

The role of pre-emptive Transjugular Intrahepatic Portosystemic Shunt in acute variceal bleeding: a literature review

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Abstract: The development of portal hypertension has serious implications in the natural history of liver cirrhosis, leading to complications such as ascites, hepatic encephalopathy and variceal bleeding. The management of acute variceal bleeding has improved in the last two decades, but despite the advances in endoscopic methods the overall prognosis remains poor, particularly within a subgroup of patients with more advanced disease. The role of Transjugular Intrahepatic Portosystemic Shunt (TIPSS) is a well-established method of achieving haemostasis by immediate portal decompression; however, its use in an emergency setting as a rescue strategy is still associated with high mortality. It has been shown that 'early' use of TIPSS as a pre-emptive strategy in a patient with acute variceal bleed in addition to the standard of care confers superior survival outcomes in a subgroup of patients at high risk of treatment failure and death. The purpose of this review is to appraise the literature around the indications, patient selection, utility, complications and economic considerations of pre-emptive TIPSS.

Keywords: Pre-emptive; early; transjugular intrahepatic portosystemic shunt; TIPS; TIPSS; portal hypertension; acute variceal bleed; oesophageal varices; hepatic encephalopathy

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Introduction

The presence of portal hypertension is fundamental to the development of severe complications of cirrhosis such as acute variceal bleeding (AVB), ascites and hepatic encephalopathy (HE). These complications define a major turning point in the natural history of liver cirrhosis with high short to medium-term mortality and recurrent hospital admissions.

Despite improvement in the pharmacological and endoscopic management of AVB over the last decade, AVB still carries a high 6-week mortality.¹ Treatment failure with uncontrolled bleeding and recurrent bleeding episodes are risk factors and indeed predictors of higher mortality. As such, patients with these high-risk features are the ideal targets for further focussed management in order to improve survival. In a UK national audit report,² two-thirds of patients presenting with AVB already had a prior history of variceal bleeding. Transjugular intrahepatic portosystemic shunt (TIPSS) is a

non-surgical method of portal decompression, and its role in achieving haemostasis in AVB is well established. However, the creation of TIPSS shunt is a highly specialised procedure and its availability is limited to specialised liver units. In a UK-based National Confidential Enquiry into Patient Outcome & Death (NCEPOD)³ report looking into the death of patients from AVB, the TIPSS procedure was found to be underutilised.

The idea of TIPSS first came to light in the 1960s when accidental portal access was obtained during a transjugular cholangiography procedure.^{4,5} By 1988, the first human TIPSS metallic stent insertion was successfully performed.⁶ Over time the technique has been refined, moving from bare metal stents to Polytetrafluoroethylene (PTFE)-covered stents in the early 2000s with improved stent patency.⁷

Within the management of a variceal bleed, there are various points at which TIPSS can be enlisted.

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Recent advancements and research into AVB management over the last decade have brought into focus the relatively new concept of ‘early’ or ‘pre-emptive’ TIPSS. This refers to TIPSS insertion within 72 h of diagnostic endoscopy (ideally within 24 h where possible⁸) for AVB in haemodynamically stable patients who have received standard care [defined as vasoactive drugs + endoscopic band ligation (EBL) + prophylactic antibiotics] and are likely to be at high risk of future re-bleeding and bleeding-related mortality, with the primary aim of improving survival outcome.

Since its formal conception in 2004,⁹ there has been renewed interest and debate in the use of pre-emptive TIPSS and several studies have attempted to address this with a proven benefit in re-bleeding risk and also a trend towards survival advantage. However, there remain some uncertainties around the real survival benefit of such practice, and as such this concept has not yet been universally adopted. International guidelines also differ in their recommendations. The aim of this review is to examine the literature around the utilisation of pre-emptive TIPSS in the management of AVB.

The concept of early or pre-emptive TIPSS

Variceal haemorrhage is the most common complication of portal hypertension and remains life threatening despite advances in medical therapy.² Patients with AVB remain at high risk of recurrent bleeding. The use of TIPSS is proposed to significantly reduce re-bleeding rates; however, when performed as an emergency or rescue treatment, the mortality rate remains high despite subsequent achievement of haemostasis.

In the 2007 UK national audit,² results indicated that overall 30-day mortality in patients with AVB was as high as 15% with a re-bleeding rate of 26%, compared with a 30-day mortality of 7% in those patients who did not re-bleed.

It is therefore desirable to identify those individuals who are at highest risk of further bleeding and treatment failure and intervene ‘early’ as a preventative strategy to reduce the treatment failure and re-bleeding rate, thereby improving mortality. This prompt intervention in the form of pre-emptive TIPSS was first formally examined in a large multi-centre randomised controlled trial (RCT) by Monescillo *et al.*⁹

This proof-of-concept study demonstrated a clear survival advantage and reduction in treatment failure when pre-emptive TIPSS was performed in a selected high-risk group of patients. High-risk individuals were identified using an invasive haemodynamic measurement of hepatic venous pressure gradient (HVPG). The patient cohort was bifurcated into two groups using HVPG cut-off of 20 mmHg. The high-risk group (HVPG \geq 20 mmHg) received pre-emptive TIPSS, whereas the low-risk group received standard of care comprising endoscopic sclerotherapy and a non-selective beta blocker (NSBB). Pre-emptive TIPSS was found to significantly reduce treatment failure (12% *versus* 50%, $p=0.003$) and improve 1-year mortality (31% *versus* 65%, $p=0.01$). Encouragingly, TIPSS placement was not found to increase *de novo* HE.

Although the study convincingly demonstrated clear 1-year survival and reduced treatment failure it did not translate into increased utilisation, as patients in the non-TIPSS arm were perceived to have received sub-optimal endoscopic therapy by way of sclerotherapy as opposed to variceal band ligation therapy, the latter proven to be the superior endoscopic technique.¹⁰ It is to be noted that the bare metal stent used in this study was subsequently abandoned in future practices in favour of a covered stent, with much superior durability.

