Variable efficacy of TIPSS in the management of ectopic variceal bleeding: a multicentre retrospective study

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Summary
Background: Evidence for the efficacy of TIPSS in ectopic variceal bleeding (EctVB) is largely based on relatively small series.

Aim: To define the efficacy of TIPSS in EctVB.

Methods: Retrospective analysis of consecutive patients with chronic liver disease who presented with EctVB and received TIPSS in three tertiary centres in 1992-2016.

Results: The study included 53 patients (70% male, median age 61 years, median model for end-stage liver disease (MELD) score 11). The ectopic varices were located around the insertion of stomas (40%), duodenum (23%), rectum (17%) and at other sites (20%). Three-quarters of the patients had previously received unsuccessful medical, endoscopic or surgical therapy. The median follow-up was 14.0 months. Following TIPSS, bleeding recurred in 12 patients: 6 of 12 (50%) with duodenal varices, 2 of 9 (22%) with rectal varices and one each with stomal (1/21), intraperitoneal (1/3), hepaticojejunostomy (1/2) and ascending colon varices (1/2). The risk factors for re-bleeding were MELD score at TIPSS placement (HR: 1.081 per point; 95% confidence interval (CI): 1.012-1.153; P = 0.034), varices located at site other than an enterostomy (HR: 9.770; 95%CI: 1.241-76.917; P = 0.030) and previous local therapy (HR: 5.710; 95%CI: 1.211-26.922; P = 0.028). The estimated cumulative re-bleeding rate was 23% at 1 year, 26% at 3 years and 32% at 5 years. Post-TIPSS hepatic encephalopathy manifested or worsened in 16 of 53 patients (30%).

Conclusion: TIPSS provides long-term control of bleeding in most cirrhotic patients with EctVB. TIPSS is particularly effective in stomal EctVB, the most frequent cause of EctVB, but might not be as effective in duodenal EctVB.
1 | INTRODUCTION

Approximately 5% of variceal bleedings occur outside the cardioesophageal junction and are denoted as ectopic.\(^1\) Ectopic varices are predominantly located in the small and large intestine and around enterocutaneous stomas, but can also be present in the peritoneum, biliary tree and pelvic organs.\(^2\) Abdominal and pelvic surgery is a well-known risk factor because postoperative adhesions and the creation of an enterostomy facilitate the formation of portosystemic collaterals.\(^1,2\)

The management of ectopic variceal bleeding (EctVB) is challenging and not based on the results of controlled trials. Local endoscopic treatment modalities (band ligation, injection sclerotherapy, clips, argon plasma coagulation) and selective variceal embolisation frequently fail to prevent rebleeding with reported recurrence rates up to 80% within 6 months.\(^3,4\) Surgical treatment, such as local sutures, devascularisation procedures or stoma revision with resiting, will only occasionally provide long-term control of bleeding in selected patients. The creation of surgical portosystemic shunts is associated with significant morbidity and mortality, particularly in patients with decompensated cirrhosis, and is rarely performed nowadays.\(^5-7\)

TIPSS creation is used to treat patients suffering from EctVB.\(^8\) Although evidence suggests that TIPSS is usually effective to prevent recurrent bleeding, research publications are restricted to patient series including only 8-28 patients.\(^9-13\) Also, variable results have been published with respect to concomitant variceal embolisation, and the additional therapeutic value of embolisation combined with TIPSS placement remains unclear.\(^9,11-14\)

We therefore aimed, in a multicentre cohort of patients with EctVB, to further determine the efficacy of TIPSS and to evaluate outcomes in subgroups with different types of ectopic varices. We also intended to explore the benefit of concomitant vascular embolisation of collateral vessels feeding the ectopic varices.

