Journal of Clinical and Translational Hepatology **2022** vol. 10(6) | 1223–1228
DOI: 10.14218/JCTH.2022.00240

Review Article

Pre-emptive TIPSS in Acute Variceal Bleeding: Current Status, Controversies, and Future Directions

Yu Jun Wong[1,2*], Wei Ling Danielle Ho[1] and Juan G. Abraldes[3]

[1]Department of Gastroenterology and Hepatology, Changi General Hospital, Singapore; [2]Duke-NUS Medical School, Singapore; [3]Division of Gastroenterology, University of Alberta, Edmonton, Canada

Received: 18 May 2022 | **Revised:** 28 June 2022 | **Accepted:** 11 July 2022 | **Published:** 29 July 2022

Abstract

Acute variceal bleeding (AVB) is associated with significant short-term morbidity and mortality. Pre-emptive transjugular intrahepatic portosystemic shunt (p-TIPSS) is recommended to prevent rebleeding in AVB patients with a high risk of rebleeding. Despite the benefit of preventing rebleeding and *de-novo* ascites, the uptake of p-TIPSS remains low because logistic challenges in the real-world setting. In this review, we summarize the current evidence and controversies on p-TIPSS including patient selection for p-TIPSS, particularly in the setting of NASH cirrhosis and acute-on-chronic liver failure, the role of sarcopenia, renal impairment in the setting of p-TIPSS. Finally, we summarize both pharmacological and nonpharmacological strategies to optimize outcomes in patients undergoing p-TIPSS.

Citation of this article: Wong YJ, Ho WLD, Abraldes JG. Pre-emptive TIPSS in Acute Variceal Bleeding: Current Status, Controversies, and Future Directions. J Clin Transl Hepatol 2022;10(6):1223–1228. doi: 10.14218/JCTH.2022.00240.

Introduction

Acute variceal bleeding (AVB) is a common and lethal complication in cirrhosis patients, with short-term mortality ranging between 20% and 30%.[1] The goal of management in AVB is to control bleeding, prevent rebleeding and bleeding-related mortality from infection and acute-on-chronic liver failure. Considering bleeding-related mortality as an important complication of AVB, the Baveno-VII consensus recommended 6 week mortality as the primary endpoint in studies evaluating treatment for AVB.[2] Current guidelines recommend vasoactive drugs, prophylactic antibiotics, early endoscopy (within 12 hour), and restrictive blood transfusion to improve survival in AVB. Moreover, variceal eradication and beta-blocker combination therapy have been recommended as secondary prophylaxis to prevent rebleeding in these patients.[3]

Transjugular intrahepatic portosystemic shunt (TIPSS), the creation of a side-to-side shunt between the hepatic vein and portal vein, was introduced in the 1960s as a salvage therapy for AVB refractory to standard treatment.[4] TIPSS was first performed in humans using expandable metallic stents in the 1980s.[5] On one hand, by rapidly reducing the portal pressure, TIPSS effectively prevents rebleeding in AVB and other portal hypertension-related complications, including refractory ascites and hepatic hydrothorax.[3] On the other hand, the diversion of portal blood flow may precipitate hepatic encephalopathy and liver decompensation. While the uncovered metallic stent used in the early days of TIPSS was associated with an increased risk of stent dysfunction and early thrombosis, this dreadful complication was mitigated by the use of expanded polytetrafluoroethylene (e-PTFE) stents to reduce TIPSS dysfunction.[6]

While TIPSS was originally designed as salvage therapy in AVB, the concept of using TIPSS as secondary prophylaxis for AVB was tested in a randomized trial by Jalan *et al*.[7] in 1997. In that randomized controlled trial (RCT), pre-emptive TIPSS (p-TIPSS) insertion following endoscopic hemostasis was found to significantly reduce rebleeding risk in AVB patients, even though the overall survival was similar to that of patients who had received only endoscopic hemostasis.[7] That trial was followed by a study by Monescillo *et al*.,[8] which was the first to demonstrate the survival benefit of p-TIPSS when inserted in high-risk AVB patients with a hepatic venous pressure gradient (HVPG) ≥20 mmHg However, they used uncovered metal stents and sclerotherapy for variceal treatment, which is no longer considered standard of care. Moreover, the use of HVPG to risk-stratify patients for p-TIPSS was also limited by the availability of expertise to perform HVPG outside of specialized centers.

Pre-emptive TIPSS: current status

A landmark study by Garcia-Pagan *et al*.[9] was pivotal in redefining the role of p-TIPSS in the management of AVB. Using simple clinical scores to identify Child-Turcott-Pugh (CTP) class C or CP-B patients with active bleeding during endoscopy and with a high risk of rebleeding, early placement of TIPSS within 72 hour successfully prevented rebleeding and decreased mortality in these patients.[2] The benefits of p-TIPSS go beyond preventing rebleeding to preventing mortality and *de-novo* ascites, without signifi-

Keywords: Transjugular intrahepatic portosystemic shunt; Hemorrhage; Portal hypertension; Cirrhosis.