A subsequent study by García-Pagán *et al.* in 2010⁸ addressed the drawbacks of the Monescillo *et al.*⁹ study by comparing pre-emptive TIPSS with the current standard of care of EBL + NSBB therapy. It offered a simpler, more clinically relevant way of identifying high-risk patients by Child–Pugh score and endoscopic findings (high-risk defined as Child–Pugh C cirrhosis \leq 13 or Child–Pugh B cirrhosis with active bleeding). They demonstrated a significant reduction in treatment failure and re-bleeding rate, culminating in a clear survival advantage in the pre-emptive TIPSS group. Only 3% of the pre-emptive TIPSS group reached the endpoint of treatment failure or re-bleeding, compared with 45% of the standard care group. One-year survival was 86% in the TIPSS group *versus* 61% receiving standard care ($p < 0.001$). Seven of the standard care patients required a rescue TIPSS, of which four died, a higher mortality than for pre-emptive TIPSS. The findings of this landmark paper proved to be a turning point and generated

a renewed interest in the utilisation of pre-emptive TIPSS both in clinical practice and as a matter for further clinical research.

Pre-emptive TIPSS in light of modern literature

Following on from the above landmark papers, a number of studies have compared outcomes of pre-emptive TIPSS with standard care, which we will examine further in this review. A summary of the papers reviewed can be found in Table 1.

The landmark study by Garcia-Pagán *et al.* was later followed by a post-RCT surveillance study conducted by the same group.¹¹ The aim of this study was to validate the findings in their earlier study. Similar to their initial study, patients treated with pre-emptive TIPSS had a much lower incidence of re-bleeding or failure to control bleeding (7% *versus* 50%; $p < 0.001$). On the contrary, however, 1-year actuarial survival failed to reach statistical significance (86% *versus* 70%, $p = 0.056$). Nevertheless, in keeping with the previous studies TIPSS resulted in a significant reduction in composite primary outcomes [e.g. ascites and spontaneous bacterial peritonitis (SBP)] in both Child–Pugh B (+AVB) and Child–Pugh C patients. Based on the results defined in this paper, it was recommended that pre-emptive TIPSS be offered to this well-defined high-risk subset of patients, rather than risking TIPSS as a rescue technique in potentially much sicker patients. It is noteworthy that only 75 patients over a 4-year period met inclusion out of 659 patients admitted with AVB, highlighting the fact that this group represents a small subset of patients with AVB who require early identification and appropriate onwards referral to centres with expertise in delivering TIPSS services.

Published only a year later, a matched prospective study¹² of 31 patients admitted to a Parisian Intensive Care Unit (ICU) failed to show a survival benefit in pre-emptive TIPSS (1-year actuarial survival 66.8% *versus* 74.2% $p = 0.78$), though significantly more patients remained free of re-bleeding.

Deltenre *et al.*¹³ conducted the first meta-analysis of its kind and observed reduced rates of mortality and re-bleeding in pre-emptive TIPSS cohorts within 1 year. This well-designed meta-analysis was deliberately stringent on its inclusion and

exclusion criteria, limiting the number of included trials to only four papers^{8,9,12,14} (see Table 1). Some heterogeneity was observed among the studies; the two earlier RCTs found a significant increase in survival in those who underwent pre-emptive TIPSS¹⁴ (in contrast to the latter) but did not power the study sufficiently to consider survival as the primary end point. No significant difference in mortality was observed between Child–Pugh B and C patients; however, the limited sample size and disproportionate number of Child–Pugh C patients with a score ≥ 14 seen in the study by Rudler *et al.*¹² may account for this observed effect.

A ‘real-life’ depiction of practice in a multi-centre French audit across 58 centres by Thabut *et al.*¹⁶ in 2017 found TIPSS to be ‘feasible’ on a daily basis; however, akin to Holster *et al.*,¹⁵ few centres were actively participating in this service. In total only 6.7% of eligible patients actually underwent pre-emptive TIPSS, indicating the important difference between feasibility and practicality. Furthermore, 6.4% had TIPSS placement beyond 72 h. One-year actuarial probability of survival was found to be 86% *versus* 59% ($p = 0.04$). However, patients selected for pre-emptive TIPSS placement were found to have less severe liver disease, and this could have introduced a bias towards a more promising survival outcome. Remarkably, no survival benefit was observed in 29% of Child–Pugh B patients with active bleeding. The only factor that was found to be independently associated with survival benefit at 1 year was severity of liver disease (82.9% Child–Pugh A *versus* 42.5% Child–Pugh C). Unfortunately, this well-conducted study did not record secondary complications such as HE, ascites or re-bleeding rates, which could have been invaluable in depicting these ‘real-world’ data of complications post pre-emptive TIPSS.

Thereafter, two observational studies were published^{17,21} in which pre-emptive TIPSS was again observed to significantly reduce mortality and re-bleeding rates compared with standard care. Hernández-Gea *et al.*²¹ performed a subgroup analysis of Child–Pugh C patients compared with Child–Pugh B with AVB, and found the former showed a significant survival benefit with pre-emptive TIPSS, whereas overall mortality in Child–Pugh B + AVB was low and not significantly different between TIPSS and standard therapy.

Table 1. Summary of pre-emptive TIPSS studies (2013–2020) comparing pre-emptive TIPSS with standard care.

