Expanding Indications of TIPS in the Management of Portal Hypertension Complications

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Abstract

Transjugular intrahepatic portosystemic shunt (TIPS) is a nonsurgical intervention to reduce portal pressure by creating a low-resistance channel between the portal and systemic circulations. It is a well-accepted treatment for gastroesophageal varices and refractory ascites. This review aims to discuss the evidence-based applications of TIPS in other complications of portal hypertension beyond gastroesophageal varices and refractory ascites.

Introduction

Transjugular intrahepatic portosystemic shunt (TIPS) is widely used in treating the complications of portal hypertension (PH). PH is defined as an increase in the portal pressure that may lead to the formation of portosystemic collaterals to divert the portal blood to the systemic circulation.¹ PH can be due to structural liver disorders or prehepatic or posthepatic vascular occlusion.¹ Hepatic venous pressure gradient (HVPG) of ≥ 6 mm Hg is diagnostic of PH. Individuals with PH can be asymptomatic or present with ascites, pleural effusion (hepatic hydrothorax [HH]), gastrointestinal (GI) bleeding from variceal hemorrhage, or portal hypertensive gastropathy (PHG), renal failure from hepatorenal syndrome (HRS), and dyspnea from hepatopulmonary syndrome (HPS). These complications develop when the HVPG is ≥ 10 mm Hg, termed clinically significant PH.² TIPS involves the creation of a conduit between the portal and systemic circulations through the liver parenchyma, thereby reducing the HVPG. Although the technique was introduced in the 1960s, it required additional upgrades to improve patency and mortality rates.³ To date, many studies described the effectiveness of TIPS in the management of refractory ascites and esophageal varices (EV).⁴ In this article, we discussed the evidence in support of other indications of TIPS (→Table 1).

Hepatic Hydrothorax

HH is defined as the accumulation of transudative fluid (> 500 mL) in the pleural cavity secondary to abdominal ascites. It is prevalent among 5 to 10% of patients with end-stage liver disease.⁵,⁶ The movement of ascitic fluid...
through the diaphragmatic defects and negative intrathoracic pressure contribute to HH development.\textsuperscript{7} HH is seen in the right hemithorax in 85% of cases and in the left among 13% of cases.\textsuperscript{8} The presenting symptoms include chest pain and dyspnea on exertion, which worsens with increased fluid accumulation.\textsuperscript{8} HH can cause spontaneous bacterial empyema without underlying pneumonia and is observed in 13 to 16% of patients with HH.\textsuperscript{9} Diagnosis of HH is by thoracentesis, which demonstrates transudative pleural fluid characteristics as described in Table 2.\textsuperscript{2} Management consists of a low sodium diet, diuretics, and therapeutic thoracentesis. Patients requiring repeated thoracentesis every 2 to 3 weeks, albeit on diuretics and sodium-restricted diet, are considered refractory to medical therapy, and they constitute 25% of cases.\textsuperscript{5} As such, the definitive therapy is to identify and treat the etiology of ascites through liver transplantation. TIPS can be considered in patients with contraindications to liver transplantation or as a bridge to liver transplantation in patients with refractory HH.\textsuperscript{5}

Table 3 summarizes the studies involving patients who underwent TIPS for refractory HH. Ditah et al and Campos et al reported that TIPS provided symptomatic relief in three-fourths of the study participants with refractory HH.\textsuperscript{5,8} According to Ditah et al and Jindal et al’s study, the 45-day mortality rate (17.74%), the 6-month mortality rate (35.9%), and the 1-year survival rate were comparable to the formal indications of TIPS, refractory ascites, and bleeding varices.\textsuperscript{5,10} Elderly age group, severe liver disease (Child–Pugh class C, Model for End-Stage Liver Disease [MELD] >15, Child–Turcotte–Pugh [CTP] score >10), elevated creatinine, and lack of response to TIPS are recognized as the predictors of patient mortality.\textsuperscript{5} Jindal et al proposed that MELD score > 25, spontaneous bacterial peritonitis (SBP), and septic shock are independent predictors of mortality.\textsuperscript{10} Although post-TIPS hepatic encephalopathy (HE) (11–66%) was reported in the literature, it was usually responsive to medical therapy without contributing to high mortality rates.\textsuperscript{5,8,10} Considering the efficacy of TIPS in HH, its early inclusion may be beneficial as a bridge to definitive treatment.\textsuperscript{6}

### Budd–Chiari Syndrome

Budd–Chiari syndrome (BCS) is secondary to thrombotic occlusion ranging from the level of the hepatic vein to the portal venous system.

