstent or Viatorr Gore stents (29 cases), and uncoated 8/39 Corinthian-Stent (1 case). Nine studies did not report information on the stent type (125 cases).

Results from a biopsy performed before TIPS placement were available for 63 patients. Among these patients, recurrent hepatitis C was the most common finding (57.1 %; $n = 36$), with a median interval from OLT to TIPS of 19.5 months (range = 5–120 months). The second most common finding was biliary cirrhosis (12.7 %; $n = 8$), with a median interval from OLT to TIPS of 14 months (range = 4–192 months). Various vascular etiologies were reported in 7 cases (11.1 %), including veno-occlusive disease ($n = 5$), Budd–Chiari syndrome ($n = 1$), and thrombosis of the portal vein at the anastomosis ($n = 1$), with a median interval from OLT to TIPS of 2.7 months

Table 1 Main characteristics of included studies

Reference	Location	Study design	Number of patients (sex)	Age (years)	Indications for TIPS	Duration from OLT to TIPS (months)
Schemmer et al. [25]	Germany	Case report	1 (M)	21	Variceal bleeding, 1	24
Senzolo et al. [26]	United Kingdom	Case report	2 (1 M; 1 F)	55/57	Variceal bleeding, 2	35/13 days
Cura et al. [22]	United States	Case report	1 (M)	50	Variceal bleeding, 1	48
Kitajima et al. [23]	United States	Case report	2 (1 M; 1 F)	67/58	Refractory ascites, 2	7.3/2.2
Miraglia et al. [24]	Italy	Case report	1	18	Variceal bleeding, 1	192
Wang et al. [27]	Baltimore	Case report	1 (M)	44	Variceal bleeding, 1	120
Campos-Varela et al. [21]	Spain	Case report	1 (M)	54	Refractory ascites, 1	2.7
Xiao et al. [28]	China	Case report	1 (M)	56	Refractory ascites, 1	Not available
Amesur et al. [10]	United States	Retrospective	12 (8 M; 4 F)	45 (33–58)	Refractory ascites, 6; variceal bleeding, 6	64.5 (6–150)
Lerut et al. [18]	Italy	Retrospective	8	Not available	Refractory ascites, 6; variceal bleeding, 1; hydrothorax, 1	Not available
Abouljoud et al. [9]	United States	Retrospective	8 (5 M; 3 F)	54 ± 8	Refractory ascites, 8	11.5 (2–36)
Van Ha et al. [20]	United States	Retrospective	6 (4 M; 2 F)	5–67	Refractory ascites, 5; variceal bleeding, 1	14.5 (3–113)
Vasta et al. [7]	Italy	Retrospective	5	Not available	Refractory ascites, 5	10–180 days
Kim et al. [16]	United States	Retrospective	14 (4 M; 2 F)	52 (13–68)	Refractory ascites, 8; variceal bleeding, 6	46 (3–183)
Choi et al. [11]	United States	Retrospective	19 (15 M; 4 F)	51 (16–63)	Refractory ascites, 17; variceal bleeding, 2	2.3 (0.5–46.7)
Finkenstedt et al. [14]	Austria	Retrospective	10 (7 M; 3 F)	57 (37–71)	Refractory ascites, 8; variceal bleeding, 1; hydrothorax, 1	13 (4–158)
El Atrache et al. [12]	United States	Retrospective	15 (10 M; 5 F)	55 ± 12	Refractory ascites, 12; variceal bleeding, 2; hydrothorax, 1	21 (2–96)
Ghinolfi et al. [15]	Spain	Retrospective	19 (14 M; 5 F)	55 ± 6	Refractory ascites, 13; hydrothorax, 6	21 (5–50)
Feyssa et al. [13]	United States	Retrospective	26 (20 M; 6 F)	49 (35–61)	Refractory ascites, 26	17 (1–89)
King et al. [17]	United Kingdom	Retrospective	22 (9 M; 13 F)	49 (29–78)	Refractory ascites, 14; variceal bleeding, 8	44.8 (0.3–143)
Saad et al. [19]	United States	Retrospective	39 (29 M; 10 F)	54 (17–65)	Refractory ascites, 36; variceal bleeding, 3	29 (2–127)

(range = 0.3–7.3 months). Biopsies also identified 2 cases of chronic rejection, 2 cases of small-for-size syndrome, and 1 case each of chronic active hepatitis, fibrotic disease, recurrent sarcoidosis, recurrent hepatitis B, and recurrent vascular proliferation nodular regenerative hyperplasia. The biopsy findings were unreported in 3 cases.