Author	Country	Study type	No. of patients (TIPSS/control)	Predominant cohort Pathology	Pre-emptive TIPSS criteria	Percentage Child–Pugh A/B/C	Treatment failure/re-bleeding outcomes (pre-emptive TIPSS versus standard care)	Mortality/Survival (pre-emptive TIPSS versus standard care)	HE incidence (pre-emptive TIPSS versus standard care)
García-Pagán <i>et al.</i> ¹¹	Europe	Surveillance study	75 (45/30)	ETOH 57% HCV 12% HCV + ETOH 8% Other 23%	CP-C 10–13 or CP-B + AVB	0/37/63%	Total treatment failure/re-bleeding = 7% versus 50% ($p < 0.001$) 1-year actuarial probability of treatment failure/re-bleeding 7% versus 4.7% ($p < 0.001$)	1-year mortality = 14% versus 30% ($p = 0.056$) 1-year actuarial survival = 86% versus 61% ($p < 0.001$)	51% versus 50% ($p = 1.00$) 1-year actuarial probability 52% versus 49% ($p = n.s.$)
Rudler <i>et al.</i> ¹²	France	Cohort study	62 (31/31)	ETOH 77% Virus 5% ETOH + virus 13% Other 5%	CP-C ≤ 15 or CP-B + AVB	0/23/77%	Total treatment failure/re-bleeding = 0% versus 29% ($p < 0.001$) 1-year actuarial probability of treatment failure/re-bleeding = 3% versus 49% ($p < 0.001$)	1-year mortality = 26% versus 29% ($p = 0.77$)	45.1% versus 51.6% ($p = 0.61$)
Deltenre <i>et al.</i> ¹³	Europe	SR + MA	252	See associated studies ^{8,9,12,14}	See associated studies ^{8,9,12,14}	See associated studies ^{8,9,12,14}	Total treatment failure/re-bleeding = 8% versus 51% ($p < 0.001$)	Absolute mortality = 20% versus 40% ($p = 0.02$)	Pre-emptive TIPSS was not associated with higher rates of HE (OR = 0.84, 95% CI = 0.50–1.42, $p = 0.5$)
Holster <i>et al.</i> ¹⁵	Netherlands	RCT	72 (37/35)	ETOH 43% HBV/HCV 11% ETOH + HBV/HCV 8% Autoimmune 25% Other 13%	n/a – only excluded CP > 13	36/51/13%	Re-bleeding = 0% versus 29% ($p = 0.001$) Treatment failure = 38% versus 34% ($p = 0.685$)	Absolute mortality = 32% versus 26% ($p = 0.41$) 2-year survival = 92% CP-A, 76% CP-B, 56% CP-C	Early HE (within 1 year) = 35% versus 1.4%; $p = 0.035$ Long-term HE = 38% versus 23%; $p = 0.121$

(Continued)

Table 1. (Continued)

Author	Country	Study type	No. of patients (TIPSS/control)	Predominant cohort Pathology	Pre-emptive TIPSS criteria	Percentage Child-Pugh A/B/C	Treatment failure/re-bleeding outcomes (pre-emptive TIPSS versus standard care)	Mortality/Survival (pre-emptive TIPSS versus standard care)	HE incidence (pre-emptive TIPSS versus standard care)
Thabut <i>et al.</i> ¹⁶	France	Audit	964	ETOH 67% Viral 15% (HCV13%, HBV 2%) Other 18% (NASH 3%)	CP-C 10-13 or CP-B + AVB	21/44/35%	Re-bleeding = 4.5% versus 9.5% at day 42 ($p = \text{not stated}$)	Absolute mortality = 9% versus 18.5% at day 42, 23% versus 33% at 1 year ($p = \text{not stated}$) 1-year actuarial probability of survival 86% versus 59% ($p = 0.04$)	Not available
Njei <i>et al.</i> ¹⁷	USA	Observational study	142,539	Not specified	N/a - not specified	Not specified	In-hospital re-bleeding = 0.5% versus 15.4% ($p < 0.01$)	In-hospital mortality = 1.5% versus 5.6% ($p < 0.01$)	30.1% versus 27.3% ($p = 0.19$)
Hermie <i>et al.</i> ¹⁸	Belgium	Observational cohort study	32 (32/0)	ETOH 84% HCV 6% PSC 6% NASH 3%	CP-C 10-13 or CP-B + AVB	0/56/44%	Not available	6-week mortality = 31.3% 1-year mortality = 31.3%	Not available
Ly <i>et al.</i> ¹⁹	China	RCT	132 (86/46)	ETOH 10% HBV 56% HCV 6% Other 29%	(1) MELD ≥ 19 (2) CP-C (3) CP-B + AVB or CP-C ≤ 13 (4) CP-C with creatinine ≥ 1 mg/dL	35/55/8%	Total treatment failure/re-bleeding = 10.7% versus 40.7% ($p < 0.001$) Cumulative incidence at 6 weeks [5.8% versus 28.1%, $p < 0.001$] and 1 year (10.7% versus 40.1%, $p < 0.001$)	6-week mortality = 3.6% versus 10.6% ($p = 0.002$) 1-year mortality = 14.1% versus 17.3% ($p = 0.218$) at 1 year	25.7% versus 20.4% ($p = 0.41$) at 6 weeks 37.4% versus 20.4% ($p = 0.57$) at 1 year
Ly <i>et al.</i> ²⁰	China	Observational study	1425	ETOH 5% HBV 74% HCV 5% AIH 3% PBC 3% Cryptogenic 10%	CP-C10-13 or CP-B + AVB	0/78/22%	Total treatment failure/re-bleeding = 13% versus 38% ($p < 0.0001$) Actuarial probability of remaining free from uncontrolled bleeding/re-bleeding at 1 year 89% versus 66% ($p = 0.001$ for ARD)	Absolute mortality = 18% versus 33% ($p = 0.04$) Actuarial transplantation-free survival at 6 weeks 99% versus 84% ($p = 0.02$ for ARD), at 1 year 86% versus 73% ($p = 0.046$ for ARD)	35% versus 36% ($p = 0.72$)