#### Table 1: Level of evidence of the indications

<table>
<thead>
<tr>
<th>Indication</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic hydrothorax</td>
<td>4</td>
</tr>
<tr>
<td>Hepatic veno-occlusive disease and Budd–Chiari syndrome</td>
<td>4</td>
</tr>
<tr>
<td>Hepatorenal syndrome</td>
<td>4</td>
</tr>
<tr>
<td>Portal hypertensive gastropathy</td>
<td>2B</td>
</tr>
<tr>
<td>Ectopic varices</td>
<td>4</td>
</tr>
</tbody>
</table>

#### Table 2: Diagnostic criteria for noninfective hepatic hydrothorax

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural fluid WBC</td>
<td>&lt; 250/mm\textsuperscript{3}</td>
</tr>
<tr>
<td>Pleural fluid protein</td>
<td>&lt; 2.5 g/dL</td>
</tr>
<tr>
<td>Ratio of pleural fluid and serum total protein levels</td>
<td>&lt; 0.5</td>
</tr>
<tr>
<td>Ratio of pleural fluid and serum LDH levels</td>
<td>&gt; 0.6</td>
</tr>
<tr>
<td>Ratio of pleural fluid and serum albumin levels</td>
<td>&gt; 1.1</td>
</tr>
<tr>
<td>Ratio of pleural fluid serum bilirubin levels</td>
<td>&lt; 0.6</td>
</tr>
<tr>
<td>pH</td>
<td>&gt; 7.4</td>
</tr>
</tbody>
</table>

#### Table 3: Summary of the studies of TIPS in refractory hepatic hydrothorax

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Sample size</th>
<th>Patient characteristics</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ditah et al\textsuperscript{5}</td>
<td>Refractory HH</td>
<td>198</td>
<td>Child class C - 56.9%; Child class B - 40.7%; mean pre-TIPS HVPG - 20.14 mm Hg</td>
<td>CR: 55.8%; PR: 17.6%; AR: 21.2%; 45-day mortality: 17.74%; Overall mortality: 50.17%; HE: 11.7%</td>
</tr>
<tr>
<td>Campos et al\textsuperscript{8}</td>
<td>Refractory HH</td>
<td>19</td>
<td>Cirrhosis and MELD - 16: 84.2%; Child class C: 47.4%; Child class B: 42.1%</td>
<td>CR: 40%; PR: 33.3%; 30-day mortality: 25%; 1-year mortality: 42.8%; HE: 66.6%</td>
</tr>
<tr>
<td>Jindal et al\textsuperscript{10}</td>
<td>Refractory HH</td>
<td>51</td>
<td>CTP score: 9.9 ± 1.6; MELD: 18.7 ± 5.4</td>
<td>CR: 20%; PR: 49%; pressure gradient pre- and post-TIPS: 23.1 ± 3.8 mm Hg and 7.2 ± 2.5 mm Hg; HE: 15%; 6-month mortality rate: 35.9%</td>
</tr>
</tbody>
</table>

Abbreviations: AR, absent response; CR, complete response; CTP score, Child–Turcotte–Pugh score; HE, hepatic encephalopathy; HH, hepatic hydrothorax; HVPG, hepatic venous pressure gradient; MELD, Model for End-Stage Liver Disease; PR, partial response; TIPS, transjugular intrahepatic portosystemic shunt.
right atrium. The incidence of BCS is one in every 2.5 million person-years. Various etiologies of BCS include primary myeloproliferative disorders, hypercoagulable states, oral contraceptive usage and pregnancy, Behcet syndrome, and external compression due to abscess or neoplasms. The classical triad of BCS includes ascites, abdominal pain, and hepatomegaly. The standard management of BCS comprises of anticoagulation and treatment of underlying etiology. An exclusive medical treatment imposed a high mortality rate of 86% in these patients, according to the study by McCarthy et al. An improvement in the survival rate (18% vs. 32%) was reported if the management included thrombolysis, angioplasty, or stent placement. However, Mancuso reported that anticoagulants are the preferred treatment in treating individuals without any signs of PH.

Nonetheless, TIPS is the most common treatment employed in BCS that is complicated by PH. Early TIPS could help prevent the disease progression and hepatic fibrosis, alongside improving the survival outcomes. Liver transplantation is the rescue therapy in individuals with hepatic failure. Critically ill BCS patients awaiting liver transplants may not survive until the surgery and require an emergent procedure such as TIPS to reduce the severity of symptoms. Success rates of TIPS are around 98 to 100% in patients with BCS. The most prevalent indication for TIPS is ascites and variceal bleeding, reported in 100 and 30.9% of cases, respectively. Preprocedural HE and jaundice without hepatic insufficiency are not risk factors for postoperative HE and jaundice. And hence are not considered a contraindication to TIPS. Postprocedural complications such as bleeding, HE, and stent malposition were reported to be around 21.4, 2 to 3, and 6%, respectively. Seijo et al validated that the treatment of BCS with TIPS can result in a good outcome regardless of the timing of the procedure. In their study of 157 patients, the overall survival rate at 1-, 3-, and 5-year intervals was 88, 83, and 72%, respectively, compared with orthotopic liver transplantation-free survival rates, 85, 78, and 72%, respectively. Based on current evidence, TIPS is highly recommended in early BCS patients as a sole therapy. It might be technically challenging in cases with extensive occlusion of hepatic and suprahepatic veins.