Abbreviations: AVB, acute variceal bleeding; CTP, Child-Turcotte-Pugh; CSHP, clinically significant portal hypertension; HE, hepatic encephalopathy; HVPG, hepatic venous pressure gradient; NASH, nonalcoholic steatohepatitis; p-TIPSS, pre-emptive transjugular intrahepatic portosystemic shunt.

[*]**Correspondence to:** Wong Yu Jun, Department of Gastroenterology & Hepatology, Changi General Hospital, 2, Simei Street 3; Duke-NUS Medical School, 8 College Road, 169857, Singapore. ORCID: https://orcid.org/0000-0002-0727-1183. Tel/Fax: +65-67888833, E-mail: eugene.wong.y.j@singhealth.com.sg

cantly increasing the risk of hepatic encephalopathy.[3] The benefits of early p-TIPSS were also described in an RCT by Lv *et al*.,[10] independent of active bleeding during endoscopy. In contrast, the survival benefit of p-TIPSS was not observed in an RCT by Dunne *et al*.,[11] yet a higher risk of hepatic encephalopathy following p-TIPSS was observed. Unfortunately, the survival benefit was inconclusive because this study was underpowered because of slow recruitment. To reconcile the controversies on the survival benefit of p-TIPSS, a recent meta-analysis and trial sequential analysis showed that the evidence from current RCTs is insufficient to support a 6 week survival benefit with p-TIPSS compared with the standard of care.[12] A summary of all RCTs evaluating p-TIPSS is shown in Table 1.[7–11,13]

Pre-emptive TIPSS: ongoing controversies

Ongoing controversies in defining the optimal role of p-TIPSS include patient selection, particularly in NASH cirrhosis patients with associated cardiovascular risk factors and in patients with acute-on-chronic liver failure, and the role of sarcopenia and renal impairment in the setting of p-TIPSS.

Patient selection

There are conflicting views on whether patients with Child-Pugh-Turcotte (CPT) class B disease and active bleeding or with MELD scores between 12 and 18 would benefit from pre-emptive TIPSS.[14,15] Whether p-TIPSS remains beneficial when performed after 72 hour is debatable, because real-world evidence suggests that benefits may be observed in patients who underwent TIPSS[16] after 72 hour of AVB. While active bleeding was defined as the presence of active bleeding during the insertion of endoscope, the reliability of the finding is also subject to the time that endoscopy was performed. The finding of active bleeding was associated with an increased risk of death among CTP class B patients in some studies,[15] but not in others.[10,17] Patient selection for pre-emptive TIPSS using the CTP score may be limited by subjective variables within the CTP score as it does not distinguish between the individual phenotype of liver dysfunction (liver synthetic dysfunction versus portal hypertension-related).[18] Moreover, data on the efficacy of pre-emptive TIPSS in preventing rebleeding and death with gastric variceal bleeding is also scarce. A multicenter trial (GAVAPROSEC) is currently underway to compare the benefit of pre-emptive TIPSS and glue obliteration in preventing rebleeding and death in bleeding gastric varices. Lastly, the survival benefit of p-TIPSS was recently questioned,[12] because the standard of care (carvedilol, variceal band ligation, and early access to endoscopy) has improved since the landmark trial conducted a decade ago.[7–9] A large multicenter randomized trial (REACT-AVB) comparing p-TIPSS with the standard of care in patients with Child-Turcotte-Pugh scores 7–13 is underway in the United Kingdom.[19] The trial will address fundamental questions on the survival benefits and the ideal target population for p-TIPSS in cirrhosis patients with AVB.

Pre-emptive TIPSS in NASH-related cirrhosis

Given the rising obesity pandemic, NASH cirrhosis will likely emerge as the driving cause of cirrhosis.[20] However, the impact of p-TIPSS on NASH cirrhosis is not clear, as NASH-related cirrhosis has been under-represented in all the existing trials, in which the primary etiologies were alcoholic cirrhosis and chronic hepatitis B.[7–11] There are several considerations when selecting NASH cirrhosis patients with AVB for p-TIPSS. First, cardiovascular complications, a key exclusion criterion for TIPSS, are prevalent in NASH cirrhosis.[21] Cardiac evaluation is paramount because p-TIPSS may potentially unmask undiagnosed cardiovascular disease. TIPSS insertion shunts a significant volume of blood from the splanchnic into the systemic circulation, with consequential increases in cardiac output and right heart pressure. While the sudden rise in right heart pressure following TIPSS is usually transient, the development of cardiac decompensation following TIPSS can be detrimental.[22,23] Patients with severe left ventricular dysfunction,[24] severe aortic stenosis, or severe pulmonary hypertension should not proceed with p-TIPSS. Current guidelines recommend a 12-lead electrocardiogram and N-Terminal pro-B-type natriuretic peptide before TIPSS insertion.[3,25,26] The fact that NASH cirrhosis patients experience portal hypertension-related at a lower HVPG may affect patient selection for p-TIPSS using HVPG.[27] That is further confounded by the inter-observer variability of HVPG, particularly in cases with decompensated NASH cirrhosis.[28] In summary, TIPSS can be associated with an increased risk of HE and renal dysfunction in NASH-related cirrhosis.[29] Therefore insertion of p-TIPSS in NASH cirrhosis patients must consider co-existing cardiac and renal comorbidities to minimize potential TIPSS-related complications in those patients.