(Continued)

Table 1. (Continued)

Author	Country	Study type	No. of patients (TIPSS/control)	Predominant cohort Pathology	Pre-emptive TIPSS criteria	Percentage Child-Pugh A/B/C	Treatment failure/re-bleeding outcomes (pre-emptive TIPSS versus standard care)	Mortality/Survival (pre-emptive TIPSS versus standard care)	HE incidence (pre-emptive TIPSS versus standard care)
Hernández-Gea <i>et al.</i> ²¹	Europe and Canada	Observational study	671	ETOH 76% Viral 30% Other 12%	CP-C 10–13 or CP-B + AVB	0/35/65%	Total treatment failure/re-bleeding = 4.5% versus 23.3% (<i>p</i> = not stated) Cumulative incidence remaining free of treatment failure/re-bleeding: 92% versus 74% (<i>p</i> = 0.017)	Absolute mortality = 18% versus 35% (<i>p</i> = not stated) 1 year mortality 22% versus 47% (<i>p</i> = 0.002)	42% versus 38%
Trebicka <i>et al.</i> ²²	Europe and Canada	Observational study	2138	ETOH 47.1% Viral 23.7% ETOH & viral 13.2% Other 15.9%	CP-C 10–13 or CP-B + AVB	22/51/27%	In patients with ACLF, pre-emptive TIPSS was associated with a lower 42-day re-bleeding rate (percentages unavailable) HR 0.128; 95% CI 0.017–0.937	In patients with ACLF: 42-day mortality = 13.6% versus 51% (<i>p</i> = 0.002) 1-year mortality = 22.7% versus 56.5% (<i>p</i> = 0.002)	Not stated
Dunne <i>et al.</i> ²³	UK	RCT	58 (28/29)	ETOH 93% NAFLD 5% Viral 2%	CP-C 10–13 or CP-B + AVB	0/43/57%	1-year re-bleeding = 24.1% versus 34.6% (<i>p</i> = 0.86)	Overall mortality = 21% versus 24% (<i>p</i> = not stated) 6-week survival 89.6% versus 96.5% (<i>p</i> = not stated) 1-year survival 78.3% versus 75.9% (<i>p</i> = 0.79)	46.1% versus 20.7%

ACLF = acute on chronic liver failure; AIH = autoimmune hepatitis; ARD = absolute risk difference; AVB = acute variceal bleeding; CI = confidence interval; CP = child-pugh; HBV = hepatitis B virus; HCV = hepatitis C virus; ETOH = alcohol; HE = hepatic encephalopathy; n/a = not applicable; NAFLD = non-alcoholic fatty liver disease; NASH = non-alcoholic steatohepatitis; MA = meta-analysis; MELD = model for end-stage liver disease; PBC = primary biliary cholangitis; RCT = randomised controlled trial; SR = systematic review; TIPSS = transjugular intrahepatic portosystemic shunt; UK = United Kingdom; USA = United States of America

More recently, the promising results of pre-emptive TIPSS in the earlier Western studies seem to be replicated in the Chinese cohorts of two studies carried out by the same group,^{19,20} the first showing a lower cumulative incidence of failure to control bleeding or re-bleeding at both 6 weeks and 1 year. The latter study²⁰ used survival as the primary end point, and confirmed that pre-emptive TIPSS was superior in improving transplant-free survival at 6 weeks (99% *versus* 84% $p=0.04$, absolute risk difference 15%) and 1 year (86% *versus* 73% $p=0.0460$) and reducing treatment failure (13% *versus* 38%, $p<0.0001$). It is worth mentioning that the predominant aetiology of liver disease in these cohorts was viral hepatitis [74% had chronic Hepatitis B (HBV) infection], thus providing external validation to the earlier Western studies in which the predominant aetiologies have been alcohol related. This confirms beneficial effect of pre-emptive TIPSS across different population groups irrespective of the aetiology of liver disease. It is also worth mentioning that HBV cirrhosis patients with persistent detectable HBV DNA were treated with Entacavir and were equally represented in both arms.

Uniquely, Lv *et al.*²⁰ excluded all patients with previous combined therapy of NSBB and EBL, therefore these *de novo* patients are likely to be dissimilar to the real-life patient population presenting at centres globally with an AVB. It is also important to note that this study included all patients with Child–Pugh B and C disease, irrespective of active bleeding at endoscopy, and therefore this cohort is likely to contain a mixture of higher and lower-risk patients. This could, in addition to the slightly lower numbers of Child–Pugh C patients compared with other studies, account for the observed higher survival rate. The study also performed collateral embolisation in 49% of patients post TIPSS, the role of which currently remains unclear.

Conversely, the most recently published UK-based RCT by Dunne *et al.*²³ concluded that pre-emptive TIPSS intervention does not confer survival advantage. It is, however, notable that this study ran from 2012 to 2018 and only succeeded in recruiting 58 patients (29 in each arm), thereby being significantly underpowered and prone to type 2 error. Remarkably, a significant proportion (55%) of patients in the pre-emptive TIPSS groups either did not undergo TIPSS at all or underwent TIPSS insertion >72h from endoscopy. Within

the intention-to-treat analysis, there was no significant difference in survival or re-bleeding between groups, although per-protocol analysis did identify an improvement in re-bleeding rate with TIPSS (0% *versus* 27.6%, $p=0.04$). Given that only 13 patients (45% of the original pre-emptive TIPSS group) were included in this per-protocol analysis, the reliability and statistical power to detect the difference in the primary outcome is likely to be compromised. Interestingly the standard of care group had much better survival outcome (86%) compared with the original Garcia-Pagán study, which may reflect an improvement in the general, pharmacological and endoscopic management of AVB over time, perhaps discrediting the utility of TIPSS alone.