Hepatorenal Syndrome

HRS is characterized by renal failure as a result of cirrhosis and PH that meet the International Club of Ascites-Acute Kidney Injury criteria. It usually develops in patients with decompensated cirrhosis. Previously, HRS was classified into type 1 and type 2 based on serum creatinine. HRS type 1 is defined as a rapidly progressive renal failure in the setting of a precipitating event such as SBP. HRS type 2 comprises slowly progressive renal dysfunction and refractory ascites. According to the International Club of Ascites, HRS type 1 is characterized by serum creatinine > 2.5 mg/dL in < 2 weeks and glomerular filtration rate < 20 mL/min. HRS type 2 is diagnosed when initial serum creatinine is < 2.5 mg/dL. Current criteria for HRS include an increase in serum creatinine by ≥ 0.3 mg/dL within 48 hours or by ≥ 50% over the baseline within 1 week. An increased hepatic sinusoidal pressure due to cirrhosis leads to systemic vaso-dilation and vascular underfilling, stimulating renal neurohumoral mechanisms. As a result, sodium and water retention and renal vasoconstriction develop, contributing to HRS. Vasoconstrictor medications along with albumin are the first-line treatment in patients with HRS. Liver transplantation is the standard therapy; however, TIPS can be considered in medically unresponsive patients or in candidates who are unsuitable to transplantation.
**Table 4** Summary of the studies of TIPS in Budd–Chiari syndrome

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Sample size</th>
<th>Patient characteristics</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garcia-Pagán et al11</td>
<td>BCS</td>
<td>124</td>
<td>Myeloproliferative disorder: 52%; associated IVC thrombus and PV thrombus: 15% and 10%, respectively; mean MELD: 17; refractory ascites: 64%; GI bleed: 15%</td>
<td>1- and 5-year OLT-free survival rate: 88% and 78%, respectively; 5-year OLT-free survival in high-risk patients compared with estimation by Rotterdam BCS index: 71% versus 42%, respectively; TIPS dysfunction: 41%; HE: 21%</td>
</tr>
<tr>
<td>Seijo et al22</td>
<td>BCS</td>
<td>62</td>
<td>Refractory ascites: 69%; liver failure: 13%; variceal bleeding: 7%</td>
<td>1-, 3-, and 5-year rates of actual survival and OLT-free survival were 88%, 83%, and 72%, and 85%, 78%, and 72%, respectively</td>
</tr>
<tr>
<td>Sonavane et al13</td>
<td>BCS</td>
<td>42</td>
<td>Mean MELD: 15.38; ascites: 100%; myeloproliferative disease: 40.4%; hyperhomocysteinemia: 12%; all three hepatic vein occlusion: 1005; additional IVC obstruction: 17%</td>
<td>Deaths during follow-up: 26% (36% within 1 month, 18% in 6 months, and 27% in the following period) Causes of death: hematologic disorder: 36%, HE: 27%, intra-abdominal bleed: 18%, and gastrointestinal bleeding: 9% cumulative 1-, 5-, and 10-year OLT-free survival rates were 86%, 81%, and 76%, respectively</td>
</tr>
<tr>
<td>Qi et al65</td>
<td>BCS</td>
<td>Meta-analysis including 17 studies (each study with &gt; 10 patients)</td>
<td>Refractory ascites; recurrent variceal bleeding</td>
<td>Technical success rates: 91–100%; pre- and post-TIPS PSG: 27.5 versus 9 mm Hg; clinical improvement: 80–100%; one- and 5-year cumulative survival rate: 80–100% and 74–78%, respectively; complications: 0–56%; HE: 0–25%; shunt dysfunction: 18–100% (bare stents: 73%; PTFE stents: 16%)</td>
</tr>
<tr>
<td>Fitsiori et al19</td>
<td>Re refractory BCS</td>
<td>14</td>
<td>BCS-TIPS PI score ≤ 7; chronic myeloproliferative disorder: 57%; hyperhomocysteinemia: 7%; Churg-Strauss syndrome: 7%; paroxysmal nocturnal hemoglobinuria: 7%</td>
<td>Technical success rate: 100%; primary patency: 93%, 85%, 59% at 6, 12, and 24 months, respectively; secondary patency: 100%, 100% and 85% at 6, 12, and 24 months, respectively. TIPS dysfunction: 28.6%</td>
</tr>
<tr>
<td>Qi et al66</td>
<td>BCS</td>
<td>51 (early TIPS: 19, converted TIPS: 32)</td>
<td>Diffuse hepatic veins obstruction: 23.5%; liver failure: 3%; liver function deterioration: 15.6%; refractory ascites: 19.6%; variceal bleeding: 37.2%</td>
<td>Technical success rate: 100%; portal vein pressure reduced from 28.78 ± 0.78 mm Hg to 19.90 ± 0.77 mm Hg; HE: 23.5%; shunt dysfunction: 49%; cumulative 1-, 2-, and 3-year rates of being free from shunt dysfunction were 61.6%, 43.9%, and 23.4%, respectively; 1-, 2-, 3-, 4-, and 5-year survival rates were 83.8%, 81.2%, 76.9%, 67.3%, and 56.09%, respectively</td>
</tr>
</tbody>
</table>
reduces the portal pressure, thereby improving the intravascular volume and cardiac output.