Acute-on-chronic liver failure

Acute-on-chronic liver failure (ACLF) is a clinical syndrome associated with multiorgan failure and high short-term mortality. Because the hemodynamic changes following TIPSS insertion may precipitate cardiac and liver failure, application of p-TIPSS in the setting of ACLF must be supported by strong evidence. In a multicenter prospective cohort study of 2,138 patients with AVB, the presence of ACLF retrospectively defined following European Association for the Study of the Liver–Chronic Liver Failure (EASL-CLIF) consortium criteria predicted mortality in patients with AVB.[30] Among 380 patients (17.8%) who had ACLF, p-TIPSS was associated with a decreased risk of 6-week rebleeding (hazard ratio: 0.128; 95% confidence interval: 0.017–0.937; p=0.043), 42-day mortality (13.6% vs. 51.0%, p=0.002 and 1-year mortality (22.7% vs. 56.5%, p=0.002). However, before confirming the survival benefit of p-TIPSS in the setting of ACLF, there are several key considerations. First, the benefit of p-TIPSS was derived from only 22 ACLF patients (5.6% of the overall ACLF cohort), which raises concerns of the generalizability of the findings. Second, observational studies are subject to selection and indication bias. Subjects who underwent p-TIPSS had lower baseline MELD scores and less severe ACLF grade than those who did not undergo p-TIPSS. Third, there are differences in the definition, clinical phenotype, and primary etiology of ACLF between different ACLF consortia, which complicates patient selection for p-TIPSS in this setting.[31] Between ACLF subjects with or without p-TIPSS, it is important to know the proportions of ACLF patients with intrinsic liver failure and with ongoing sepsis that may deter consideration of p-TIPSS. While p-TIPSS can reduce rebleeding, is it sufficient to change the trajectory of ACLF that results in a survival benefit in ACLF? Given the relative paucity of data, randomized trials are required to confirm the survival benefits on p-TIPSS in the setting of ACLF.

Sarcopenia

Sarcopenia is present in 40% of patients with decompen-

Table 1. Summary of randomized trials evaluating pre-emptive TIPSS in the setting of acute variceal bleeding

Author	Patient characteristics		No. of patients (TIPSS vs. control)	Type of stent	Standard of care	Main findings	HE (%; TIPSS vs. control)
	Definition of high risk	Predominant etiology					
Jalan *et al*. 1997[7]	Not defined	ETOH	31 vs. 27	Expandable uncovered stent	EVL repeated weekly until eradication, and then at 3 and 6 months, and 6-monthly intervals thereafter	Variceal rebleeding frequency and severity reduced with TIPSS (p<0.0006). No significant difference in mortality rates or frequency of HE	36% vs. 33%
Pomier-Layrargues *et al*. 2001[13]	CTP 7–12	ETOH, cryptogenic	41 vs. 39	Not defined	EVL performed on days 1 and 10, then every 3–4 weeks until obliteration. 3-monthly surveillance thereafter	Variceal rebleeding significantly lower in TIPSS group at 2 years (p<0.001) but no difference in survival rate. No difference in probability of HE	47% vs. 44%
Monescillo *et al*. 2004[8]	HVPG ≥ 20mmHg within 24hrs of AVB	ETOH, HCV	26 vs. 26	Uncovered stent	Sclerotherapy then NSBB, or EVL if NSBB contraindicated or not tolerated	No difference in 6-week mortality. Reduction in in-hospital and 1-year mortality with TIPSS (p=0.02, p=0.01 respectively). No increase in de no HE with TIPSS	31% vs. 35%
García-Pagán *et al*. 2010[9]	CTP C≤13 or CTP B with AVB	ETOH, HCV	31 vs. 32	e-PTFE-covered stent	Optimization of NSBB and ISMN. Second EVL within 7–14 days then every 10–14 days until eradication	6-week and 1-year survival higher in early TIPSS (NNT=3.3, NNT=4.0 respectively). Reduction in 1-year rebleeding (p<0.001). No difference in HE (p=0.13)	25% vs. 39%
Lv *et al*. 2019[10]	CTP B or C<14	HBV, HCV, ETOH	86 vs. 46	e-PTFE-covered stent	Optimization of NSBB. Second EVL within 7–14 days, then every 14 days until eradication	Transplant-free survival higher in TIPSS at 6-weeks and 1 year (p=0.02, p=0.046). No difference in HE (p=1.00)	35% vs. 36%
Dunne *et al*. 2020[11]	CTP B and C≤13	ETOH	29 vs. 29	e-PTFE-covered stent	Optimization of NSBB. Endoscopy at 2- to 4-week intervals until variceal eradication	No difference in 6-week or 1-year survival with early TIPSS. Trend toward reduced rebleeding with TIPSS (p=0.09). HE more common with TIPSS (p=0.04)	41% vs. 17%