Although the validity of these results is questionable, this study does highlight the logistical difficulty and failure to deliver pre-emptive TIPSS ‘within the time frame’, which has also been reflected in previous studies.^{15,16} This is an important factor when considering recommendations and targets for TIPSS insertion in day-to-day practice.

In summary, there is evidence that pre-emptive TIPSS is successful in the reduction of treatment failure and re-bleeding rates. However, the data are less clear cut with regards to reduction in mortality rates, as seen in the conflicting outcomes from numerous studies.^{15,24} However, its beneficial effects seen in ameliorating secondary complications such as ascites and without increasing HE, may provide a significant argument in its favour.

Defining the high-risk group

Patients with advanced liver disease have more severe portal hypertension and poorer hepatic reserve. It is therefore important to accurately identify this high-risk group to focus on targeted further therapy with pre-emptive TIPSS to improve outcomes. In their proof-of-concept study, Monescillo *et al.*⁹ used HVPG measurement of ≥ 20 mmHg to define the high-risk group within 24h of hospital admission with AVB. In their study, patients with HVPG ≥ 20 mmHg had more treatment failures (50% *versus* 12%, $p=0.0001$), transfusion requirements (blood units 3.7 ± 2.7 *versus* 2.2 ± 2.3 , $p=0.002$), need for intensive care (16% *versus* 3%, $p<0.05$), and worse actuarial probability of survival than the patients with

HVPG measurement of <20 mmHg (low-risk group). Although HVPG measurement is a reliable prognostic marker, it is invasive and adds an additional significant step in the management of these very unwell patients. Additionally, its practicality and availability are limited to a few specialised centres.

Other well-established prognostic tools such as Child–Pugh score and the Model for End Stage Liver Disease (MELD) score have been studied in this context and in fact almost exclusively adopted in subsequent studies on pre-emptive TIPSS. The MELD score was established in 2000 as a prognostic marker for both pre-procedure risk stratification and post-TIPSS outcomes in patients undergoing elective TIPSS in general.²⁵ Since then, MELD has been studied and proved to be a useful tool in predicting post-TIPSS mortality in the emergent setting and also shown to risk stratify patients regarding treatment failure and early death due to AVB.

Studies using the Child–Pugh scoring system to prognosticate patients with AVB clearly demonstrate variations in mortality according to risk stratification, with Child–Pugh A patients having the lowest mortality whilst Child–Pugh B and C pose the highest risk of treatment failure and early death. In García-Pagán's landmark paper, those at high risk of treatment failure were defined as either Child–Pugh C cirrhosis (≤ 13) or Child–Pugh B with active bleeding at time of endoscopy. The authors convincingly demonstrated the survival advantage of early intervention in this high-risk group. More recently however, whilst Child–Pugh C patients have been shown to benefit from early intervention due to their higher risk of treatment failure and early death, patients with Child–Pugh B disease, even with active bleeding at the time of endoscopy, do not seem to universally benefit from pre-emptive intervention with TIPSS, as their overall mortality is low and remains unchanged even with pre-emptive TIPSS. There is ongoing interest in this area, with a very recent meta-analysis of individual patient data revealing improved survival and control of bleeding in both subgroups.²⁶

A large retrospective study by Conejo *et al.*²⁷ analysed a cohort of patients with AVB treated with standard care (endotherapy \pm pharmacotherapy, plus rescue TIPSS in case of treatment failure) and sought to compare mortality using three

different risk stratification criteria: pre-emptive TIPSS criteria (as per García-Pagán), MELD score (≥ 19 indicating high-risk) and C-C1 criteria (low risk defined as Child–Pugh A or B, or Child–Pugh C with creatinine <1 mg/dL, high risk as Child–Pugh C with creatinine ≥ 1 mg/dL).

Out of a total sample size of 915 patients they identified 523 patients theoretically eligible for pre-emptive TIPSS. Overall 6-week mortality in this group was 17%, and the authors categorised the risk of mortality using the above three criteria. All three scoring systems performed well in detecting patients with high risk of mortality post AVB and therefore would be suitable for selecting patients for pre-emptive TIPSS. Some 28.3% of the patients classified as high risk by the pre-emptive TIPSS criteria died whereas only 7.0% of patients classified as low risk died. However, it is notable that the mortality was significantly lower among patients with Child–Pugh class B (11.7%) than with Child–Pugh class C (35.6%) ($p=0.001$). Furthermore, mortality was similar between Child–Pugh B patients with or without active bleeding (11.7%). MELD score also performed well in discriminating mortality, with 46.0% of patients with MELD ≥ 19 dying *versus* 8.1% of patients classified as low risk (MELD <19). Similarly, 51.9% of patients classified as high risk by the Child C-C1 criteria died compared with 10.9% of patients classified as low risk. Overall, patients with Child–Pugh A cirrhosis or MELD scores of 11 or less had low mortality (2–4%), patients with Child–Pugh B or MELD scores of 12–18 had intermediate mortality (10–12%), and patients with Child–Pugh C or MELD scores of 19 or more had high mortality (22–46%).