Table 7 summarizes the studies involving patients who underwent TIPS for HRS. Song et al reported that the 1-year survival rate of HRS-2 and refractory ascitic patients treated with TIPS was 64 and 65%, respectively. Compared with medical management, TIPS improved renal function (52% vs. 83–93%) within a week, and a significant improvement was noticed after 4 weeks. The pooled rate of HE was 49% and was effectively managed with medications. Song et al concluded that TIPS could benefit patients with HRS by improving renal function and survival rates. Charilaou et al conducted a cohort study to compare the efficacy of TIPS and dialysis in HRS patients. They found that the mortality rate was higher in the dialysis-only group compared with the TIPS group (48% vs. 18%). Patients in the TIPS group were three times less likely to be admitted as inpatients than the dialysis-only group (adjusted odds ratio: 0.31; \( p < 0.001 \)). Shunting with TIPS may impede the progression of renal dysfunction and the need for transplantation. It is more useful in HRS type 2 and could be used to bridge to liver transplantation in medically responsive HRS type 1 individuals. Further studies are required to elaborate on the long-term role of TIPS in HRS patients.

### Portal Hypertensive Gastropathy

PHG is seen among 20 to 80% of individuals with PH and described as vascular ectasia of mucosal/submucosal capillaries without any signs of inflammation. The patients with PHG present with acute or chronic GI bleeding that mimics gastric antral vascular ectasia (GAVE). PHG and GAVE have their specific characteristic features on endoscopy, which assists in differentiation. On endoscopy, GAVE displays red spots that can blur together, giving the appearance of a watermelon stomach. PHG appears as a classic mosaic snakeskin-like pattern in the gastric body or fundus progressing to brown or red bulging spots with severity. The severity of PHG correlates with the high CTP score, presence of EV, thrombocytopenia, or splenomegaly. Vasoconstrictors along with resuscitative measures form the mainstay of treatment in acute bleeding. Beta-blockers such as propranolol were evaluated to prevent recurrent bleeding effectively. TIPS is indicated in individuals with recurrent GI

### Table 4 (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Sample size</th>
<th>Patient characteristics</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tripathi et al</td>
<td>BCS</td>
<td>67</td>
<td>MELD: 16.1 ± 7; CTP score: 8.8 ± 2.0; hematological risk factors: 78% of patients; ascites: 91%; variceal bleeding: 8.9%</td>
<td>Mean follow-up: 82 months; HE: 15%; primary patency rates were 76% and 27% in covered and uncovered stents; shunt reinterventions were 22% and 100% in covered and uncovered stents; six, 12-, 24-, 60- and 120-month survival rates were 97%, 92%, 87%, 80%, and 72%, respectively</td>
</tr>
<tr>
<td>Fan et al</td>
<td>BCS</td>
<td>60</td>
<td>Ascites: 100%; upper gastrointestinal bleed: 20%; hepatorenal syndrome: 10%; Impaired liver function: 100%; mean CTP score: 9.65 ± 2.31; proximal ostial occlusion of hepatic vein: 30%; concomitant IVC stenosis: 15%; extensive hepatic vein occlusion: 35%; hepatic venular occlusion: 20%</td>
<td>Technical success: 100%; portal pressure reduced from 41.23 ± 10.46 cm H(_2)O to 26.68 ± 6.46 cm H(_2)O; shunt occlusion of intrahepatic portal vein: 5%; hepatic vein reocclusion: 5%</td>
</tr>
<tr>
<td>Rosenqvist et al</td>
<td>BCS</td>
<td>13 (from 2003 to 2015)</td>
<td>Hepatomegaly, abdominal pain and ascites: 71%; ascites and fatigue: 21%; unknown clinical presentation: 7%</td>
<td>Technical success rate: 100%; median follow-up period: 3 years; shunt patency: 85% at 1-year and 67% at 2-year follow-up Shunt dysfunction: 30%; HE: 23%; 1- and 5-year LST-free survival rates were 100% and 93% compared with 47% and 28%, respectively, in 1986–2003</td>
</tr>
</tbody>
</table>

