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Review article

Transjugular intrahepatic portosystemic shunt as a bridge to liver transplant: Current state and future directions

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ABSTRACT

Liver transplantation is one of the mainstays of treatment for liver failure due to severe chronic liver disease. Bridging therapies, such as placement of a transjugular intrahepatic portosystemic shunt (TIPS), are frequently employed to control complications of portal hypertension such as ascites, hydrothorax, and variceal bleeding, and thereby reduce morbidity in patients awaiting transplant. There is no significant difference seen in either graft survival or patient survival between those receiving TIPS pre-transplant and those who do not, although those receiving TIPS placement on average have a longer waiting time on the transplant waitlist. Locoregional therapies, such as thermal ablation or chemoembolization, can be efficacious in patients with HCC and pre-existing TIPS; however there is a risk for increased adverse events in patients receiving these therapies who have TIPS compared to those who do not. In summary, TIPS is a safe, effective treatment that can be used to ameliorate the complications that are sequelae of portal hypertension. While it does not appear to improve survival post-transplant, TIPS placement pre-transplant may increase survival time to transplant, thus improving overall survival as well as quality of life.

Contents

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1. Introduction

Liver transplantation in humans has evolved from a dangerous eleventh-hour experimental procedure to one of the mainstays of treatment for liver failure due to acute or chronic liver disease, with one-year survival rates often over 90% [1,2]. The main indications for liver transplant include liver failure due to advanced cirrhosis from a variety of etiologies, liver neoplasms, and metabolic disorders such as Wilson's disease and alpha-1 anti-trypsin deficiency and for acute fulminant liver failure.

In 2015, the Organ Procurement and Transplant Network (OPTN) reported 7127 liver transplants in adults, with the vast majority of organs (95.0%) coming from deceased donors and the rest (5.0%) from living donors. Although this was the first time that adult liver transplants had surpassed 7000, approximately 14,000 patients in the United States still remained on the liver transplant waiting list [3]. The median waiting time for patients with Model for End-Stage Liver disease (MELD) score > 35 was 8 days. For patients with lower MELD scores of 15–35, the median waiting time in 2015 was 11.1 months [3].

While patients are waiting for their transplant, bridging therapies are often employed to control symptoms or reduce morbidity of chronic liver disease. A transhepatic intrajugular portosystemic shunt (TIPS) is the most commonly used bridging therapy regardless of the etiology of chronic liver disease, although loco-regional treatments (LRT), such as transarterial chemoembolization (TACE), radiofrequency ablation (RFA), and cryoablations are frequently used in patients with hepatocellular carcinoma (HCC) to decrease tumor burden and improve quality of life [4]. As TIPS is the most common and general bridging therapy prior to liver transplantation, this review article aims to explore the world of TIPS and the related outcomes in those receiving this procedure while awaiting liver transplant.

2. Transhepatic intrajugular portosystemic shunt

Although the origins of TIPS date back to the 1960's [5], the first reported use of the procedure in humans was not until 1989 [6]. Since the TIPS shunt was first introduced, both the materials used and the methods involved in its successful placement have improved. The first procedures were performed with bare metal stents, followed by covered stents and most recently, polytetrafluoroethylene-covered stents [7]. As described more fully by others, TIPS connects the high-pressure portal vein to the low-pressure hepatic venous system, thus allowing for decompression of the portal venous system and reducing portal hypertension. The target for reduction in the hepatic venous portal gradient (HVPG) following TIPS placement is to reduce the gradient to <12 mmHg.

2.1. Indications for TIPS

TIPS is indicated to treat several sequelae of portal hypertension (Fig. 1). Multiple cohort studies and randomized controlled trials have shown the effectiveness of TIPS for secondary prevention of variceal bleeding and for the treatment of refractory ascites [8–15]. According to the Clinical Practice Guidelines of the European Association for the Study of the Liver (EASL), TIPS in patients with ascites should be reserved for patients with frequent requirement of large-volume paracentesis, in those with loculated ascites, and for those in whom paracentesis is otherwise ineffective [16].