AVB, acute variceal bleeding; CTP, Child-Turcott-Pugh; ETOH, alcohol; EVL, endoscopic variceal ligation; HBV, hepatitis B virus; HCV, hepatitis C virus; HE, hepatic encephalopathy; HVPG, hepatic venous pressure gradient; NNT, number needed to treat; NSBB, Nonselective beta-blocker; TIPSS, transjugular intrahepatic portosystemic shunt.

sated cirrhosis and has been associated with an increased risk of hepatic encephalopathy and death in cirrhosis patients.[32] Sarcopenia has been associated with an increased risk of HE following TIPSS,[33] this association was not consistently demonstrated.[34] On the other hand, TIPSS was associated with an improvement in sarcopenia.[35] Retrospective analysis of 27 patients showed that the skeletal muscle index improved 6 months following TIPSS insertion. Current guidelines recommend sarcopenia assessment before TIPSS insertion,[25] but sarcopenia should not be considered as contraindication for p-TIPSS. Further studies are required to understand the role of sarcopenia in patient selection for p-TIPSS.

Renal impairment

Most studies on p-TIPSS excluded patients with severe renal impairment[7–11] because TIPSS was associated with a higher risk of hepatic encephalopathy[36] and a lower natriuretic effect in these patients.[37] The presence of acute kidney injury in the setting of AVB is generally not considered a contraindication for p-TIPSS. Among advanced cirrhosis patients with hepatorenal syndrome, TIPSS placement was associated with improvement in renal function, but a significantly higher risk of HE following TIPSS.[38] Moreover, a recent meta-analysis highlighted significant heterogeneity among the included studies and the lack of high-quality studies evaluating TIPSS in patients with hepatorenal syndrome. Due to the increased risk of HE, p-TIPSS in the setting of AVB with hepatorenal syndrome or severe chronic renal impairment is currently considered experimental.

Post-TIPSS hepatic encephalopathy

HE is generally considered a relative contraindication in the setting of rescue TIPSS, as the risk of HE is outweighed by the survival benefit of TIPSS as a life-saving procedure. However, the concern of HE is reasonable in stable patients scheduled for elective p-TIPSS. Overall, the prevalence of post-TIPSS HE in RCTs evaluating p-TIPSS ranges from 25% to 47% (Table 1). Although a meta-analysis of randomized trials suggested a similar rate of HE following p-TIPSS,[12] that information should be interpreted with caution, given that the studies generally excluded patients with recurrent HE or severe renal impairment, yet sarcopenia and covert HE were not systematically assessed in the p-TIPSS setting.

Pre-emptive TIPSS: the way forward

Despite the benefit to prevent rebleeding, p-TIPSS has not been widely adopted because of important logistic challenges, even in expert centers. The feasibility of pre-emptive TIPSS must be considered before adoption because p-TIPSS is a highly specialized and resource-intensive procedure with limited access in most centers in the real-world setting. The challenge in delivering pre-emptive TIPSS within 72 h was reflected in a nationwide French audit including 964 patients with AVB from 58 centers. Even though 35% of the patients fulfilled the criteria for p-TIPSS, only 6.8% underwent p-TIPSS.[39] In a recent randomized trial by Dunne *et al*.,[11] 55% of patients in the p-TIPSS group either had TIPSS performed after 72 h or did not undergo TIPSS at all. The implementation of p-TIPSS also involves transferring critically-ill patients from low-volume centers, which may potentially overwhelm high-volume referral centers. That being said, rather than not performing p-TIPSS, the considerations should guide us in personalizing p-TIPSS in cirrhosis patients with AVB. How can we, then, optimize the outcomes of patients undergoing p-TIPSS? Numerous strategies have been proposed to mitigate the potential complications with p-TIPSS. First, HE is a common occurrence in 35–50% of patients following TIPSS, and is driven by increased ammonia load, infection, inflammation, or liver failure. One should recognize the risk factors of post-TIPSS HE such as advanced age, higher CPT scores, history of overt HE, and sarcopenia. Rifaximin may be considered as a primary prophylaxis for HE prevention before and after p-TIPSS. In a randomized trial including 197 patients undergoing TIPSS, rifaximin before TIPSS was associated with a decreased risk of overt HE (OR: 0.48) compared with placebo.[40] That is in contrast with an earlier trial by Riggio *et al*.[41] which showed that rifaximin did not reduce post-TIPSS HE The urgency to perform p-TIPSS within 72 hour of AVB may influenced the adoption of rifaximin as primary prophylaxis for HE following p-TIPSS. Currently, a European multicenter RCT (the PEARL trial) of combined treatment with rifaximin and lactulose for HE prophylaxis is currently ongoing. The results are highly anticipated.[42]