Abbreviations: BCS, Budd–Chiari syndrome; BCS-TIPS PI, BCS-TIPS prognostic index; CTP, Child–Turcotte–Pugh Score; GI, gastrointestinal; HE, hepatic encephalopathy; IVC, inferior vena cava; MELD, Model for End-Stage Liver Disease; OLT, orthotopic liver transplantation; PSG, portosystemic gradient; PTFE, polytetrafluoroethylene; PV, portal vein; TIPS, transjugular intrahepatic portosystemic shunt.
The published data are described in Table 8. TIPS has shown significant improvement in the frequency of GI bleeding and transfusion requirements. However, TIPS is found to be ineffective in controlling symptoms of GAVE. Hence, proper diagnostic differentiation and patient selection are essential among PHG and GAVE.

Gastric Varices

Gastric varices (GV) are prevalent in 5 to 33% of cirrhotic and PH patients. They develop at advanced stages of liver disease and constitute 10 to 30% of bleeding episodes with a mortality rate of 45 to 55%. Studies noted that GV bleeding occurs at lower portosystemic gradient (PSG) compared with EV (17–20 mm Hg vs. 20–23 mm Hg) and hence warrants prompt management. The reason for lower PSG among GV can be explained by its drainage into large caliber gastrorenal shunts in a “downhill” (less resistant caudal flow) process, whereas EVs drain into small-caliber azygous veins in an “uphill” (more resistant cranial flow) process and hence elicit higher PSG.

Table 7 Summary of the studies of TIPS in hepatorenal syndrome

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Sample size</th>
<th>Patient characteristics</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Song et al</td>
<td>HRS</td>
<td>128</td>
<td>HRS-1: 77; HRS-2: 51</td>
<td>Short-term, 1-year survival rate in HRS-1 and HRS-2: 72%, 47% and 86%, respectively; HE: 49%; 1-year mortality in HRS-1 and HRS-2: 0–80% and 31–44%, respectively</td>
</tr>
<tr>
<td>Brensing et al</td>
<td>HRS</td>
<td>31</td>
<td>HRS-1: 14; HRS-2: 17</td>
<td>Pre- and post-TIPS PPG: 21 and 13 mm Hg; 3-month survival rate in TIPS and non-TIPS group: 63% and 10%, respectively</td>
</tr>
</tbody>
</table>

Abbreviations: HE, hepatic encephalopathy; HRS, hepatorenal syndrome; PPG, portosystemic pressure gradient; TIPS, transjugular intrahepatic portosystemic shunt.
Table 8 Summary of the studies of TIPS in portal hypertensive gastropathy

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Sample size</th>
<th>Patient characteristics</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mezawa et al⁴⁰</td>
<td>PHG</td>
<td>16</td>
<td>Mild PHG: 12; severe PHG: 4</td>
<td>Improved in 4 of 4 severe PHG and 5 of 12 mild PHG patients; pre- and post-TIPS PSG: 23.4 and 14 mm Hg</td>
</tr>
<tr>
<td>Kamath et al⁴¹</td>
<td>PHG</td>
<td>54</td>
<td>Mild PHG: 30; severe PHG: 10; GVE: 14</td>
<td>Endoscopic resolution in 75% of severe PHG and 89% of mild PHG and 0% of GVE patients; 1-year mortality: 50% (27/54); HE: 66%</td>
</tr>
</tbody>
</table>

Abbreviations: GVE, gastric vascular ectasia; HE, hepatic encephalopathy; PHG, portal hypertensive gastropathy; PSG, portosystemic gradient; TIPS, transjugular intrahepatic portosystemic shunt.

Table 9 Theories explaining the suboptimal efficacy of TIPS in gastric varices

<table>
<thead>
<tr>
<th>Theory</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximity theory</td>
<td>Ineffective decompression due to farther location of GV from the TIPS</td>
</tr>
<tr>
<td>Throughput theory</td>
<td>TIPS dysfunction due to supramaximum of prominent GRS</td>
</tr>
<tr>
<td>Recruitment theory</td>
<td>Emerging of feeding vessels during postembolization of GV period</td>
</tr>
</tbody>
</table>

Abbreviations: GRS, gastrorenal shunt; GV, gastric varices; TIPS, transjugular intrahepatic portosystemic shunt.