While is there is not as much documentation of its effectiveness in the literature, TIPS has also been used for the treatment of recurrent hepatic hydrothorax [17–20], hepatorenal syndrome [21,22], and Budd-Chiari syndrome [23–25]. Although several studies have shown improved outcomes with TIPS intervention, the majority lacked a control group of patients for comparison and therefore are not as reliable. TIPS placement has also been used to treat acute variceal hemorrhage that is refractory to endoscopic sclerotherapy [26,27].

2.2. Contraindications

Absolute contraindications to TIPS placement include the primary prevention of variceal bleeding, congestive heart failure, severe tricuspid regurgitation (indicative of pulmonary hypertension, see below), multiple hepatic cysts, uncontrolled systemic infection or sepsis, and unrelieved biliary obstruction. Severe pulmonary hypertension (mean pulmonary arterial pressures >45 mmHg) is also a contraindication [28].

Relative contraindications include anatomical variants or conditions that might complicate the placement of the shunt, such as hepatomas, especially if central; obstruction of all hepatic veins; portal vein thrombosis; severe coagulopathy (INR > 5); thrombocytopenia of <20,000/cm^3, and moderate pulmonary hypertension [28]. The difficulty of placing the shunt must be compared against the benefits that the patient will receive. In certain cases the improvement in clinical outcomes may exceed the risk of placing a shunt in an otherwise high risk patient, such as palliative TIPS placement in patients with hepatomas, patients with refractory variceal bleeding, or recanalization of occluded portal veins [28].

2.3. Effectiveness of TIPS

TIPS has been shown to be effective in the prevention of rebleeding from gastric and ectopic varices (including intestinal, stomal, and anorectal varices). Rossle et al. [29]. found the risk of rebleeding following TIPS revision in patients whose hepatic venous pressure gradient (HVPG) had been reduced by 0%, 25% - 50%, and > 50% to be 18%, 7%, and 1% respectively (see Fig. 2). Another study, conducted by Urata, saw a 1-year rate of rebleeding of 11% in patients with a 50% reduction in the initial HVPG and a 31% probability of rebleeding in the first year in patients with a lesser degree of HVPG reduction [14]. Sanyal et al. [8] showed equivalence between TIPS and endoscopic sclerotherapy in terms of reducing the risk of rebleeding.

Following TIPS placement, roughly 61% to 69% of patients have improvement in their ascites, as compared to 0–18% of patients treated with paracentesis [10,11]. Recurrent ascites may be seen in up to 42% of patients treated with TIPS, while patients treated with other therapies (paracentesis or diuretics) showed recurrence rates of 84–89% [13,30]. Multiple primary studies have shown a significant improvement in ascites (39–84%) in patients treated with TIPS as compared to those treated solely with medical therapy and large-volume paracentesis [9–13]. A series of meta-analyses also showed reduced recurrence of ascites in patients treated with TIPS [30–34].