The existence and diameter of the portosystemic shunt (SPSS) is an independent predictor of post-TIPSS hepatic encephalopathy.[43] A recent randomized trial by Lv *et al*.[44] reported a lower risk of HE following TIPSS with concurrent embolization of a large spontaneous portosystemic shunt in patients undergoing TIPSS. Following embolization of large collaterals, the amount of blood shunting through TIPSS was reduced, as it was limited by the diameter of the TIPSS, which is often smaller than the co-existing large SPSS. The benefit of embolization of SPSS during TIPSS was demonstrated in an observational study by Leng *et al*. in which the risk of HE was similar in patients who underwent SPSS embolization and in those without SPSS.[45] It makes sense that the risk of HE was decreased by creating a new, smaller portosystemic shunt, further randomized trials are needed to confirm safety from the perspective of variceal bleeding and ascites management. Meanwhile, a fully covered, small-diameter controlled-expansion stent can be used to use to minimize the risk of HE following p-TIPSS.[46] Meanwhile, a smaller 8 mm covered stent can be considered as it has been shown equally effective in preventing rebleeding while reducing the risk of post-TIPSS HE by 47% compared with a 10 mm stent.[47] Special attention should be paid to patients with sarcopenia, diabetes mellitus, or renal impairment, in whom the risk of HE is inherently greater.[34,46–49] Patients should maintain sufficient caloric intake of 35–40 kcal/kg/body weight/day and a protein intake of 1.2–1.5 g/kg/body weight per day. Prolonged fasting should be avoided whenever possible. Finally, to reduce the risk of renal impairment, nephrotoxic drugs should be stopped before p-TIPSS, and the amount of iodinated contrast used during TIPSS should be minimized with the help of endovascular ultrasound and carbon dioxide venography.[50]

Conclusions

In summary, p-TIPSS is an important tool to reduce rebleeding in cirrhosis patients with AVB. While the benefits of reducing rebleeding and *de-novo* ascites are evident, controversies remain concerning patient selection, particularly among those with NASH cirrhosis and acute-on-chronic liver failure. Hepatologists must be familiar with the strength and limitations of p-TIPSS and be aware of the strategies to optimize outcomes in patients undergoing p-TIPSS. Future work should focus on improving access to p-TIPSS and individualizing p-TIPSS in the setting of AVB.

Funding

YJW is supported by Nurturing Clinician Scientist Scheme, Duke-NUS Academic Medical Program.

Conflict of interest

YJW has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2020. The authors have no conflict of interests related to this publication.

Author contributions

Study concept (YJW, JGA), drafting the manuscript (YJW, WLDH), critical review of the final manuscript (YJW, JGA).