Endovascular therapies such as TIPS and balloon-occluded retrograde transvenous obliteration (BRTO) are considered in patients not responding to medical and endoscopic management. TIPS and BRTO can achieve hemostasis in 90 and 95%, respectively, of patients with GV bleed. However, studies reported a lower rebleeding rate (0–20% vs. 25–30%) in the BRTO group compared with the TIPS group.⁶ The suboptimal effectiveness of TIPS can be explained by three theories, “proximity,” “throughput,” and “recruitment” (→Table 9).⁶

The incidence of spontaneous portosystemic shunts (SPSs) such as gastrorenal and splenorenal shunts is around 28% in patients with PH.⁴² The TIPS placement augments the shunt volume in individuals with SPS and further decreases the portal blood flow (PBF). Reduced PBF enhances the incidence of postinterventional HE, reported by Choi et al., to be around 18%.⁴² In contrast, BRTO increases PH by increasing the PBF. Hence, it reduces HE incidence but worsens EV bleeds, ascites, hydrothorax, and PHG.⁶,⁴⁶ Wang et al reviewed the literature comparing TIPS and BRTO procedures. They reported a significant difference in overall survival (risk ratio [RR]: 0.81; p = 0.03) and rebleeding rates (RR: 2.61; p = 0.03) between TIPS and BRTO groups.⁴⁷

In conclusion, the benefits and complications of TIPS and BRTO complement each other, and recently there has been increased application of combined TIPS-BRTO in the management of GV. Implementing BRTO first provides an advantage of increasing the portal vein diameter, making access to TIPS less challenging.⁵ The patency of TIPS is also improved with the combined TIPS-BRTO due to the obliteration of competitive SPS.⁴³

Ectopic Varices

Ectopic varices can be observed at various abdominal locations such as small bowel, stomas, falciform ligament, biliary tract, vagina, bladder, rectum, umbilicus, and peritoneum.⁴⁸ They bleed when the expanding force in varix overcomes the maximum vessel wall tension.⁴⁸ Ectopic varices account for 5% of cases presenting with variceal bleed.⁴⁹ Management comprises resuscitative measures, vasoconstrictors, endoscopic sclerotherapy, variceal band ligation, transcatheter embolization, or TIPS.⁵⁰

→Table 10 summarizes the studies involving patients who underwent TIPS for ectopic variceal bleed. A study by Oey et al.⁵¹ confirmed the efficacy of TIPS in 77% of the patients with ectopic varices, particularly the varices located near enterostomas and associated with mild-moderate liver disease. The rebleeding rate at 1 year was significantly reduced from 39 to 23% due to the usage of expanded polytetrafluoroethylene-covered stents. However, the rebleeding rate of the ectopic varices rate is higher when compared with rebleeding in gastroesophageal varices (94–100% vs. 77%).⁵¹ Increased rebleeding in ectopic varices is attributed to the higher rebleeding rates (50%) in ectopic duodenal varices. The shunt dysfunction is another factor that contributed to rebleeding in three-fourths of the patients and is seen more often in TIPS with a bare-metal stent. Post-TIPS HE was noticed in 30% of patients but manageable with medical treatment or diameter adjustment.

In a study by Kochar et al., TIPS achieved hemostasis in 67% of patients with ectopic varices⁴⁸ and 21% presented with rebleeding. According to Vangeli et al., the rebleeding rate was higher in patients who underwent TIPS alone compared with those who underwent a combination of TIPS and variceal embolization (VE) (48% vs. 28%). The patients with rebleeding responded to consecutive VE, and hence Vangeli et al. endorsed the inclusion of VE alongside TIPS in the management of ectopic varices.⁴⁸,⁵² However, the routine recommendation of VE needs further studies to demonstrate its efficacy and complications such as propagative thrombus and paradoxical embolization into the systemic circulation.⁶
As a Bridge to Liver Transplantation

Liver transplantation is the definitive therapy in liver failure. TIPS can be employed to manage ascites, variceal bleed, and HH in patients waiting a liver transplant.

Around 14% of patients requiring liver transplantation undergo TIPS placement as a transitory procedure for prompt regulation of illness. Table 11 summarizes the studies involving patients who underwent TIPS prior to liver transplantation. Studies of Sellers et al, Valdivieso et al, and Mumtaz et al reported increased intraoperative time, blood transfusion requirement, and length of hospital stay in TIPS patients compared with no-TIPS patients. The increased length of hospital stay was due to advanced HE, elderly age, increased cold ischemia time, and MELD scores in a study by Mumtaz et al. However, TIPS allowed patient stabilization and prolonged the waiting time between TIPS intervention and transplant surgery. Graft survival rates, mortality rate, and retransplant rates in TIPS patients were noted to be similar to those in no-TIPS patients.