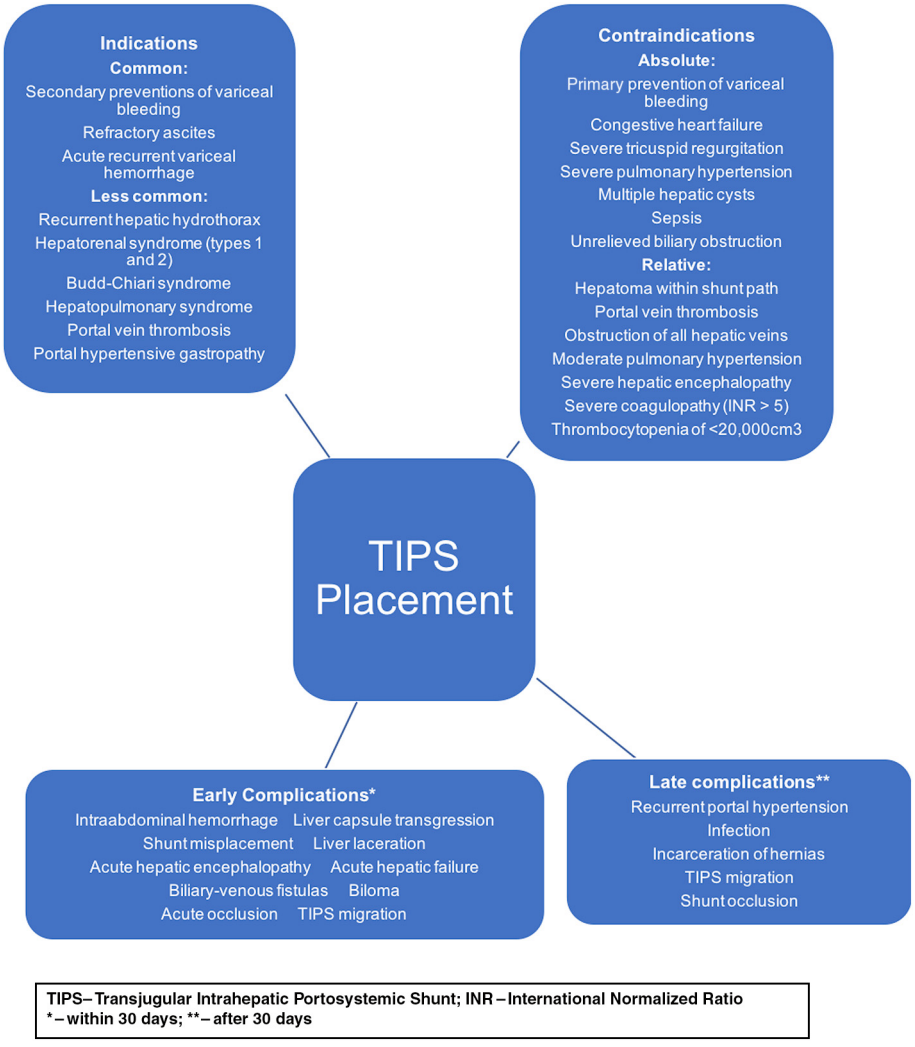

Fig. 1. Indications, contraindications, and complications of TIPS.

There is no consensus on the impact of TIPS on survival in patients with severe liver disease. Multiple studies saw no improvement in survival in patients treated with TIPS for refractory ascites in comparison to patients treated with large-volume paracentesis (LVP) [9,10,12,13].

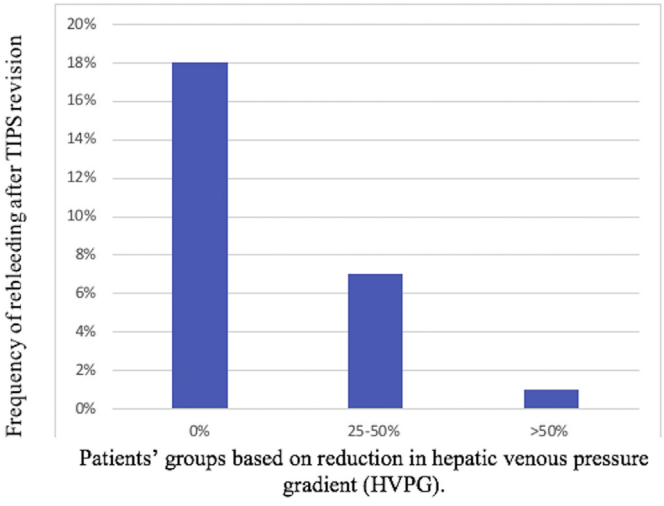

Fig. 2. Risk of rebleeding following TIPS revision by reduction in HVPG. *Data from Rossle* [29].

Endoscopic sclerotherapy has been shown to achieve higher survivals than treatment with TIPS [8]. However, other researchers have found that TIPS placement does improve survival when compared to medical treatment or more conservative options. For example, Rossle et al. [11] found the probability of survival without liver transplantation was 69% and 58% at one and two years respectively in the TIPS treatment arm vs. 52% and 32% in the paracentesis treatment arm ($p = 0.11$).