2 | PATIENTS AND METHODS

2.1 | Study design and data collection

We included all consecutive patients with advanced chronic liver disease, who underwent TIPSS placement for EctVB using bare metal stents or expanded polytetrafluoroethylene (e-PTFE)-covered nitinol stents (Viatorr, W.L. Gore & Associates Inc, Flagstaff, AZ, USA) in three tertiary referral centres: Erasmus MC, Rotterdam, the Netherlands, between January 1992 and December 2016; Academic Medical Center (AMC), Amsterdam, the Netherlands, between January 1998 and December 2016; and UZ Leuven, Leuven, Belgium, between January 2000 and December 2013. Demographic, biochemical clinical and survival data were collected from patient hospital records and entered into a database for statistical analysis. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in approval by the Medical Ethics Committee Erasmus MC, Rotterdam, the Netherlands, on 18 April 2017 (MEC-2017-217), stating that written informed consent was not necessary considering the retrospective study design.

2.2 | Definitions

The diagnosis of advanced chronic liver disease was based on liver histology, or a combination of clinical, biochemical and radiological findings.\(^15\) The model for end-stage liver disease (MELD) score was calculated with the formula: \(0.957 \times \log(\text{creatinine in mg/dL}) + 0.378 \times \log(\text{bilirubin in mg/dL}) + 1.120 \times \log(\text{INR}) + 0.643\).\(^16,17\) Comorbidity with a cardiovascular condition, pulmonary condition or renal condition was defined as a condition requiring long-term medical treatment for which regular specialist follow-up care was necessary. Early TIPSS was defined as TIPSS insertion within 72 hours after an EctVB episode.\(^18\) Bleeding was defined as a decrease in haemoglobin (Hb) by 2 g/dL (1.24 mmol/L), or the requirement of more than 2 units of packed red cells within 24 hours to stabilise Hb concentration or signs of volume depletion (systolic blood pressure below 100 mm Hg and/or heart rate above 100/min).\(^13\) Rebleeding was defined as a single episode of clinical significant recurrent melena or hematemesis from portal hypertensive sources after day 5 that resulted in any of the following: (a) hospital admission, (b) blood transfusion, (c) drop in Hb of 3 g/dL (1.86 mmol/L) or (d) death within 6 weeks.\(^19\)

The standard follow-up protocol for stent function differed per centre: in the Erasmus MC, a functional assessment of bare TIPSS stents with Doppler ultrasound (US) was performed 2, 7 and 30 days after placement, at 3-month intervals during the first year of follow-up, and every 6 months thereafter. Following TIPSS with covered stents, standard follow-up imaging was not performed. In the AMC, all stents were assessed at 3-7 days, 3 months, 6 months and 12 months after placement, and every year thereafter. In UZ Leuven, stent function was assessed every 6 months. In all centres, patients received an angiography with venous portal pressure measurements when shunt dysfunction was suspected based on findings during Doppler US or clinical symptoms. Shunt dysfunction was defined as shunt stenosis greater than 50% of the shunt and/or hepatic venous portal gradient higher than 12 mm Hg.\(^20\)

2.3 | Statistical analysis

Continuous variables were reported as mean with standard deviation (SD), after visual confirmation of approximate normality, and compared using a T test. A median and range from the first to the third quartile (IQR, interquartile range) was computed for continuous variables with a non-normal distribution and compared using a Mann-Whitney test. Categorical variables were reported as count with proportion and compared using the chi-squared test.

The actuarial probabilities of being free of shunt dysfunction (shunt dysfunction as event, censoring at death or liver transplantation), being free of rebleeding (rebleeding as event, censoring at death or liver transplantation) and transplant-free survival (death as event, censoring at liver transplantation) after TIPSS creation were
estimated using the Kaplan-Meier method and compared using log-
rank tests.

A univariable Cox regression analysis was carried out to identify
risk factors for rebleeding at TIPSS placement using candidate pre-
dictor variables, hereinafter mentioned, as described in the litera-
ture and based on the clinical and research experiences of co-investiga-
tors: MELD score, location of EctVB, local treatment of the EctVB,
urgency placement of TIPSS, type of stent used during TIPSS, portal
pressure gradient after TIPSS placement above 12 mm Hg and con-
comitant embolisation.2,11-13,18,21,22 The univariable Cox regression
models were adjusted with a propensity score to take into account
differences in MELD score at TIPSS placement for each individual
covariate.