Outcomes after TIPS

Technical success of the TIPS procedure was achieved in 208 patients (98 %) (Table 2). The procedure failed in four patients because of portal venous thrombosis ($n = 2$), inferior vena cava (IVC) tear ($n = 1$), or technical inability and patient instability ($n = 1$); the cause of failure was unknown in 1 additional case. Thirty-four patients required TIPS revision because of shunt dysfunction. After the TIPS procedure, 40 patients eventually underwent retransplantation for unspecified indications ($n = 21$), failed TIPS procedure ($n = 6$), recurrent hepatitis C ($n = 5$), graft failure with or without multiorgan failure ($n = 5$), liver donor availability in those patients who had planned retransplantation before TIPS procedure ($n = 2$), or hepatic artery thrombosis ($n = 1$).

Refractory ascites was completely or partially resolved in 96 (57 %) of 168 patients, variceal bleeding was controlled in 25 (69 %) of 36 patients, and hydrothorax was

Table 2 Clinical outcomes of each study

Reference	Technique success, n (%)	Revision, *n*	Clinical efficacy, *n*	Retransplantation, *n*	Death, *n*	Survival, *n*	Hepatic encephalopathy, *n*
Schemmer et al. [25]	1 (100)	0	Variceal bleeding, 1	1	0	1	Not available
Senzolo et al. [26]	2 (100)	0	Variceal bleeding, 2	0	0	2	Not available
Cura et al. [22]	1 (100)	1	Variceal bleeding, 1	0	1	0	Not available
Kitajima et al. [23]	2 (100)	0	Refractory ascites, 1	1	0	2	Not available
Miraglia et al. [24]	1 (100)	0	Variceal bleeding, 1	0	0	1	0
Wang et al. [27]	1 (100)	0	Variceal bleeding, 1	0	1	0	Not available
Campos-Varela et al. [21]	1 (100)	0	Refractory ascites, 1	0	0	1	0
Xiao et al. [28]	1 (100)	0	Refractory ascites, 1	0	1	0	0
Amesur et al. [10]	12 (100)	3	Refractory ascites, 1; variceal bleeding, 4	5	4	8	2
Lerut et al. [18]	8 (100)	Not available	Refractory ascites, 5; variceal bleeding, 1; hydrothorax, 1	0	5	3	6
Abouljoud et al. [9]	8 (100)	1	Refractory ascites, 7	2	3	5	Not available
Van Ha et al. [20]	6 (100)	2	Refractory ascites, 5	2	2	4	Not available
Vasta et al. [7]	5 (100)	2	Refractory ascites, 1	3	0	5	0
Kim et al. [16]	11 (78.6)	0	Refractory ascites, 4; variceal bleeding, 2	0	10	1	9
Choi et al. [11]	18 (95)	5	Refractory ascites, 8; variceal bleeding, 2	6	9	9	Not available
Finkenstedt et al. [14]	10 (100)	3	Refractory ascites, 5; variceal bleeding, 1	1	9	1	7
El Atrache et al. [12]	15 (100)	3	Refractory ascites, 7	4	7	8	2
Ghinolfi et al. [15]	19 (100)	1	Refractory ascites, 13; hydrothorax, 4	0	14	5	6
Feyssa et al. [13]	26 (100)	5	Refractory ascites, 15	2	16	10	10
King et al. [17]	22 (100)	8	Refractory ascites, 11; variceal bleeding, 6	2	15	7	Not available
Saad et al. [19]	38 (97)	Not available	Refractory ascites, 11; variceal bleeding, 3	11	17	21	7
Total	208 (98)	34	Refractory ascites, 96; variceal bleeding, 25; hydrothorax, 5	40	114	94	49

resolved in 5 (56 %) of 9 patients. Hepatic encephalopathy was reported in 12 studies, with a total of 49 new-onset or worsening cases (33 %; 49/152). Hepatic encephalopathy was controlled medically in 30 cases (61 %), TIPS reduction was required in 4 cases, and retransplantation in 2 cases. Death occurred in 2 cases, 1 as a result of aspiration pneumonia and the other as a result of renal failure. Both these patients had unresolved encephalopathy. Overall, death was reported in a total of 114 cases.

Severe procedure-related complications were reported in five cases. Caval tear was reported in one case, resulting in hemodynamic instability; the TIPS procedure was aborted in this case [16]. Graft failure was reported in one patient due to multiorgan failure after the TIPS procedure; this patient underwent an emergency retransplantation with an organ from a deceased donor [19]. Acute liver infarction developed in one patient [27]. In another patient, ischemic hepatitis developed but later resolved spontaneously [17]. Death occurred in one patient 35 days after the TIPS procedure due to sepsis [15].