2.4. Complications of TIPS

Despite the effectiveness of TIPS, there are two main concerns that remain: namely restenosis of shunts and development or recurrence of hepatic encephalopathy. In recent years, the development of expanded polytetrafluoroethylene (e-PTFE)-covered stents had led to improvements in TIPS patency and decreased shunt stenosis. Historically, the patency of TIPS when performed with bare metal stents was found to be 30–70% at 6–12 months [35]. With the use of e-PTFE stents, however, patency rates have been found to approach 80–90% at 12 months and 70 to 80% at 24 months [35].

Another frequent issue that occurs in the acute phase post-TIPS is the development or recurrence of hepatic encephalopathy (HE), with rates of hepatic encephalopathy in patients as high as 42–55% [14,31]. This remains a significant concern following TIPS because the shunt directs nutrient-rich blood from the portal vein to the hepatic veins, bypassing the liver parenchyma. As a result, ammonia and other compounds are not taken up and metabolized by hepatocytes, leading to

increased concentrations of ammonia in the blood and thus a higher risk of hepatic encephalopathy [36]. The North American Study for the Treatment of Refractory Ascites found higher rates of acute moderate to severe hepatic encephalopathy with TIPS placement and medical management compared to patients treated with medical management (a loop diuretic in combination with a distal-acting diuretic) alone, with an incidence of 38% in the TIPS group vs. 21% in the control group [13]. However, these differences were not statistically significant ($p = .058$). Higher rates of new or worsened hepatic encephalopathy also occured in TIPS patients as compared to those treated with large-volume paracentesis (LVP): 20–60% of patients w/ TIPS vs. 0–43% of pts. treated with LVP [9–12]. In a meta-analysis, Papatheodoridis saw hepatic encephalopathy in 34% of TIPS recipients as compared with 19% of patients treated with endoscopic sclerotherapy (Odds ratio 0.43; 95% CI: 0.30–0.60; $p < .001$) [37].

The first line treatment for post-TIPS HE is standard medical management. When that fails, it has been proposed that endovascular shunt reduction may be key to improving and controlling symptoms [36]. However, the ultimate treatment for post-TIPS HE is liver transplant.

Other early complications of TIPS include acute intrabdominal hemorrhage, liver capsule transgression, acute hepatic failure, and biliary complications [38]. Some patients may develop an acute exacerbation of their pulmonary vascular pressures and right ventricular dysfunction that can increase hepatic congestion. Renal insufficiency can develop as a result of contrast nephropathy, and in patients with marginal renal function sparing of contrast can be accomplished with procedures performed with carbon dioxide instead of standard contrast agents.

Late complications of TIPS placement include TIPS stenosis with recurrent portal hypertension, which can lead to recurrent ascites or variceal bleeding, infection, and incarceration of existing abdominal wall hernias [38]. Occlusion and/or migration of the stent can occur either acutely in the early period or as a later complication. For a schematic of the indications, contraindications, and complications of TIPS placement in patients with portal hypertension, refer to Fig. 1.

3. TIPS prior to OLT

Roughly 14% of patients undergoing liver transplantation will first undergo TIPS placement [39,40]. TIPS is described as a bridging therapy to transplant because it is a stop-gap measure. While shunt placement decompresses the portal circulation and decreases the HPVG, it does not treat the etiology of the portal hypertension; it improves the symptoms but not the cause.

3.1. Intraoperative outcomes of the liver transplantation

3.1.1. Intraoperative time

No differences in intraoperative time were seen by 10 of the studies reviewed [41–50]. However, Valdivieso et al. compared 825 OLT patients (49 with pre-transplant TIPS, 776 without) and found that the TIPS group had increased total surgery time, as well as increased hepatectomy time, anhepatic phase time, caval anastomosis time, and portal anastomosis time [51]. Median warm and cold ischemia times were similar between the groups (TIPS vs non-TIPS; median warm ischemia time, 29 min vs 28 min, p = NS; median cold ischemia time 323 min vs 295 min, p = NS). Of note, 32.5% of TIPS (16 pts) in this study were found misplaced or otherwise in malposition at the time of transplant, which is on the higher end of the proportion of malpositioned TIPS in the studies reported here, although Guerrini also reported high rates of TIPS migration at the time of transplantation (17 patients, 27.9%) [52]