References

[1] Baiges A, Magaz M, Turon F, Hernández-Gea V, García-Pagán JC. Treatment of Acute Variceal Bleeding in 2021-When to Use Transjugular Intrahepatic Portosystemic Shunts? Clin Liver Dis 2021;25(2):345–356. doi:10.1016/j.cld.2021.01.001, PMID:33838854.
[2] de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Baveno VII Faculty. Baveno VII - Renewing consensus in portal hypertension. J Hepatol 2022;76(4):959–974. doi:10.1016/j.jhep.2021.12.022, PMID:35120736.
[3] Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology 2017;65(1):310–335. doi:10.1002/hep.28906, PMID:27786365.
[4] Rösch J, Hanafee WN, Snow H. Transjugular portal venography and radiologic portacaval shunt: an experimental study. Radiology 1969;92(5):1112–1114. doi:10.1148/92.5.1112, PMID:5771827.
[5] Richter GM, Noeldge G, Palmaz JC, Roessle M. The transjugular intrahepatic portosystemic stent-shunt (TIPSS): results of a pilot study. Cardiovasc Intervent Radiol 1990;13(3):200–207. doi:10.1007/BF02575474, PMID:2121348.
[6] Angeloni S, Merli M, Salvatori FM, De Santis A, Fanelli F, Pepino D, *et al*. Polytetrafluoroethylene-covered stent grafts for TIPS procedure: 1-year patency and clinical results. Am J Gastroenterol 2004;99(2):280–285. doi:10.1111/j.1572-0241.2004.04056.x, PMID:15046218.
[7] Jalan R, Forrest EH, Stanley AJ, Redhead DN, Forbes J, Dillon JF, *et al*. A randomized trial comparing transjugular intrahepatic portosystemic stent-shunt with variceal band ligation in the prevention of rebleeding from esophageal varices. Hepatology 1997;26(5):1115–1122. doi:10.1002/hep.510260505, PMID:9362350.
[8] Monescillo A, Martínez-Lagares F, Ruiz-del-Arbol L, Sierra A, Guevara C, Jiménez E, *et al*. Influence of portal hypertension and its early decompression by TIPS placement on the outcome of variceal bleeding. Hepatology 2004;40(4):793–801. doi:10.1002/hep.20386, PMID:15382120.
[9] García-Pagán JC, Caca K, Bureau C, Laleman W, Appenrodt B, Luca A, *et al*. Early use of TIPS in patients with cirrhosis and variceal bleeding. N Engl J Med 2010;362(25):2370–2379. doi:10.1056/NEJMoa0910102, PMID:20573925.
[10] Lv Y, Yang Z, Liu L, Li K, He C, Wang Z, *et al*. Early TIPS with covered stents versus standard treatment for acute variceal bleeding in patients with advanced cirrhosis: a randomised controlled trial. Lancet Gastroenterol Hepatol 2019;4(8):587–598. doi:10.1016/S2468-1253(19)30090-1, PMID:31153882.
[11] Dunne PDJ, Sinha R, Stanley AJ, Lachlan N, Ireland H, Shams A, *et al*. Randomised clinical trial: standard of care versus early-transjugular intrahepatic porto-systemic shunt (TIPSS) in patients with cirrhosis and oesophageal variceal bleeding. Aliment Pharmacol Ther 2020;52(1):98–106. doi:10.1111/apt.15797, PMID:32452561.
[12] Hussain I, Wong YJ, Lohan R, Lin S, Kumar R. Does preemptive transjugular intrahepatic portosystemic shunt improve survival after acute variceal bleeding? Systematic review, meta-analysis, and trial sequential analysis of randomized trials. J Gastroenterol Hepatol 2022;37(3):455–463. doi:10.1111/jgh.15714, PMID:34665473.
[13] Pomier-Layrargues G, Villeneuve JP, Deschênes M, Bui B, Perreault P, Fenyves D, *et al*. Transjugular intrahepatic portosystemic shunt (TIPS) versus endoscopic variceal ligation in the prevention of variceal rebleeding in patients with cirrhosis: a randomised trial. Gut 2001;48(3):390–396. doi:10.1136/gut.48.3.390, PMID:11171831.
[14] Lv Y, Wang Z, Li K, Wang Q, Bai W, Yuan X, *et al*. Risk Stratification Based on Chronic Liver Failure Consortium Acute Decompensation Score in Patients With Child-Pugh B Cirrhosis and Acute Variceal Bleeding. Hepatology 2021;73(4):1478–1493. doi:10.1002/hep.31478, PMID:32706906.
[15] Nicoară-Farcău O, Han G, Rudler M, Angrisani D, Monescillo A, Torres F, *et al*. Effects of Early Placement of Transjugular Portosystemic Shunts in Patients With High-Risk Acute Variceal Bleeding: a Meta-analysis of Individual Patient Data. Gastroenterology 2021;160(1):193–205.e10. doi:10.1053/j.gastro.2020.09.026, PMID:32980344.
[16] Dunne P, Sinha R, Tripathi D, Hayes P. ATU-06 Does the timing of TIPSS in patients with acute oesophageal variceal bleeding alter patient outcome? Gut 2019;68(Suppl 2):A109.
[17] Lv Y, Zuo L, Zhu X, Zhao J, Xue H, Jiang Z, *et al*. Identifying optimal candidates for early TIPS among patients with cirrhosis and acute variceal bleeding: a multicentre observational study. Gut 2019;68(7):1297–1310. doi:10.1136/gutjnl-2018-317057, PMID:30415233.
[18] Kok B, Abraldes JG. Child-Pugh Classification: Time to Abandon? Semin Liver Dis 2019;39(1):96–103. doi:10.1055/s-0038-1676805, PMID:30634187.
[19] Randomised controlled trial of EArly transjugular intrahepatiC porTosystemic stent-shunt in Acute Variceal Bleeding (REACT-AVB). Funding and Awards 2022. Available from: https://fundingawards.nihr.ac.uk/award/NIHR130883.