Similarly, in another multi-centre non-randomised observational study¹⁹ using a large sample size over an extended period of follow-up, the authors compared survival advantage of pre-emptive TIPSS across four different risk categories using Child's Pugh score, MELD, Childs C-1 score and pre-emptive TIPSS criteria. They were able to divide the population into low, medium, and high-risk groups for each category. Although re-bleeding and survival advantages were shown across the cohort, the survival advantage was most pronounced in the high-risk group. Although patients in the intermediate risk groups had a clear benefit in 6-week mortality, the effect was less pronounced beyond this period. Additionally in this study, a MELD score of >19 was for the first time shown

to be strongly associated with mortality reduction with pre-emptive TIPSS as compared with the 'medical group'. This contrasts with previous findings of high MELD beyond 19 being associated with poor outcomes post TIPSS.²⁴ The authors speculated that this effect is probably due to the favourable effect of reduced portal pressure on the gut permeability and subsequent beneficial effect of reduction of bacterial translocation and systemic inflammatory state. However, we believe the findings should be interpreted with caution. Firstly, their predominant sample population consisted of Hepatitis B and Hepatitis C patients with an average bilirubin of 30 µmol/L. Secondly, overall representation of MELD >19 patients was small (<10%). For these reasons the suggestion of beneficial effect of TIPSS in MELD 19 or beyond should be met with some caution and may not be applicable to other aetiologies such as alcohol where serum bilirubin level is usually high. It is clear, however, that the beneficial effect of pre-emptive TIPSS is mostly limited to high-risk patients who are at most risk of death due to recurrent bleeding and the multiple organ failure that ensues. The other significant finding of this study was that the benefit of pre-emptive TIPSS *versus* medical therapy persisted even in those in the medical group who required rescue TIPSS due to recurrent bleeds, confirming the role of TIPSS as a pre-emptive strategy. Findings of this study also confirmed that active bleeding at the time of endoscopy is prognostically relevant, and indeed Child–Pugh B cirrhosis with active bleeding represented a high-risk group who benefitted from early intervention with TIPSS, countering earlier studies.⁸ However, it was not without significant heterogeneity in this group between centres, which highlights the inherent problem of subjectivity and the timing of endoscopy.

In another multi-centre observational study²¹ involving 34 centres, high-risk patients benefiting from early intervention with TIPSS was limited to Child–Pugh C patients, whereas Child–Pugh B patients with active bleeding were found to have a low mortality and did not benefit from pre-emptive TIPSS.

A further study¹⁸ evaluated prognostic markers (including MELD) in their post-TIPSS patients meeting pre-emptive TIPSS high-risk criteria. They found that patients with MELD score ≥ 19 had a significantly lower survival rate post-TIPSS compared with MELD <19 (6-week mortality

57.1% *versus* 11.1%). The presence of haemodynamic instability at presentation was associated with a 6-month mortality of 64.3%, compared with 6.3% for haemodynamically stable patients. They concluded that the poor outcomes seen post-TIPSS in patients with high MELD may warrant the current pre-emptive TIPSS criteria encompassing all Child–Pugh C and Child–Pugh B with AVB to be redefined.

It is to be noted that it is not yet clear at what level a patient is deemed too sick to be able to be considered for pre-emptive TIPSS therapy, and certainly a Child–Pugh score of 14 or beyond and bilirubin level of 80 µmol/L or above are probably considered prohibitive.

Demystifying the risk of hepatic encephalopathy and pre-emptive TIPSS

HE is a common complication of TIPSS, with one-third of patients estimated to develop HE post-TIPSS insertion.²⁸ In rescue TIPSS this has generally been accepted as a risk factor outweighed by the clinical benefit and need for TIPSS as a lifesaving procedure. In the setting of pre-emptive TIPSS, however, HE remains a very legitimate concern in a patient who is otherwise stable and has received the standard of care. Therefore, any benefit of pre-emptive TIPSS has to be appropriately balanced out with the risk of HE. Reassuringly, the data of pre-emptive TIPSS have not shown a statistically significant difference of increased HE in the pre-emptive TIPSS patients in the majority of studies. It is to be borne in mind that studies looking at the benefit of pre-emptive TIPSS will inevitably be subject to selection bias, excluding patients who are deemed to be high risk of HE, for example patients with previous episodes of HE. Twelve aforementioned studies have assessed the risk of HE post-TIPSS insertion, with the majority finding that pre-emptive TIPSS within 72h of admission leads to a significant improvement in relevant clinical outcomes without increasing rates of HE^{9,11,13,21} (see Table 1).

HE remains a concern in two RCTs^{15,23} demonstrating increased rates of HE in the pre-emptive TIPSS groups. One significant finding was the occurrence of HE akin to the pre-covered stent era. Early HE (within 1 year) was found to be significantly more frequent in the TIPSS group (35% *versus* 14%; $p=0.035$), but during

long-term follow-up this difference did not persist (38% versus 23%; $p=0.121$).¹⁵

It should be noted that not only is the percentage of eligible patients actually undergoing TIPSS often small,^{11,17} but this group of patients are usually highly selected, with stringent exclusion criteria based on adverse predictive characteristics such as age, history of previous encephalopathy and sepsis, making this subgroup of patients intrinsically at lower risk of developing HE compared with their counterparts. Equally, baseline characteristics of the patients including use of lactulose and or rifaximin are not routinely explicitly stated in the majority of the above studies. Although overt encephalopathy is the defining feature in most of these studies, covert HE is subtle and subjective and could easily be under-reported.

Current guidelines²⁸ recommend screening all elective TIPSS patients for covert and overt HE using at least two of the following methods: psychometric hepatic encephalopathy score (PHES), quantitative electroencephalogram (EEG), Stroop testing and critical flicker frequency. In cases of AVB, however, such investigations are not always practical or readily available even in the semi-elective state of pre-emptive TIPSS. In such cases a more simplified clinical assessment based on a detailed clinical history and readily available clinical parameters could offer a more pragmatic and timely approach.