3.1.2. Blood product requirements

Intraoperative blood requirements were evenly distributed between post-TIPS and no-TIPS patients. The majority of studies reported no significant differences in blood product requirements during transplantation [42–45,47,48,50,53]. One exception to this was the study performed by Tripathi, et al., who found transfusion requirements to be greater in patients with TIPS where the placement of the TIPS led to technical difficulties during transplantation [46]. Valdivieso also found that the TIPS group utilized increased numbers of packed red blood cells (median 6 units) and plasma (median 14.5 units) compared to the non-TIPS group (median 4.0 units, $p = 0002$; and median 13.5 units, $p = .31$ respectively) [51]. Antonini reported similar total blood product requirements between the TIPS and non-TIPS groups until the hepatic phase of the surgery was reached [41]. Freeman noticed a trend toward decreased blood requirements in TIPS patients, but it was not significant [49].

3.1.3. TIPS migration and misplacement

One of the most frequent intraoperative complications revolved around the location of the shunt at the time of transplant. Rates of TIPS migration or misplacement ranged from 1.6–32.5% [51,54], but in the majority of cases, transplant surgery was able to continue without severe complications. In a study examining 72 transplant patients post-TIPS and 136 without TIPS, Barbier et al. found 10% of TIPS occluded and 32% misplaced at the time of transplant, which led to difficult shunt removal in 17% of TIPS and necessitated vena cava clamping in 10% [43]. Intra-operative portocaval anastomosis was also required more frequently in TIPS than non-TIPS; however, shunt occlusion or misplacement were not associated with higher intra-operative or post-operative complication rates [43]. Another study reported that temporary intraoperative portocaval shunt or bypass were required in 20 out of 31 TIPS patients (64.5%) and 20 out of 55 non-TIPS patients (36.4%); however, these differences were not statistically significant [42].

TIPS complicated the operating course in 22% of one small cohort (5 out of 23 patients), in part due to shunt misplacement and damage of the vascular intima the site of anastomosis. In one of these five patients, TIPS placement led to bile duct perforation at the time of placement with subsequent diffuse biliary peritonitis [53]. Zhou et al. [48] reported that one out of 5 patients undergoing liver transplantation post-TIPS had a shunt extending into the portal vein, which required division of the stent with the recipient portal vein for successful removal. While Gandini et al. [55] noted no occluded or misplaced stents, they did experience difficult stent removal in 2 cases (12.5%). However, complete extraction was still achievable despite extensive vein-wall encapsulation.

3.2. Immediate post-operative outcomes of the liver transplantation

3.2.1. Post-operative complications

Barbier saw increased post-operative ascites in TIPS patients post-transplant vs non-TIPS patients (7.6 L vs 6.9 L, $p = .036$) [43]. Castellani et al. [42] also reported higher amounts of total ascites on days 0–7 post-transplant in TIPS patients vs non-TIPS patients. Although Moreno and Valdivieso both reported no significant differences in postoperative complications in liver transplant patients with and without TIPS, Tripathi found higher rates of dialysis required in TIPS patients vs non-TIPS patients (41.3% vs 9.4%, $p < .0001$) and less frequent post-op pulmonary infections in TIPS patients ($p < .05$) [45,46,51].

3.2.2. Hospital length-of-stay

The majority of studies examined did not find any significant difference in length of days spent in the ICU [45,47,51,52] (See Fig. 3a) or total days spent in the hospital [43,45,47–51,56,57] (See Fig. 3b) between TIPS and non-TIPS groups during the transplant admission. While Tripathi reported a significantly longer hospital length-of-stay in the TIPS group (40.7 ± 7.6 days) vs the control group (26.3 ± 3.6 days, $p < .005$), upon additional subgroup analysis, it was concluded that this extended hospital stay was likely due to patients with Child-Pugh C disease [46]. However, in reviewing the UNOS database, Mumtaz concluded that pre-transplant TIPS added 2.16 days to the overall hospital stay (95% CI: 0.92–3.38, $p = .001$) [58].