Table 11 Summary of the studies involving patients who underwent TIPS prior to liver transplantation

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Sample size</th>
<th>Patient characteristics</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mumtaz et al</td>
<td>TIPS prior to liver</td>
<td>1366</td>
<td>Increased waiting time for transplant (408 ± 553 days) compared with no-TIPS (183 ± 330 days); no significant effect of TIPS was noted on mortality and retransplant rate</td>
<td></td>
</tr>
<tr>
<td>Amesur et al</td>
<td>TIPS prior to liver</td>
<td>12</td>
<td>Variceal bleeding: 50%; ascites: 50%</td>
<td>Child A patients had superior survival; two patients with ascites experienced death within 1 week due to liver failure</td>
</tr>
</tbody>
</table>

Abbreviation: TIPS, transjugular intrahepatic portosystemic shunt.

TIPS after Liver Transplantation

Recurrence of liver disease can lead to the development of PH in patients with liver transplants. TIPS procedure is challenging in liver transplant recipients due to changes in the liver anatomy. Lerut et al pointed the difficulty of cannulating the graft hepatic and portal veins during the TIPS procedure in individuals who underwent piggyback cavo-caval anastomoses.

Table 12 summarizes the studies involving patients who underwent TIPS after liver transplantation. Chen et al studied patients who underwent liver transplantation and were experiencing refractory ascites, variceal hemorrhage, and HH. They reported a 98% technical success rate with a resolution of symptoms in 57% of refractory ascites, 69% of variceal bleeding, and 56% of HH patients. However, 33% of patients experienced HE, 16% required shunt revision, and 19% required retransplantation. Chen et al concluded that it was reasonable to suggest TIPS in liver transplant recipients if they develop recurrent PH. In contrast, the technical success rate was 68.2% in a study by King et al. They also...
inferred that TIPS was not beneficial in patients with MELD > 15 (hazard ratio [HR] = 5.846), and retransplant could be considered in such individuals.58

**TIPS Prior to an Abdominal Surgery**

Extrahepatic abdominal surgeries in patients with chronic liver disease (CLD) are associated with a considerable postoperative mortality rate of 10 to 76%.59 The CTP score allows the prediction of postoperative mortality, with Child–Pugh C being the worst prognostic factor and Child–Pugh A and B carrying poor outcomes. Ascites in CLD hinders wound healing, resulting in wound dehiscence and infections. Alongside, increased portal pressure leads to complications such as intraoperative bleeding and hepatic decompensation.59 Preoperative TIPS lessens the portal pressure, thereby reducing the complications.6

> Table 13 summarizes the studies involving patients who underwent TIPS prior to extrahepatic abdominal surgery. Tabchouri et al reported an 85% operability rate in patients undergoing preoperative TIPS placement.60 In 2006, Vinet et al concluded that preoperative TIPS had not demonstrated beneficial postoperative effects.61 In support of their study, Tabchouri et al described that although TIPS reduces postoperative ascites (HR = 0.3), it worsens MELD (HR = 2.3), and there is no statistically significant effect on 90-day mortality rates (HR = 0.720; 0.180–2.920) and complications (HR: 0.670; 0.270–1.680).60 In patients with HVPG > 13 mm Hg, increased intraoperative blood transfusion requirement (HR: 4.1) and increased postoperative sepsis (HR: 2.8) were reported.60 Based on current evidence,60,61 TIPS in the

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**Table 12** Summary of the studies of TIPS after liver transplantation

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Sample size</th>
<th>Patient characteristics</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al56</td>
<td>TIPS after liver transplantation</td>
<td>213</td>
<td>Refractory ascites: 78%; variceal hemorrhage: 17%; hydrothorax: 4%</td>
<td>Technical success: 98%; success rates of TIPS after OLT in patients with refractory ascites, variceal hemorrhage, and hydrothorax were 57%, 69%, and 56%; HE: 33%; 30-day mortality rate and 1-year survival rate: 11% and 53%, respectively; subsequent retransplantation: 19%</td>
</tr>
<tr>
<td>King et al58</td>
<td>TIPS after liver transplantation</td>
<td>22 transplanted patients (cases) and 44 nontransplants (controls)</td>
<td>Variceal bleeding: 36.4%; refractory ascites: 63.6%</td>
<td>Pre- versus post-TIPS PSG in cases and controls: 21.0 versus 9.9 mm Hg and 22.4 versus 6.9 mm Hg, respectively. technical success rates in cases and controls: 68.2 and 95.5%; clinical success rates: 77.2 versus 93.2%, respectively</td>
</tr>
<tr>
<td>Lerut et al57</td>
<td>TIPS after liver transplant</td>
<td>8</td>
<td>Refractory ascites: 62; HH and ascites: 12.5%; bleeding esophageal varices: 12.5%; repeated biliary surgery: 12.5%</td>
<td>Technical success rate: 1.005; complete response: 37.5%; partial response: 37.5%; unfavorable: 25%</td>
</tr>
</tbody>
</table>

Abbreviations: HE, hepatic encephalopathy; HH, hepatic hydrothorax; OLT, orthotopic liver transplantation; PSG, portosystemic gradient; TIPS, transjugular intrahepatic portosystemic shunt.