[20] Younossi ZM, Stepanova M, Ong J, Trimble G, AlQahtani S, Younossi I, *et al*. Nonalcoholic Steatohepatitis Is the Most Rapidly Increasing Indication for Liver Transplantation in the United States. Clin Gastroenterol Hepatol 2021;19(3):580–589.e5. doi:10.1016/j.cgh.2020.05.064, PMID:32531342.
[21] Sanyal AJ, Van Natta ML, Clark J, Neuschwander-Tetri BA, Diehl A, Dasarathy S, *et al*. Prospective Study of Outcomes in Adults with Nonalcoholic Fatty Liver Disease. N Engl J Med 2021;385(17):1559–1569. doi:10.1056/NEJMoa2029349, PMID:34670043.
[22] Filì D, Falletta C, Luca A, Hernandez Baravoglia C, Clemenza F, Miraglia R, *et al*. Circulatory response to volume expansion and transjugular intrahepatic portosystemic shunt in refractory ascites: Relationship with diastolic dysfunction. Dig Liver Dis 2015;47(12):1052–1058. doi:10.1016/j.dld.2015.08.014, PMID:26427586.
[23] Modha K, Kapoor B, Lopez R, Sands MJ, Carey W. Symptomatic Heart Failure After Transjugular Intrahepatic Portosystemic Shunt Placement: Incidence, Outcomes, and Predictors. Cardiovasc Intervent Radiol 2018;41(4):564–571. doi:10.1007/s00270-017-1848-1, PMID:29181605.
[24] Jansen C, Schröder A, Schueler R, Lehmann J, Praktiknjo M, Uschner FE, *et al*. Left Ventricular Longitudinal Contractility Predicts Acute-on-Chronic Liver Failure Development and Mortality After Transjugular Intrahepatic Portosystemic Shunt. Hepatol Commun 2019;3(3):340–347. doi:10.1002/hep4.1308, PMID:30984902.
[25] Tripathi D, Stanley AJ, Hayes PC, Travis S, Armstrong MJ, Tsochatzis EA, *et al*. Transjugular intrahepatic portosystemic stent-shunt in the management of portal hypertension. Gut 2020;69(7):1173–1192. doi:10.1136/gutjnl-2019-320221, PMID:32114503.
[26] Boike JR, Thornburg BG, Asrani SK, Fallon MB, Fortune BE, Izzy MJ, *et al*. North American Practice-Based Recommendations for Transjugular Intrahepatic Portosystemic Shunts in Portal Hypertension. Clin Gastroenterol Hepatol 2022;20(8):1636–1662.e36. doi:10.1016/j.cgh.2021.07.018, PMID:34274511.
[27] Bassegoda O, Olivas P, Turco L, Mandorfer M, Serra-Burriel M, Tellez L, *et al*. Decompensation in Advanced Nonalcoholic Fatty Liver Disease May Occur at Lower Hepatic Venous Pressure Gradient Levels Than in Patients With Viral Disease. Clin Gastroenterol Hepatol 2021. doi:10.1016/j.cgh.2021.10.023, PMID:34688952.
[28] Bai W, Al-Karaghouli M, Stach J, Sung S, Matheson GJ, Abraldes JG. Test-Retest Reliability and Consistency of HVPG and Impact on Trial Design: A Study in 289 Patients from 20 Randomized Controlled Trials. Hepatology 2021;74(6):3301–3315. doi:10.1002/hep.32033, PMID:34181770.
[29] Ge J, Lai JC, Boike JR, German M, Jest N, Morelli G, *et al*. Nonalcoholic Fatty Liver Disease and Diabetes Mellitus Are Associated With Post-Transjugular Intrahepatic Portosystemic Shunt Renal Dysfunction: An Advancing Liver Therapeutic Approaches Group Study. Liver Transpl 2021;27(3):329–340. doi:10.1002/lt.25949, PMID:33217178.
[30] Trebicka J, Gu W, Ibáñez-Samaniego L, Hernández-Gea V, Pitarch C, Garcia E, *et al*. Rebleeding and mortality risk are increased by ACLF but reduced by pre-emptive TIPS. J Hepatol 2020;73(5):1082–1091. doi:10.1016/j.jhep.2020.04.024, PMID:32339602.
[31] Zaccherini G, Weiss E, Moreau R. Acute-on-chronic liver failure: Definitions, pathophysiology and principles of treatment. JHEP Rep 2021;3(1):100176. doi:10.1016/j.jhepr.2020.100176, PMID:33205036.
[32] Montano-Loza AJ, Meza-Junco J, Prado CM, Lieffers JR, Baracos VE, Bain VG, *et al*. Muscle wasting is associated with mortality in patients with cirrhosis. Gastroenterol Hepatol 2012;10(2):166–173.e1. doi:10.1016/j.cgh.2011.08.028, PMID:21893129.
[33] Nardelli S, Lattanzi B, Torrisi S, Greco F, Farcomeni A, Gioia S, *et al*. Sarcopenia Is Risk Factor for Development of Hepatic Encephalopathy After Transjugular Intrahepatic Portosystemic Shunt Placement. Clin Gastroenterol Hepatol 2017;15(6):934–936. doi:10.1016/j.cgh.2016.10.028, PMID:27816756.
[34] Gioia S, Merli M, Nardelli S, Lattanzi B, Pitocchi F, Ridola L, *et al*. The modification of quantity and quality of muscle mass improves the cognitive impairment after TIPS. Liver Int 2019;39(5):871–877. doi:10.1111/liv.14050, PMID:30667572.
[35] Benmassaoud A, Roccarina D, Arico F, Leandro G, Yu B, Cheng F, *et al*. Sarcopenia Does Not Worsen Survival in Patients With Cirrhosis Undergoing Transjugular Intrahepatic Portosystemic Shunt for Refractory Ascites. Am J Gastroenterol 2020;115(11):1911–1914. doi:10.14309/ajg.0000000000000959, PMID:33156111.
[36] Haskal ZJ, Radhakrishnan J. Transjugular intrahepatic portosystemic shunts in hemodialysis-dependent patients and patients with advanced renal insufficiency: safety, caution, and encephalopathy. J Vasc Interv Radiol

