

Transjugular Intrahepatic Portosystemic Shunt toward Liver Transplant

Subjects: Pathology

Contributor: Simone Di Cola, Lucia Lapenna, Jakub Gazda, Stefano Fonte, Giulia Cusi, Samuele Esposito, Marco Mattana, Manuela Merli

Liver transplantation is currently the only curative therapy for patients with liver cirrhosis. Not all patients in the natural course of the disease will undergo transplantation, but the majority of them will experience portal hypertension and its complications. In addition to medical and endoscopic therapy, a key role in managing these complications is played by the placement of a transjugular intrahepatic portosystemic shunt (TIPS). Some indications for TIPS placement are well-established, and they are expanding and broadening over time.

Keywords: transjugular intrahepatic portosystemic shunt ; liver transplantation

1. Introduction

Cirrhosis represents an advanced stage of chronic liver disease, characterized by an unfavorable prognosis and associated with 2.4% of global deaths in 2019 ^[1] due to liver decompensation. Complications of liver cirrhosis arise from liver failure and the development of portal hypertension leading to a progressive worsening of the disease. The mortality rate ranges from less than 1% per year in patients with compensated cirrhosis to more than 20% per year after the first decompensation ^{[2][3]}.

To treat complications of portal hypertension, chronic medical treatment is indicated, with diuretics and nonselective beta-blockers (NSBBs) ^{[4][5]} or endoscopic band ligation. However, during the natural history of cirrhosis, some patients may develop difficult-to-treat/refractory ascites or a high risk of recurrent gastrointestinal (GI) bleeding, requiring a transjugular intrahepatic portosystemic shunt (TIPS) procedure ^[6]. Following TIPS placement, the pressure in the portal venous system drops, reducing the risk of variceal bleeding and improving ascites. Due to the treatment of portal hypertension (PH), a TIPS may even improve patient survival ^[7], but the progression of liver failure and its consequences frequently leave liver transplant as the only definitive treatment in these patients. For these reasons ^[8], during the clinical course of advanced liver disease, a TIPS may also be an opportunity to allow more patients to reach the time of liver transplant more safely.

2. Transjugular Intrahepatic Portosystemic Shunt toward Liver Transplant

Liver transplantation represents the only curative treatment for patients with liver cirrhosis. Bridges to transplantation are used to manage patients who are listed for an organ transplant, acting to temporize whilst patients are on the waiting list. Various approaches can be chosen depending on the underlying medical condition and individual characteristics.

In patients awaiting liver transplant, TIPS placement can be an option to manage complications associated with portal hypertension, in order to reduce morbidity and mortality. Ascites, hydrothorax, and GI bleeding represent frequent and widely recognized indications for TIPS placement, based on the well-established literature data assessing complication management and mortality as outcomes ^{[9][10]}. However, a transplant perspective may anticipate the TIPS procedure to improve a patient's clinical condition at the time of transplantation. Furthermore, in the case of portal vein thrombosis, the TIPS procedure could preserve the technical feasibility of the transplant itself.

As it is known, TIPS is sometimes needed to treat complications of portal hypertension in a bridge-to-transplant setting, even in patients at high risk of decompensation and mortality. A recent meta-analysis based on individual data showed that, compared with standard therapy, the use of TIPS reduces the incidence of further decompensation events, regardless of the indication, and so, it increases survival in highly selected patients with variceal bleeding and refractory ascites ^[11]. Patients on a liver transplant waiting list are mostly individuals with end-stage liver disease, who frequently have already experienced multiple episodes of liver decompensation. While waiting for a liver graft, they may experience further decompensation and die before being transplanted. As recently demonstrated in a further meta-analysis and a

previous study on the clinical course of cirrhosis [11], most deaths occur when episodes of decompensation become recurrent.

According to a French study published in 2022 [12], the dropout rate due to death or disease worsening in a list of 15,584 patients waiting for liver transplantation, during a 10-year observation time, was approximately 22%. Overall, 46.6% of these patients were listed for HCC. Similar results were obtained from a study on portal vein thrombosis (PVT) [13], showing dropout rates even greater than 20%, considering that PVT may also compromise the technical feasibility of liver transplantation.

Indeed, PVT is a common event in cirrhosis, with a prevalence ranging from 2% to 26% in liver transplant candidates [14], and is associated with a 62% increase in the risk of mortality compared with cirrhotic patients without PVT [15]. PVT is also associated with increased mortality in the post-transplant period [16]. A large study conducted in a single center, involving over 3200 liver transplant candidates, found that those undergoing transplantation with an occlusive PVT had a sevenfold higher risk of mortality at 30 days compared with those without PVT [17]. One retrospective study using the Organ Procurement and Transplant Network (OPTN) database reported that the prevalence of PVT at candidate registration increased between 2002 and 2014 and that the presence of PVT was associated with an increased waitlist dropout [13].