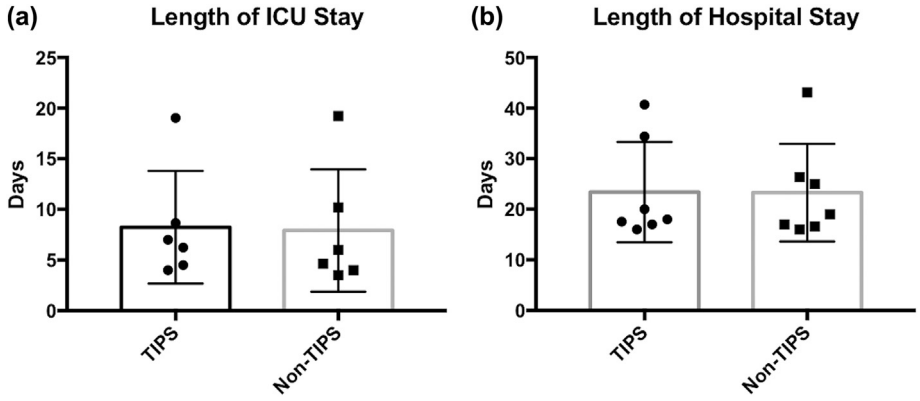

Fig. 3. Comparison of a) ICU days (Wilcoxon test $p = .6884$), and b) Hospital days (Wilcoxon test $p = 1.00$) during transplant admission among various studies (Median and/or mean days taken from multiple reports [43,45–49,51,52,56–58].

3.3. Long-term post-operative outcomes of the liver transplantation

3.3.1. Patient survival to transplant

Gandini et al. noted increased transplant-free survival time in the TIPS group vs. the non-TIPS group and attributed this to the resolution of complications from portal hypertension in the TIPS group [55]. Similarly, in a study examining 301 TIPS patients, 53 of whom went on to be transplanted, Johnson reported a 14% mortality on the waitlist for TIPS patients vs the average institutional waitlist mortality of 20%, although there was no significant difference in time spent on the waitlist between TIPS and non-TIPS groups [59]. In liver transplantation patients from the UNOS database from 2002 to 2013, patients with TIPS spent more days on the waitlist (408 ± 553 days) as compared to non-TIPS (183 ± 330 days, $p < .001$) [58], as represented in Fig. 4a. Presumably, TIPS may have served to stabilize patients, allowing them to wait longer for transplantation.

3.3.2. Patient survival from transplant

Several studies reported similar rates of long-term patient survival between TIPS and non-TIPS groups [49,50,57,58]. According to Moreno et al. [52], actuarial survival rates for their cohort at 1 and 3 years were TIPS group 96.2% and 89.3% versus control cohort 87.8% and 81.0%, respectively ($p = .33$) [45]. Guerrini noted similarly high patient survivals at 1, 3, and 5 years of 91.7%, 85.0% and 81.7%, respectively (TIPS) and 85.4%, 80.3% and 76.2% (controls)($p = .29$). Valdevieso reported that early and late mortality rates were similar for both TIPS and non-TIPS groups [51]. A study conducted in Western Australia concluded that patients who underwent TIPS pre-transplant had a 5-year survival of 71%, which was similar to the overall survival of their liver transplantation unit [60].

3.3.3. Graft survival and retransplantation

All the studies included here reported similar graft survival between both TIPS and non-TIPS patients [45–47,50,58]. In one cohort, retransplantation occurred in 5 pts. (7%) who were post-TIPS, and 4 pts. (3%) in non-TIPS (p = non-significant) [43]. Guerrini and colleagues found graft survival at 1, 3 and 5 years post-LTx to be 85.2%, 77.0% and 72.1% (TIPS) and 75.3%, 69.8% and 66.1% (controls) ($p = .27$) [52].