2008;19(4):516–520. doi:10.1016/j.jvir.2007.11.011, PMID:18375295.
[37] Wong F, Sniderman K, Liu P, Blendis L. The mechanism of the initial natriuresis after transjugular intrahepatic portosystemic shunt. Gastroenterology 1997;112(3):899–907. doi:10.1053/gast.1997.v112.pm9041252, PMID: 9041252.
[38] Song T, Rössle M, He F, Liu F, Guo X, Qi X. Transjugular intrahepatic portosystemic shunt for hepatorenal syndrome: A systematic review and meta-analysis. Dig Liver Dis 2018;50(4):323–330. doi:10.1016/j.dld.2018.01.123, PMID:29422242.
[39] Thabut D, Pauwels A, Carbonell N, Remy AJ, Nahon P, Causse X, *et al*. Cirrhotic patients with portal hypertension-related bleeding and an indication for early-TIPS: a large multicentre audit with real-life results. J Hepatol 2017;68(1):73–81. doi:10.1016/j.jhep.2017.09.002, PMID:28918131.
[40] Bureau C, Thabut D, Jezequel C, Archambeaud I, D'Alteroche L, Dharancy S, *et al*. The Use of Rifaximin in the Prevention of Overt Hepatic Encephalopathy After Transjugular Intrahepatic Portosystemic Shunt: A Randomized Controlled Trial. Ann Intern Med 2021;174(5):633–640. doi:10.7326/M20-0202, PMID:33524293.
[41] Riggio O, Masini A, Efrati C, Nicolao F, Angeloni S, Salvatori FM, *et al*. Pharmacological prophylaxis of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt: a randomized controlled study. J Hepatol 2005;42(5):674–679. doi:10.1016/j.jhep.2004.12.028, PMID:15826716.
[42] Prevention of Post-TIPS Hepatic Encephalopathy by Administration of Rifaximin and Lactulose (PEARL). ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/show/NCT04073290.
[43] Praktiknjo M, Simón-Talero M, Römer J, Roccarina D, Martínez J, Lampichler K, *et al*. Total area of spontaneous portosystemic shunts independently predicts hepatic encephalopathy and mortality in liver cirrhosis. J Hepatol 2020;72(6):1140–1150. doi:10.1016/j.jhep.2019.12.021, PMID:31954206.
[44] Lv Y, Chen H, Luo B, Bai W, Li K, Wang Z, *et al*. Concurrent large spontaneous portosystemic shunt embolization for the prevention of overt hepatic encephalopathy after TIPS: A randomized controlled trial. Hepatology 2022. doi:10.1002/hep.32453, PMID:35266571.
[45] Leng X, Zhang F, Zhang M, Guo H, Yin X, Xiao J, *et al*. Comparison of transjugular intrahepatic portosystemic shunt for treatment of variceal bleeding in patients with cirrhosis with or without spontaneous portosystemic shunt. Eur J Gastroenterol Hepatol 2019;31(7):853–858. doi:10.1097/MEG.0000000000001349, PMID:30633039.
[46] Bosch J. Small diameter shunts should lead to safe expansion of the use of TIPS. J Hepatol 2021;74(1):230–234. doi:10.1016/j.jhep.2020.09.018, PMID:32987029.
[47] Wang Q, Lv Y, Bai M, Wang Z, Liu H, He C, *et al*. Eight millimetre covered TIPS does not compromise shunt function but reduces hepatic encephalopathy in preventing variceal rebleeding. J Hepatol 2017;67(3):508–516. doi:10.1016/j.jhep.2017.05.006, PMID:28506905.
[48] Yin X, Zhang F, Xiao J, Wang Y, He Q, Zhu H, *et al*. Diabetes mellitus increases the risk of hepatic encephalopathy after a transjugular intrahepatic portosystemic shunt in cirrhotic patients. Eur J Gastroenterol Hepatol 2019;31(10):1264–1269. doi:10.1097/MEG.0000000000001452, PMID: 31136318.
[49] Wang S, Abraldes JG. Nonalcoholic Fatty Liver Disease: A Special Consideration in Transjugular Intrahepatic Portosystemic Shunts? Liver Transpl 2021;27(3):323–324. doi:10.1002/lt.25976, PMID:33345412.
[50] Gipson MG, Smith MT, Durham JD, Brown A, Johnson T, Ray CE Jr, *et al*. Intravascular US-Guided Portal Vein Access: Improved Procedural Metrics during TIPS Creation. J Vasc Interv Radiol 2016;27(8):1140–1147. doi:10.1016/j.jvir.2015.12.002, PMID:26852944.