Survival analysis

Survival analysis was based on a total of 122 patients from 18 reports for which individual patient survival information was available. Of these 122 patients, 66 patients died as a

result of graft failure or multiorgan failure ($n = 56$), hepatocellular carcinoma ($n = 3$), lung cancer ($n = 2$), thrombocytopenia ($n = 1$), chronic rejection ($n = 1$), necrotic pancreatitis ($n = 1$), complications of kidney biopsy ($n = 1$), and congestive heart failure ($n = 1$). A total of 25 patients among these 122 cases underwent subsequent retransplantation after TIPS for unknown causes ($n = 6$) or because of a failed TIPS procedure ($n = 6$), recurrent hepatitis C ($n = 5$), graft failure ($n = 5$), liver donor available ($n = 2$), or thrombosed hepatic artery ($n = 1$).

The median survival time after TIPS among these patients was 19 months (range = 0.1–100 months). The 30-day mortality rate was 11 %, and the 6-month, 1-year, and 5-year cumulative survival rates were 62, 53, and 31 %, respectively (Fig. 1). The 1-year cumulative survival rate was 54 % for patients with refractory ascites and 44 % for patients with variceal bleeding; there was no significant difference between the groups ($p = 0.418$; Fig. 2). The 1-year cumulative retransplantation-free survival rate was 41 % among 122 patients (Fig. 3). There was no significant association between the interval from OLT to TIPS and patient survival ($p = 0.80$; based on 46 cases). There were also no significant associations between patient survival and patient age ($p = 0.09$; based on 56 cases) or sex ($p = 0.50$; based on 56 cases).

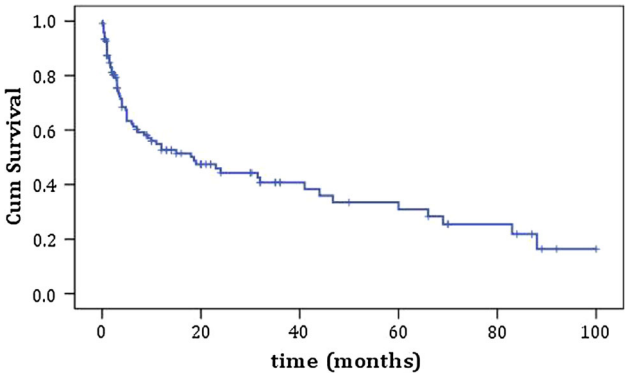

Fig. 1 Survival curve for those 122 patients with individual data available

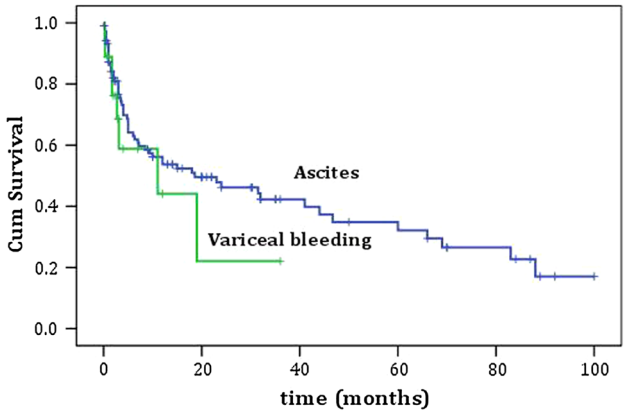

Fig. 2 Comparison of patient survival in patients with refractory ascites and those with variceal bleeding

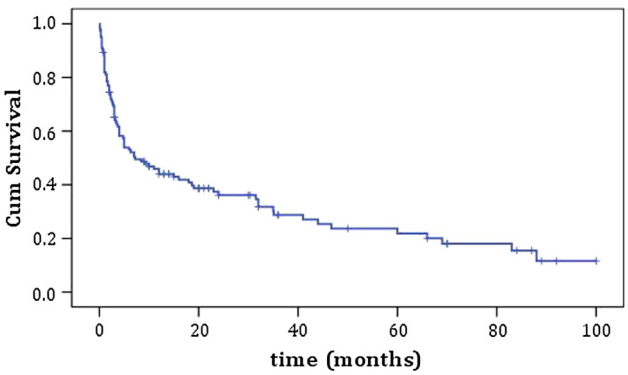

Fig. 3 Retransplantation-free survival curve for those 122 patients with individual data available

Discussion

Portal hypertension can occur after liver transplantation and has been associated with recurrence of the original disease, hepatic vein outflow obstruction, portal vein stenosis, chronic rejection, and small liver donor size [2]. The TIPS procedure is an important part of the current armamentarium used to treat the complications of portal hypertension in native cirrhosis or as a bridge for pre-transplant patients. The TIPS procedure is used to decompress the portal venous system and therefore prevent rebleeding from varices or to reduce the formation of ascites/hydrothorax. Although the TIPS procedure has been widely used to treat ascites and variceal bleeding, the role of TIPS in patients who have undergone OLT has not been fully investigated.