TIPS placement can be difficult in the setting of PVT or cavernomatosis, even though recent studies suggest that the success rate of the procedure is improving due to new technical approaches [18][19]. In a recent randomized controlled study, the success rate of TIPS placement was very high and, in addition to excellent rebleeding control, TIPS also improved recanalization of the portal vein [20]. Anticoagulation (AC) represents the first-line therapeutic strategy for PTV. In a systematic review [21] and a recent prospective observational study [22], the efficacy of AC and TIPS placement in PVT were compared. Both strategies were found to be effective in achieving portal vein recanalization.

However, anticoagulation therapy takes some time to act and can be difficult to perform in patients with advanced liver disease and very low platelet count.

In a large systematic review, including 399 PVT patients (92% of whom had cirrhosis), the success rate of the TIPS procedure was approximately 95% (95% confidence interval, CI: 89–98%), even though patients were significantly heterogeneous, primarily due to a proportion of patients with cavernomatosis [23].

To face technical difficulties caused by a complete portal thrombosis or a portal cavernomatosis, alternative techniques have been described, such as the transhepatic and trans-splenic approaches, reaching almost 100% technical feasibility and allowing many patients previously excluded from transplantation to access it [18][19]. In the clinical practice, TIPS should be proposed when anticoagulant treatment is contraindicated or unsuccessful and the radiological approach is technically feasible, or in patients with transplant perspectives presenting with other complications of portal hypertension that would benefit from shunt placement. Indeed, portal vein recanalization and TIPS may improve a patient's candidacy for liver transplantation [24].

Variceal bleeding represents one of the worst decompensations of liver cirrhosis, with a high rate of mortality. Endoscopic band ligation (EBL) and non-selective beta-blockers (NSBBs) represent the first step in the management of variceal bleeding, both in primary and secondary prophylaxis. However, there is an estimated 15–21% risk of treatment failure or rebleeding in these patients, causing a rate of mortality as high as 80% [25]. In this perspective, TIPS placement in high-risk variceal bleeding patients (pre-emptive TIPS) has been clearly demonstrated to be superior to the standard medical treatment in improving survival [26][27][28][29]. A recent individual patient meta-analysis showed that preemptive TIPS significantly increased the proportion of high-risk patients with cirrhosis and acute variceal bleeding who survived for 1 year, compared with drugs plus endoscopy (hazard ratio (HR) 0.443; 95% CI 0.323–0.607; $p < 0.001$) [30]. The placement of TIPS on time, reducing mortality and rapid deterioration of liver disease, allows more patients to access liver transplantation.

Refractory ascites is a common complication of advanced cirrhosis, involving 5–10% of patients [31]. Diuretics and repeated large volume paracentesis (LVP) are the first line strategy to manage ascites decompensation. However, as time passes, patients may experience a range of related complications, such as hypotension, acute kidney injury, hepatorenal syndrome, and spontaneous bacterial peritonitis.

TIPS placement is an effective therapy for refractory ascites and has been recently proposed also for recurrent ascites, even if results for survival benefits are controversial [32][33][34]. One meta-analysis analyzed aggregated individual patient data from four randomized controlled trials, revealing that TIPS led to a significant improvement in liver transplant-free (LTF) survival [35]. In another study, the proportions of liver disease-related deaths were 30% and 40% in the TIPS and

paracentesis groups, respectively [36], and no significant difference was observed in the number of patients who underwent liver transplantation. Based on the presented data, it is apparent that two distinct patient cohorts (LVP versus TIPS) demonstrated comparable mortality rates but diverged significantly in terms of survival duration. The improved LTF observed in TIPS patients is primarily attributed to a reduction in portal hypertension-related mortality. Another contributing factor to enhanced LTF survival is the prolonged interval before liver transplantation, as demonstrated by two studies [37][38].

In a retrospective study, cirrhotic patients who underwent TIPS for refractory ascites were compared to similar patients who underwent serial paracentesis. After adjusting for patient characteristics, TIPS patients showed improved survival compared with those who underwent paracentesis, with significant differences in survival rates at 1, 2, and 3 years [39]. However, the patient eligible for TIPS should be carefully selected, taking into account the stage of liver disease, which serves as a warning for the high rate of decompensation and death after the procedure, although a retrospective study from 2019 showed that mortality in this kind of patient (MELD > 18) appears to be independent of the therapeutic strategy (LVP vs. TIPS) [40].