From these results, it may be concluded that in the majority of cases, TIPS placement does not significantly complicate orthotic liver transplantation. Upcoming transplantation should not be prohibitive of

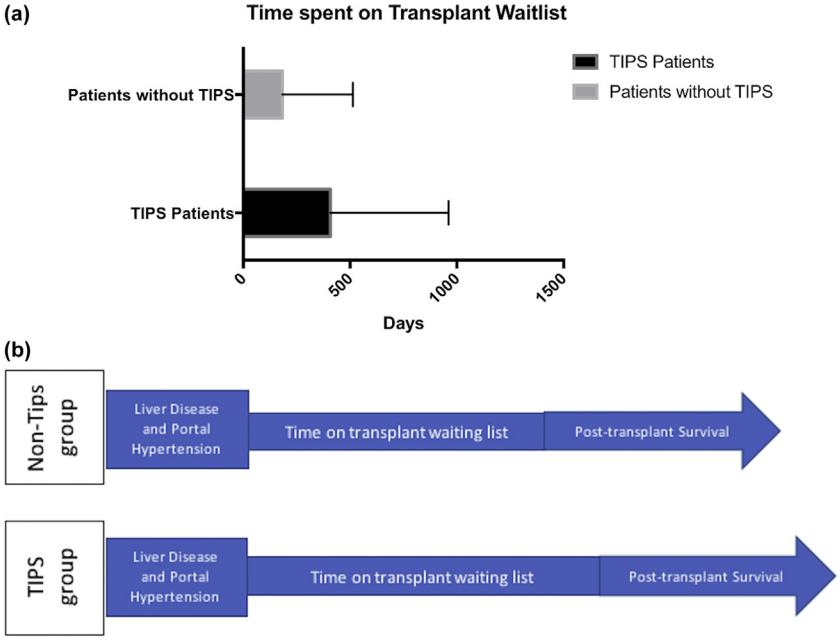

Fig. 4. a) Days spent on Liver Transplant Waitlist for patients in the UNOS database, 2002–2013, as reported by Mumtaz[57]. (TIPS vs non-TIPS 408 ± 553 days vs 183 ± 330 days, $p < .0001$) b) schematic of how TIPS might increase overall survival.

TIPS placement, and previous TIPS placement in the liver should not preclude patients from transplantation. While TIPS has not been found to increase survival time in liver transplant patients post-transplant, it has been demonstrated to increase wait-list time prior to transplant, thus increasing patients' survival to transplant and perhaps overall survival. For an schematic of how we envision that patients might benefit from pre-transplant TIPS, please see Fig. 4b.

4. Post-transplant TIPS

Multiple case studies have reported on the use of TIPS to relieve symptoms of portal hypertension post-transplant, often secondary to fibrosis and cirrhosis of the transplanted liv due to recurrent hepatitis C infection, biliary cirrhosis, or other etiologies. Common indications for TIPS post-transplant include recurrent refractory ascites (50–100%), recurrent variceal bleeding (7–50%), and hepatic hydrothorax (13–42%) [20,61–66]. Following TIPS placement, ascites resolved in 50.0% to 87.5% of cases [61,64], and there was no further rebleeding in 66.7% to 100.0% of patients with variceal bleeding [63,64].

An orthotopically transplanted liver may present technical challenges to TIPS placement, particularly in instances of cavo-caval implantation [67]. In a study of 66 TIPS insertions, in which 22 were post-OLT and 44 were non-transplant, King reported higher rates of technical and clinical success in the non-transplant group vs the OLT group (95.5% vs 68.2%, $p < .05$; and 93.2% vs 77.2%, $p < .05$, respectively) [68]. Although there was a trend toward increased shunt insufficiency among the OLT patients, the rates of complications and post-TIPS encephalopathy were similar across the two groups. Saad saw technical, hemodynamic, and clinical success rates of 100%, 95%, and 16% respectively among 19 patients with refractory ascites [69].