Furthermore, the effect of concomitant embolisation during the
TIPSS procedure compared to TIPSS alone on rebleeding and mortal-
ity was analysed. For this analysis as well, a propensity score was
calculated using a logistic regression model, estimating the probabil-
ity to receive concomitant embolisation given the following observed
baseline characteristics: MELD score, location of EctVB, type of
stent used during TIPSS and urgency placement of TIPSS as predic-
tor variables.

A two-sided P < 0.05 was considered significant for descriptive
statistics, and a P-value <0.10 was considered significant for unvari-
able regression models. All statistical analyses were performed using
IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk,
NY, USA).

3 RESULTS

3.1 Patient characteristics and TIPSS procedures

In the three centres, 53 patients received TIPSS for EctVB during
the study period, representing 5.4% of the total population (n = 979)
undergoing a TIPSS procedure (Figure 1). The study population con-
sisted predominantly of males with a median age of 61 years (IQR
51-66) and a median MELD score of 11 (IQR 9-17; Table 1). The
ectopic varices were most often located near the mucocutaneous
junction of stomas (40%), followed by the duodenum (23%), rectum
(17%) and other sites (20%). TIPSS placement was the initial treat-
ment for EctVB in 23% of the patients. About 77% of the patients
had been unsuccessfully treated for EctVB with one or multiple
modalities; 24 patients (45%) had undergone previous endoscopic
treatment (band ligation, injection therapy, coagulation), 22 (42%)
had received vasoactive medication (nonselective beta-blockers,
somatostatin, terlipressin), 9 (17%) had undergone abdominal surgery
(stoma revision or relocation, bowel resection) and 1 patient (2%)
had received endovascular treatment (embolisation).

TIPSS were created with a bare metal stent in 8 patients and with
an e-PTFE-covered stent in 45 patients (Table 2). Hemody-
namic measurements showed that the median pre-TIPSS portosys-
temic gradient (PSG) decreased from 14 mm Hg (IQR 10-20) to
6 mm Hg (IQR 4-7) after TIPSS placement. The post-TIPSS PSG
remained above 12 mm Hg in four patients. Eighteen (34%) patients
received early TIPSS and initial hemostasis was achieved in all cases.

3.2 Clinical outcome

The median follow-up time was 14.0 months (IQR 3.8-45.9). Follow-
ing TIPSS, EctVB from the same site occurred in 12 of 53 (23%)
patients (Figure 2). Bleeding recurred in 1 of 21 (5%) cases with sto-
mal varices, 6 of 12 (50%) cases with duodenal varices, in 2 of 9
(22%) with rectal varices, in 1 of 3 cases with intraperitoneal varices,
in 1 of 2 cases with varices in the ascending colon and in 1 of 2
cases with varices located at the hepaticojejunostomy. The four
patients with jejunal, caecal, sigmoid or umbilical vein ectopic varices
remained free of rebleeding.

Most rebleeds were diagnosed shortly after TIPSS creation, in
eight patients (four with duodenal varices, one with varices at the
hepaticojejunostomy, one with intraperitoneal varices, one with rec-
tal varices and one with ascending colon varices) in the first month
after the TIPSS procedure (15%), in two patients (one with duodenal
varices and one with rectal varices) after 1-6 months (4%) and in
two patients (one with duodenal varices and one with urostomal
varices) after 6 months (4%). In nine of these 12 patients, rebleeding
was associated with shunt dysfunction. After TIPSS placement, the
estimated cumulative ectopic variceal rebleeding rate was 23% at
1 year, 26% at 3 years and 32% at 5 years (Figure 3). Rebleeding
from other sources occurred in four patients: three from gastro-
oesophageal varices and one from haemorrhagic gastropathy. The
univariable Cox regression to identify risk factors for rebleeding
found three predicting variables: high MELD score (HR: 1.081 per
point; 95% confidence interval, CI: 1.012-1.153; P = 0.002), EctVB
located at another site than an enterostomy (HR: 9.770; 95% CI:
1.241-76.917; P = 0.030) and local treatment preceding TIPSS (HR:
5.710; 95% CI: 1.211-26.922; P = 0.028) (Table 3).