The TIPS procedure can be technically challenging to perform in patients who have undergone OLT due to anatomical changes after transplantation, particularly in cases usingthe cavo-caval technique (aka the "piggyback" technique, in which the donor's retrohepatic IVC is anastomosed in an end-to-side or side-to-side fashion to the recipient's IVC) [29]. Understanding the surgical anatomy of a liver transplant is key when a clinician is attempting to penetrate the portal vein. Our analysis demonstrated that the TIPS procedure can be successfully completed in 98 % of such cases.

In this study, refractory ascites was the most common indication for TIPS placement in patients who had undergone OLT. Only 57 % of refractory ascites cases in this study completely or partially resolved after the TIPS

procedure. In cases of refractory ascites in native cirrhotic livers, TIPS has been reported to be more effective (69–89 %) [30–34]. The lower success rate observed in our study may have been multifactorial but was most likely the result of significant reduction in renal function from calcineurin use [35], which occurs early after OLT, as well as the longer term effect of hepatitis C and diabetes on renal function.

Proximal splenic artery embolization (SAE) has recently been studied as an alternative to TIPS for the treatment of refractory ascites in patients who have undergone OLT. Quintini et al. [36] reported that six patients experienced significant postprocedural weight loss and a dramatic decrease in diuretic requirements and that five patients achieved a complete resolution of ascites a median of 49.5 days after proximal SAE. The authors suggested that proximal SAE may reduce portal hyperdynamic circulation by reducing the splenic vein flow. This raises the question as to which population of OLT patients with portal hypertension should be considered for the SAE procedure as an alternative to TIPS (e.g., possibly for patients in whom refractory ascites may be the result of persistent portal hyperdynamic hypertension rather than increased resistance from the portal venous return) [37]. It is likely that the population of patients who will benefit from SAE will be small.

Our analysis showed a variceal bleeding control rate of 70 %, similar to that seen in patients with native liver cirrhosis (75–100 %) [3, 38–40]; however, the case number in this study was low, so we cannot exclude the possibility of bias. The incidence of postprocedural hepatic encephalopathy in study patients was 33 % compared with 29–55 % in patients with native cirrhotic liver [3, 39–44]. More than half of the hepatic encephalopathy cases in this study were responsive to standard medical therapy, but TIPS reduction or retransplantation may be required for cases that do not respond to conservative treatment.

Our study found that there was an association between patient survival and indications. The 1-year cumulative survival rate in this study was 54 % for patients who underwent TIPS for refractory ascites compared to a 1-year survival rate of 80–85 % for OLT patients overall [45] and 63 % for patients with native cirrhosis who underwent TIPS [34]. However, the 1-year survival rate for patients who underwent TIPS after OLT for variceal bleeding was significantly lower (44 %) than the rate in patients with native cirrhosis (80 %) [3, 38, 43]. These results suggest that portal hypertension in patients who have undergone OLT is a progressive condition and that TIPS placement will not affect the course of the process that leads to recurrent cirrhosis after OLT. Because recurrent hepatitis C is the primary disease leading to the need for TIPS after OLT, effective antiviral therapy is clearly also needed, as the use of direct-acting antiviral agents after OLT will not only prevent the progression of hepatitis C but may also reverse the degree of established fibrosis [46].

This analysis was limited by its small sample size and retrospective nature. Furthermore, the cases spanned 14 years (1999–2013), making generalization difficult as both transplant outcomes and TIPS procedures have changed considerably over the past decade.

In conclusion, refractory ascites is the most common indication for TIPS placement in patients who have undergone OLT. The technical success rate with TIPS is high, but clinical improvement is low, with a rate of encephalopathy similar to that seen in pretransplant patients with portal hypertension. The rate of early death with TIPS is comparable to the rate in patients with native cirrhosis, whereas the long-term survival rate is lower than that of patients with native cirrhosis. Nevertheless, TIPS may remain a viable choice for the treatment of patients who have undergone OLT with recurrent portal hypertensive complications when medical therapy is unsuccessful.

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Conflict of interest Bin Chen, Weiping Wang, Matthew D. Tam, Cristiano Quintini, John J. Fung, and Xiao Li declare that they have no conflicts of interest to disclose.

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