Ghinolfi et al. [66] reported on nineteen patients with ascites and/or hepatic hydrothorax and saw post-TIPS patient survivals of 84.2%, 73.7% and 56.8% at six months, one year, and three years, respectively. Upon comparison with a control group of 29 post-transplant patients with HCV recurrence but without hydrothorax or refractory ascites, the post-TIPS group was noted to have poorer survival. However, TIPS patients with a MELD score less than or equal to 12 had a similar survival to the control group, suggesting that certain patients may achieve a greater benefit from TIPS post-transplant than others. In a study including 16 patients with refractory ascites, roughly 50% responded to TIPS. Subgroup analyses failed to illuminate significant differences between patients whose ascites improved with TIPS and those who did not [64]. Further work is needed to ascertain which patients will benefit most from a TIPS following liver transplant.

5. Additional and alternative bridging therapies

5.1. TIPS, hepatocellular carcinoma, and locoregional therapies

Although HCC was once a contraindication for TIPS placement, particularly in cases where the hepatoma lay in or near the path of the shunt, TIPS in patients with HCC awaiting transplant is now considered possible, provided that the placement of the shunt is controlled [70]. Multiple studies have examined the safety and efficacy of TACE, radioembolization, and radiofrequency ablation in conjunction with TIPS as bridging therapies to transplant in patients with HCC [71–75]. There is a concern that TIPS may increase the risks of hepatotoxicity and the rates of complications following locoregional therapy. For example, Kohi et al. [76] reported increased hepatobiliary sudden adverse events in patients with both TIPS & TACE as compared to patients who underwent TACE alone, and Yao and colleagues concluded that >3 treatments with TACE/TAE were associated with increased odds of hepatic encephalopathy in patients with TIPS [77]. The reasons for potential increased hepatotoxicity following TACE in TIPS patients are unclear. Shunting may result in increased numbers of chemoembolization particles being carried away from the liver and into the systemic circulation.

In a study comparing 23 patients without TIPS and 10 with TIPS following TACE, Kuo and colleagues reported a similar 3-year overall survival between the two groups when uncensored for liver transplantation ($p = .17$), as well a trend toward increased transplantation rates in the TIPS group [78]. This suggests that TACE and other locoregional therapies may be safe options in patients with HCC and pre-existing TIPS who are awaiting transplant.

5.2. Balloon-occluded retrograde transvenous obliteration

Balloon-occluded retrograde transvenous obliteration (BRTO) has also been proposed as an alternative treatment to TIPS, particularly for gastric varices. Sabri concluded that BRTO is comparable to TIPS for the management of bleeding gastric varices, with no significant differences between the two groups in terms of technical success rate, major complications, hepatic encephalopathy, or rebleeding [79]. Choi compared outcomes in patients with liver cirrhosis and active gastric variceal bleeding, dividing them into three groups by treatment allocation and presence/absence of gastrorenal shunt. There were no significant differences between patients without gastrorenal shunt (TIPS), patients with gastrorenal shunt (TIPS), and patients with gastrorenal shunt (BRTO) in terms of immediate hemostasis, rebleeding, and hepatic encephalopathy [80]. Combined TIPS + BRTO has also been shown to have decreased rates of recurrent hemorrhage at 6, 12, and 24 months vs. BRTO alone (0%, 0%, 0% vs. 9%, 9%, 21% respectively, $p = .03$) [81]. Although a handful of small cohort studies and case reports exist reviewing the use of BRTO in liver transplant recipients [82–84], there is a dearth of information about the procedure as a bridge to transplant. While it appears that BRTO may be equally successful for the control of gastric varices in comparison with TIPS and thus would likely be beneficial prior to liver transplantation, further work is required.

6. Conclusion

TIPS placement is a safe and effective treatment that can be used prior to liver transplantation in order to relieve symptoms and to decrease the morbidity of complications of chronic liver disease, thereby improving quality of life. Although TIPS does not appear to either increase or decrease survival post-liver transplant, it is associated with a longer time spent on the liver transplant wait list, implying an increase in patients' ability to make it to transplant, and perhaps an increased overall survival.

Conflicts of interests

The authors have no competing interests to disclose.

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