The rebleeding risk in the two main subcategories of EctVB—
stomal and duodenal varices—differed markedly. A comparison of
these groups with respect to aetiology of liver disease, MELD score,
type of stent, concomitant embolisation, post-TIPSS PSG >12 mm
Hg and established stent dysfunction did not reveal significant differ-
ences. However, age was significantly lower in patients with duode-
nal EctVB (54 vs 65 years, P = 0.016), and 11 of 12 duodenal EctVB
had been treated endoscopically before TIPSS, while local endo-
scopical or other procedures were performed in only 2 of 21 cases
with stomal EctVB (P < 0.001) (Figure S1).

TIPSS dysfunction was diagnosed in 6 of 8 patients with bare
metal stents (75%) compared to 10 of 45 with e-PTFE–covered
stents (22%) (P = 0.011). In six patients, shunt dysfunction was diag-
nosed at an elective follow-up visit and in nine patients after a
rebleed. Most shunt dysfunctions were diagnosed in the first
6 months after TIPSS creation, in seven patients in the first month
(13%), in 6 after 1-6 months (11%) and in three after 6 months (6%).
The estimated cumulative TIPSS dysfunction rate significantly dif-
fered (P = 0.003) for bare metal stents (1 year: 76%; 3 years: 100%)}
compared to e-PTFE-covered stents (1 year: 23%; 3 years: 24%; 5 years: 31%) (Figure 4).

A total of 31 shunt revisions were performed in the first 2 years after TIPSS creation in 13 patients. An additional stent was placed in eight patients; in four patients, angioplasty was performed (followed in two cases by additional stent placements); and in one patient, local thrombolysis was accomplished. Three patients with shunt dysfunction and rebleeding died.

Post-TIPSS hepatic encephalopathy (HE) manifested or worsened in 16 of 53 patients (30%). HE could be managed medically in 12 patients; however, in four patients radiological re-intervention was performed reducing the TIPSS diameter and improving or resolving in all cases the symptoms of HE. In no cases, a complete shunt occlusion was performed.

In this cohort, 41 patients died, five underwent liver transplantation, six were alive at the end of follow-up, and one was lost to follow-up. The causes of death were liver disease-related in 12 patients (29.3%) including three patients dying of EctVB, not liver disease-related in 12 patients (29.3%), and unknown in 17 patients (41.4%) (Figure 2). The estimated 30-day, 1-year and 5-year mortality rates were 11%, 41% and 75%, respectively (Figure S2).

3.3 | Concomitant embolisation during TIPSS
Concomitant embolisation during the TIPSS procedure was performed in 13 patients: four patients had varices located near enterocutaneous stomas, four had duodenal varices, two had rectal varices, two had intraperitoneal varices and one had varices in the ascending colon. Concomitant embolisation was performed in 4 of 9 patients with an acute bleeding and in 9 of 44 patients as a secondary prophylactic measure. There were no statistically significant differences between patients receiving embolisation and TIPSS alone with respect to age, gender, MELD score, location of varices, presentation with acute bleeding or treatment centre. After propensity score adjustment, the hazard ratio for rebleeding of concomitant embolisation compared to TIPSS alone was 0.701 (95% CI: 0.145-3.390; P = 0.659) and the hazard ratio for mortality was 0.776 (95% CI: 0.281-2.148; P = 0.626).