Acute variceal bleed in patients with severe alcoholic hepatitis and acute on chronic liver failure and the role of pre-emptive TIPSS in these subgroups

There is very little evidence available regarding TIPSS procedure for AVB in patients presenting with alcoholic hepatitis (AH). Although alcoholic liver disease has been a common aetiology in studies of AVB, AH as a distinct clinical entity has rarely been studied in the context of AVB. This is a unique clinical syndrome with distinct clinical features and histopathological correlation. Patients with AH usually have a background chronic liver disease and associated cirrhosis, though AH can occur independently of this. Patients with AH are prone to portal hypertension and can therefore have an AVB even without established cirrhosis, due to profound inflammatory infiltrates within the hepatic sinusoids. Patients with AH have a very high short-term mortality²⁹ and any bleeding complication will

inevitably confer additional prognostic burden. The incidence, prevalence, and natural history of AVB in AH is not well described in this particular setting. It is, however, a common clinical observation that patients with severe AH (with or without cirrhosis) and AVB have worse prognosis, making this group at high risk of treatment failure and mortality and therefore theoretically highly suitable for pre-emptive TIPSS placement. This point was addressed in a UK-based single-centre experience published as an abstract in 2014.³⁰ Analysis of 54 patients who received pre-emptive TIPSS as intention to treat showed that the AH subgroup had higher average MELD scores, higher HVPG measurements (pre- and post-TIPSS) and higher mortality (50% versus 13% at 6 months) compared with non-AH patients undergoing pre-emptive TIPSS. However, this study lacked comparison with AH patients not receiving pre-emptive TIPSS, and therefore it is difficult to conclude the applicability of pre-emptive TIPSS in these patients. They did, however, demonstrate that patients with AH and AVB have a poor prognosis even with early intervention with TIPSS.

Similarly, acute on chronic liver failure (ACLF) is increasingly being recognised as a distinct clinical syndrome with a high short-term mortality and multi-organ failure. AVB in this context has not been well studied, but is very likely to be associated with additional mortality risk. A recent ancillary study²² on pre-emptive TIPSS was performed to assess the impact of ACLF on variceal bleeding and the risk of TIPSS. ACLF was defined according to the EASL-CLIF consortium.³¹ It was noted that, in comparison to the generalised cohort, ACLF patients had a higher frequency of alcohol aetiology, higher MELD/Child-Pugh scores and more frequently presented with ascites, SBP, HE and hepatorenal syndrome, but a lower rate of previous bleeding.

ACLF patients with AVB had a significantly higher rate of re-bleeding than non-ACLF patients [19.1% versus 10.1% ($p<0.01$) at 42 days, 22.9% versus 17.7% ($p=0.024$) at 1 year]. Mortality was also higher in the ACLF group [47.1% versus 10.0% ($p<0.001$) at 42 days, 55.0% versus 23.1% ($p<0.001$) at 1 year]. Both the risk of re-bleeding and mortality were increased in line with severity of ACLF. Performing pre-emptive TIPSS in the ACLF cohort resulted in significantly lower mortality compared with standard care at both 42 days (13.6% versus 51.0%, $p=0.002$) and at 1 year (22.7% versus 56.5%, $p=0.002$). Pre-emptive

TIPSS was also associated with a lower 42-day re-bleeding rate. TIPSS additionally improved mortality in non-ACLF patients, but to a lesser, non-significant degree. Of note, many patients with ACLF grade 3 did not receive a TIPSS, and as such the non-TIPSS group had higher ACLF grades and higher average MELD scores. This selection bias may explain the much higher mortality rate seen in the non-TIPSS group.

There is a relative paucity of data regarding AH/ACLF, and as such more research is required. We know that mortality and re-bleeding rates are high in these patients, and therefore any proposed intervention should have a reasonable chance of achieving clinical improvement over and above standard care. One must consider that although the TIPSS procedure may improve portal pressures, it carries a well-perceived risk of precipitating further liver failure.

Cost effectiveness of pre-emptive TIPSS and real-life practicalities/service delivery

When considering the potential benefits of pre-emptive TIPSS over and above that of standard care one has to consider its cost implications and economic viability that would help argue the case for its equivalence, if not confirm its superiority. Unfortunately, no direct cost comparison of pre-emptive TIPSS in the setting of secondary prophylaxis of acute variceal bleed has been undertaken to date. However, there have been some attempts made in modelling cost effectiveness of TIPSS therapy with standard endoscopic therapy \pm NSBB.

In a UK-based economic modelling study, Harman *et al.*³² performed a cost-effectiveness analysis on a retrospective cohort over a 1-year period. Thirty-five percent of the patients presented with AVB were identified to be eligible for pre-emptive TIPSS. The actual cost of a 12-month follow-up was £138,473.50. Using 3.2% as an assumed re-bleeding rate, the authors estimated pre-emptive TIPSS insertion would save £534.70 per patient per year ($p < 0.0001$). On sensitivity analysis, pre-emptive TIPSS dominated standard care up to a pre-emptive TIPSS re-bleeding rate of 6% and remained cost-effective up to a re-bleeding rate of 12%. Based on this analysis, a careful selection of patient for TIPSS eligibility is the key to utilising TIPSS therapy in favour of healthcare cost.

A few recently published abstracts have also investigated the cost effectiveness of pre-emptive TIPSS *versus* standard treatment. In a study by Pérez-Mitru *et al.*³³ the authors utilised a 2-year Markov model in a Spanish national health care system to measure the clinical and economic consequences of pre-emptive TIPSS with PTFE stents compared with EBL \pm pharmacotherapy in patients with AVB and high risk of treatment failure. The economic model showed a minimal incremental cost per patient of €57 using pre-emptive TIPSS with PTFE-covered stent grafts (€7657 for TIPSS *versus* €7600 for endoscopic approach). Mortality was reduced with pre-emptive TIPSS by 56% compared with endoscopic treatment, resulting in 0.4 life-years gained (LYG) per patient. Consequently, incremental cost per LYG ratio resulted in €137. Sensitivity analysis indicated that model estimations were maintained across various tested scenarios. The main cost saving came from reduction in the re-bleeding rate and related EBLs. Thus the authors concluded that pre-emptive TIPSS with PTFE-covered stent grafts compared with EBL plus pharmaceuticals in high-risk patients with AVB would improve survival at a neutral incremental cost for the Spanish NHS.