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**Table 13** Summary of the studies of TIPS in extrahepatic abdominal surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Sample size</th>
<th>Patient characteristics</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinet et al61</td>
<td>Extrahepatic abdominal surgery</td>
<td>18</td>
<td>Antrectomy: 5; colectomy: 10; small bowel resection: 1; pancreatectomy: 1; nephrectomy: 1</td>
<td>No significant improvement in mortality, complications were reported</td>
</tr>
<tr>
<td>Tabchouri et al60</td>
<td>Extrahepatic abdominal surgery</td>
<td>With TIPS: 66; without TIPS: 68</td>
<td>Colorectal surgery: 68; upper GI and pancreatic surgery: 13; hernia and incisional hernia: 17; cholecystectomy: 13; other: 13</td>
<td>Operability rate: 85%; postoperative ascites hazard ratio: 0.330; similar mortality and complications such as bleeding in TIPS and no-TIPS group</td>
</tr>
</tbody>
</table>

Abbreviations: GI, gastrointestinal; TIPS, transjugular intrahepatic portosystemic shunt.
Hepatopulmonary Syndrome

HPS constitutes impaired blood oxygenation due to dilated intrapulmonary vasculature secondary to hepatic cirrhosis. It is observed among 5 to 32% of patients with liver disease. The patients present with platypnea, pathognomonic of HPS, and dyspnea. Diagnostic criteria include the presence of hepatic disease, alveolar arterial oxygen gradient (A-a O2) of ≥ 15 mm Hg (≥ 20 mm Hg in patients above 64 years old), and dilated pulmonary vasculature demonstrated on contrast-enhanced echocardiography (bubble study). Although liver transplantation is the definitive treatment for HPS, the application of TIPS is increasing due to its effective reduction in portal pressure, which in turn lowers the vasodilators causing pulmonary vascular constriction. In addition, the mortality rate is reported to be around 16 to 33% in HPS patients undergoing liver transplantation. Left portal vein (LPV) TIPS improves symptoms of HPS better than right portal vein TIPS, and the incidence of HE is diminished in LPV TIPS. A study by Tsauo et al. (Table 14) reported statistically significant improvement in A-a O2 and oxygenation after 1 month of TIPS creation. However, the recovery is transient, and they observed worsening hypoxemia 3 months after TIPS. Hence, the study concluded that TIPS cannot be performed as a solitary treatment for HPS but could be considered a bridge to definitive treatment.

Conclusion

TIPS has been widely applied to manage complications of PH. Besides its routine clinical applications—refractory ascites and EV—TIPS has gained paramount importance in varied conditions, as outlined in this article. Further prospective studies would enhance the strength of evidence and recommendations for these indications.

Conflict of Interest

S.P.K. reports grants from NIH, BD, Black Swan, and Trisalus for Institution; reports royalties from Elsevier, Springer, and Thieme for himself; reports consulting fees from Penumbra, Okami Medical, Boston Scientific, Medtronic, Covidien, US Vascular, Dova Pharmaceuticals, Instylla, and BD for himself; reports payment from Stony Brook University, American Institute of Biology, UT Houston, and NACCME for himself; reports payment for expert testimony from Southern Institute for Medical and Legal Affairs LLC for himself; reports participation from NIH for institution; reports leadership from Chief, Interventional Radiology, Massachusetts General Hospital, Boston, MA; Chair, Vascular Panel, ACR Appropriateness Criteria; International Editor, Journal of Clinical Interventional Radiology ISVIR; Assistant Editor, Radiology – Cardiothoracic, RSNA; reports stock from Biogen Inc, Clover Health Investments Corp, Inovio Pharmaceuticals, Moderna Inc, Pfizer Inc, Novavax Inc, Orphazyme, Cassava Sciences Inc, Vivos Therapeutics Inc, Ardelyx Inc, Althea Health, Sarepta Therapeutics, Clover Health Investments Corp, CureVac BV, Immunoprecise Antibodies Ltd, Infinity Pharmaceuticals Inc, Zymegren Inc, BioNTech SE, Trillium Therapeutics Inc, Thoravance BioPharma Inc, Doximit Inc, Eargus Inc, Allogent Therapeutics Inc, NRx Pharmaceuticals Inc, Atea pharmaceuticals Inc, for himself and spouse; and reports financial or nonfinancial interests as Adjunct Associate Professor from University of Texas Southwestern Medical Center.

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Expanding Indications of TIPS in the Management of Portal Hypertension Complications

Vulasala et al.


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