4 | DISCUSSION
This multicentre cohort study evaluated the efficacy of TIPSS with predominantly e-PTFE-covered stents in subgroups of patients with
TABLE 1  Clinical characteristics of the study population

| Patients with ectopic variceal bleeding (n = 53) |
|-----------------------------------------------|
| Male gender (%)                               | 37 (69.8) |
| Age in years, median (IQR)                    | 61 (51-66) |
| Aetiology of portal hypertension (%)          |           |
| Alcoholic cirrhosis                           | 25 (47.2) |
| PSC/PBC/autoimmune hepatitis                  | 11 (20.8) |
| Cryptogenic cirrhosis                         | 7 (13.2) |
| Viral hepatitis                               | 2 (3.8) |
| Other                                         | 8 (15.0) |
| Child-Pugh classa (%)                         |           |
| A                                             | 34 (65.4) |
| B                                             | 15 (28.8) |
| C                                             | 3 (5.8) |
| MELD score,a median (IQR)                     | 11 (9.4) |
| Portal vein thrombosis (%)                    |           |
| Location of bleeding ectopic varices (%)      |           |
| Enterostoma*                                 | 21 (39.7) |
| Colostomy                                    | 11        |
| Ileostomy                                    | 8         |
| Urostomy                                     | 3         |
| Duodenum                                     | 12 (22.6) |
| Rectum                                       | 9 (17.0)  |
| Intraperitoneal                               | 3 (5.7)   |
| Hepaticojejunostomy                          | 2 (3.8)   |
| Ascending colon                              | 2 (3.8)   |
| Jejunum                                      | 1 (1.9)   |
| Caecum                                       | 1 (1.9)   |
| Sigmoid                                      | 1 (1.9)   |
| Umbilical vein                               | 1 (1.9)   |
| Number of previous episodes of ectopic variceal bleeding (%) |           |
| 1-3                                          | 26 (49.1) |
| 4-6                                          | 7 (13.2)  |
| 7 or more                                    | 20 (37.7) |
| Previous treatment of ectopic variceal bleeding (%) |           |
| None                                         | 12 (22.6) |
| Medication*                                   | 22 (41.5) |
| Non-selective β-blocker                      | 14        |
| Somatostatin                                 | 12        |
| Terlipressin                                 | 1         |
| Endoscopic*                                  | 24 (45.3) |
| Band ligation                                | 9         |
| Injection therapy                            | 17        |
| Coagulation                                  | 2         |
| Endovascular embolisation*                   | 1 (1.9)   |
| Surgery*                                     | 9 (16.9)  |

IQR: interquartile range; MELD: model for end-stage liver disease.

aData regarding liver disease severity missing in 1 case.

bPatients could have multiple concomitant comorbidities or received multiple treatment modalities, either concomitant or successive.

cTwo patients had a history with two malignancies.

dOne patient presented with concomitant colostomy and urostomy bleeding.

bleeding from ectopic varices. The present study confirms that TIPSS was an effective treatment by completely preventing rebleeding in the large majority (77%) of cases. TIPSS was particularly effective in patients with less severe liver disease and with varices located at enterostomas. In contrast, the rebleeding risk in patients with duodenal varices was unexpectedly high.

The observed cumulative 23% rebleeding rate at 1 year is comparable with previously reported rates varying from 23% to 39%.11-13 While the 26% rate at 2 years was considerably lower than previously reported,12 it seems likely that the superior long-term bleeding control is attributable to the use of e-PTFE-covered stents in the large majority of cases. The actuarial risk of remaining free from rebleeding in the present series in comparison with the risk observed in TIPSS-treated gastro-oesophageal bleeding reported in two recently published studies originating from the participating centres was 77% versus 94-100% at 1 year, 74% versus 92-94% at 3 years and 68% versus 90-92% at 5 years, respectively.22,23 Thus, the overall rebleeding risk in TIPSS-treated EctVB appears to be

(Continues)
higher than that in gastro-oesophageal bleeding. Our data indicate that this seems attributable to the relevant high rebleeding risk in TIPSS-treated duodenal EctVB. In our cohort, shunt dysfunction was diagnosed in three-quarter of the patients with rebleeding and occurred three times more often in bare metal stents compared to e-PTFE-covered stents. In total,
unsuccessful endoscopic therapies frequently preceded TIPSS. In our poor. A potential explanatory factor may be that local, but ultimately EctVB, who had a disappointing 50% rebleeding risk, was relatively trend that e…in the study from Kochar et al. Although these rates vary notably, the approximately 20% in the study from Kochar et al and 49% in the study from Vidal et al. 