In a similar economic modelling³⁴ from the UK healthcare national database, using pre-emptive TIPSS with stent grafts compared with EBL plus pharmacotherapy was estimated to save £1655 per patient over 2 years. Although initial TIPSS cost was over £4000 higher than the EBL arm, savings regarding fewer endoscopic procedures/pharmaceuticals, fewer re-bleeding episodes and reduction in encephalopathy outweighed this. Mortality was also reduced in the TIPSS arm. Sensitivity analyses showed the results were sensitive to device costs, frequency of EBL procedures and the relative rates of severe HE per patient.

Another potential desired outcome of TIPSS creation is resolution of ascites and related improved quality of life. Given that the high-risk patients of AVB are more likely to have concurrent ascites, the combined effect on ascites resolution and reduction in re-bleeding rate makes TIPSS a more attractive option in the longer term.

Studies looking into the cost effectiveness of TIPSS in the setting of (refractory) ascites have tended to favour TIPSS. In a relatively recent study³⁵ the authors concluded that

Table 2. Summary of current international guidelines regarding pre-emptive TIPSS.

Guidelines	Year	Pre-emptive TIPSS recommendation	Definition of high-risk group (patients most likely to benefit from pre-emptive TIPSS)
Baveno VI Consensus Workshop ¹	2015	Pre-emptive TIPSS with PTFE-covered stents within 72 h (ideally <24 h) must be considered in patients with variceal bleeding at high risk of treatment failure after initial pharmacological and endoscopic therapy. Criteria for high-risk patients should be refined.	CP-C <14 or CP-B with active bleeding
British Society of Gastroenterology (BSG) ³⁶	2015	After satisfactory haemostasis, and depending on local resources, pre-emptive covered TIPSS (<72 h after index variceal bleed) can be considered in selected patients.	CP-C <14 or CP-B with active bleeding
American Association for the Study of Liver Diseases (AASLD) ³⁷	2016	In patients at high risk of failure or re-bleeding who have no contraindications, Pre-emptive TIPSS within 72 h may benefit selected patients.	CP-C cirrhosis or CP-B with active bleeding
The European Association for the Study of the Liver (EASL) ³⁸	2018	Pre-emptive covered TIPSS (within 24–72 h) can be suggested in selected high-risk patients. However, the criteria for high-risk patients, particularly CP-B with active bleeding, remain debatable and need further study.	CP-C <14
British Society of Gastroenterology ²⁸	2019	Pre-emptive TIPSS (within 72 h) can be considered in high-risk haemodynamically stable patients, where local resources allow. Large multi-centre RCTs are necessary to determine whether patients with CP-B and active bleeding or with MELD 12–18 benefit from pre-emptive TIPSS.	CP-C <14 or MELD ≥19

CP = child-pugh; h = hours; MELD = model for end-stage liver disease; PTFE = polytetrafluoroethylene; RCT = randomised controlled trial; TIPSS = transjugular intrahepatic portosystemic shunt

TIPSS placement early in the natural history of recurrent ascites has a better incremental cost-effectiveness ratio adjusted by Quality-Adjusted Life Year as compared with large-volume paracentesis (LVP) + albumin infusion.

One of the key factors which could neutralise and potentially tilt the economic benefit and patient quality of life balance against pre-emptive TIPSS is the development of post-TIPSS encephalopathy, which has been described in the section as above.

Pre-emptive TIPSS in light of international guidelines and consensus

International guidelines have some variation their recommendations of pre-emptive TIPSS (see Table 2).

Summary and conclusion

Overall, the early or pre-emptive use of TIPSS in the management of AVB shows a trend towards improved outcomes in the currently published literature. There has unarguably been a clear statistically significant reduction in the 6-week and 1-year treatment failure and re-bleeding rates.^{11–13,17,19–21} Although the survival advantage of pre-emptive TIPSS has been convincingly demonstrated in the landmark study⁸ and many subsequent studies,^{11,13,16,17,20–22} this has not been a universal finding. It is to be noted that there are several additional factors which may influence long-term survival outcomes. For example, both the severity of underlying liver disease and the subsequent treatments of disease aetiology such as antiviral therapy or maintained abstinence from alcohol will have an impact on the subsequent disease trajectory and prognosis. Furthermore, individual centre expertise in

providing endoscopic treatment and subsequent follow-up banding programmes, as well as general management of patients with AVB and access to ICUs, may also affect outcomes. As TIPSS is a highly specialised intervention with its availability limited to tertiary centres, any inability to provide TIPSS in a timely manner is also likely to impact on the success of such additional therapy.

It is also worth pointing out and encouraging to see that the promising results of early intervention in the European TIPSS studies^{13,17,21} have been reproduced in the subsequent Chinese studies,^{19,20} with this demographically and aetiologically distinct patient group observing similar benefits and improved survival.

Given the known inherent high mortality associated with AVB, identifying a subgroup of patients at risk of treatment failure is crucial and any additional intervention to prevent and or reduce risk of future bleeding is integral and highly welcomed. In addition to the demonstrated positive effects on bleeding, pre-emptive TIPSS could confer additional desired outcomes such as resolution of ascites and its associated complications.

We recognise that TIPSS is a highly specialised procedure with limited access and is resource heavy. Since some of the recent studies have shown conflicting survival outcomes it would be highly desirable for further high-powered, randomised control studies to be conducted using the current standard of care as a comparator and with survival advantage as a primary outcome, whilst also addressing additional factors that may influence the disease course.

Further work is required to define the high-risk group, as reflected in the most recent guidelines. Future research should also be targeted on the role of pre-emptive TIPSS in gastric varices, AH, its role in combination with variceal embolisation, and additional pharmacological options to reduce portal pressure, such as statin therapy.

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