Malnutrition is a common feature of cirrhosis and significantly impacts the disease's prognosis [41][42][43][44]. The rate of sarcopenia is directly related to the stage of liver disease [45]; for this reason, alterations in nutritional status can significantly impact the prognosis in patients waiting for liver transplantation [46]. Sarcopenia can sometimes represent a relative contraindication for surgery due to the higher rate of death or complication during and after liver transplantation [45][47].

A strong interrelation has been reported between TIPS placement and patient nutritional status. On the one hand, patients with advanced sarcopenia have a worse prognosis after TIPS in terms of hepatic decompensation, acute-on-chronic liver failure, and survival [48][49][50]. On the other hand, TIPS placement may improve nutritional status and sometimes can even reverse the condition of sarcopenia [51]. Montomoli et al., in a prospective observational study, investigated the effect of TIPS on malnutrition in portal hypertensive cirrhotic patients, and they observed that dry lean mass increased in low- or normal-weight patients after TIPS placement but did not in overweight patients [52]. It is still under debate whether TIPS placement could be anticipated in some patients with complications of portal hypertension and also to prevent advanced malnutrition and sarcopenia [51].

In this context, TIPS placement within a “therapeutic window” may lead to improved nutritional status for the patient and prevent advanced malnutrition from also becoming a risk factor for liver transplant surgery.

Lastly, it is important to note that cirrhosis is a chronic condition characterized by persistent and recurring complications, which significantly contribute to the overall burden of healthcare costs. In this context, TIPS, allowing a reduction in the rate of liver decompensation, a decrease in portal hypertension-related complications, and limiting frequent hospitalizations may lead to cost reduction, better management, and an improved economic impact [53]. This consideration could be particularly true if researchers consider patients with refractory/recurrent ascites who require frequent LVP, access to day hospitals or hospitalizations, and treatment for further decompensations. This savings would allow for a larger amount of resources to be available for diagnostic and therapeutic needs for patients awaiting liver transplantation.

The choice of the best timing for TIPS placement during the natural history of cirrhosis is at present an important topic with no definitive answers. However, even if researchers cannot provide, based on the current literature, a specific recommendation regarding the timing of TIPS placement, researchers suggest carefully considering and balancing indications and contraindications of the procedure at any new clinical event in order to manage portal hypertension complications and timely predict potentially unfavorable conditions for LT. In some patients, a multidisciplinary discussion and a team decision could be helpful to take care, accurately, of the complete patient's individual context. Indeed, it is well-known that TIPS placement can also give rise to several adverse effects, including an acceleration of liver failure due to decreased blood supply [54][55], the exacerbation of cardiomyopathy [56][57], and the occurrence of HE [58][59], which stands out as the most prevalent clinical complication during the early period following TIPS placement. All these adverse events need to be taken carefully into account before the TIPS procedure. Nonetheless, recent evidence indicates that HE is preventable [60] and treatable in the majority of patients and does not impact a patient's long-term prognosis [61].

Interestingly, a retrospective, single-center study purposely investigated the role of TIPS as a bridge therapy in liver transplant-eligible patients [62]. Of the 98 patients who were enrolled, 73 had TIPS placed before being listed, and 25 underwent the TIPS procedure while on the waiting list. Both groups were compared to a control group of 60 patients without TIPS. The timing of TIPS placement, before or after being listed, did not impact the survival rate before transplantation. The mortality rate of the patients on the waiting list was reported to have decreased after TIPS placement

was introduced as an option, according to clinical indications compared with historical data reported in the same center. Some patients were even delisted due to clinical improvement after TIPS placement; in this latter group, the authors showed a similar 5-year overall survival rate compared with those who underwent liver transplantation.

In the past, TIPS was investigated as a potential technique to mitigate intraoperative blood loss during transplantation, thereby positively influencing short-term outcomes [63][64][65][66]. Moreno et al. conducted an extensive comparative longitudinal retrospective study of 875 patients aimed at assessing the short- and long-term outcomes of liver transplantation by comparing individuals with TIPS and those without. The study evaluated various endpoints, including the duration of surgery, cold ischemia time, warm ischemia time, blood product need, postoperative complications (both vascular and non-vascular), length of stay in the Intensive Care Unit (ICU), total hospital stay, re-transplantation rates, and 1- and 3-year survival rates. Remarkably, no statistically significant differences were observed between the two groups in any of these parameters [67]. Similar conclusions were reported by Dell'Era et al., who found no significant differences between patients with prior TIPS placement and a control group with regard to transfusion requirements, operative time, overall length of hospital stay, ICU length of stay, and complication rates [68].

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