![Figure 3](image)

**Figure 3** Actuarial probability (red line) with 95% confidence interval (black dashed lines) of remaining free of rebleeding following TIPSS

**Table 3** Univariable analysis of ectopic variceal rebleeding

|                      | HR      | 95% CI    | P-value |
|----------------------|---------|-----------|---------|
| MELD score (per point) | 1.081   | 1.012-1.153 | 0.020   |
| Location of ectopic varices* |        |           |         |
| Enterostral          | 1       |           | 0.030   |
| Other site           | 9.770   | 1.241-76.917 |        |
| Previous local therapy* | 5.710   | 1.211-26.922 | 0.028   |
| Early placement of TIPSS* |        |           |         |
| ≤72 h after EctVB episode (reference) | 1       |           | 0.653   |
| >72 h after EctVB episode | 0.737   | 0.195-2.787 |        |
| Type of TIPSS* |        |           |         |
| Bare (reference)   | 1       |           | 0.887   |
| e-PTFE-covered     | 0.9894  | 0.193-4.148 |        |
| Post-TIPSS PSG* |        |           |         |
| ≤12 mm Hg (reference) | 1       |           | 0.884   |
| >12 mm Hg           | 1.171   | 0.149-9.735 |        |
| Concomitant embolisation* | 1.133   | 0.304-4.221 | 0.852   |

CI: confidence interval; e-PTFE: expanded polytetrafluoroethylene; EctVB: ectopic variceal bleeding; HR: hazard ratio; MELD: model for end-stage liver disease; PSG: portosystemic gradient.

*T: Hazard ratio adjusted with propensity score for MELD score at TIPSS placement.

TIPSS dysfunction occurred in 23% at 1-year follow-up compared to approximately 20% in the study from Kochar et al and 49% in the study from Vidal et al. Although these rates vary notably, the trend that e-PTFE-covered stents have improved shunt patency is in line with widely reported experience. To the best of our knowledge, we report the largest multicentre cohort of patients with TIPSS for EctVB with predominantly e-PTFE-covered stents and our data reflect real-life practice in three university hospitals. Despite the retrospective study design, only one patient was lost to follow-up. This is the first study allowing a preliminary assessment of the efficacy of TIPSS in subgroups of EctVB, although the results should be interpreted cautiously considering the size of the patient population. Ideally, prospective trials could provide more clarity about the role of TIPSS in subgroups of EctVB as well as on the role of concomitant embolisation. However, such studies may never be performed considering the low prevalence of the disease, the heterogeneity in varices location and the technical inability to embolise all culprit collateral vessels.

In conclusion, our study demonstrates that TIPSS effectively prevents rebleeding in the majority of patients presenting with EctVB. TIPSS is particularly effective in bleeding from enterostomas, the most frequent type of EctVB. However, the results in duodenal experience, endoscopic treatment, in particular repeated tissue glue injections, may lead to significant duodenal ulcers that can be the cause of repeated bleeding in their own right. In such cases, it may be very difficult to distinguish portal hypertensive-related bleeding from other causes, and management may be troublesome. Another possibility is that local tumorous vascular ingrowth or thrombosis could cause (re)bleeding unrelated to portal hypertension. However, in our two cases with duodenal variceal bleeding and a previous diagnosis of pancreatic cancer, there was no evidence for residual or recurrent tumour. Also with respect to other malignancies, there was no indication that these were of aetiological importance. Further studies in this type of EctVB are required to further address the timing of TIPSS and whether alternative therapeutic approaches, in particular balloon-occluded retrograde-transvenous-obliteration may be a preferable strategy.
EctVB, with a 50 per cent rebleeding rate, were disappointing and highlight the need for alternative therapeutic approaches.

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**SUPPORTING INFORMATION**

Additional supporting information will be found online in the Supporting Information section at the end of the article.

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