




Covered Transjugular Intrahepatic Portosystemic Shunt Improves Hypersplenism-Associated Cytopenia in Cirrhosis

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Abstract

Background Patients with cirrhosis often develop portal hypertension-associated splenomegaly and hypersplenism, potentially causing severe cytopenia.

AIMS Systematic assessment on the impact of transjugular intrahepatic portosystemic shunt (TIPS) implantation on platelet count (PLT), hemoglobin (Hb), and white blood cell count (WBC).

Methods Patients with cirrhosis undergoing covered TIPS implantation were retrospectively included. Patients with malignancies or hematologic disorders were excluded. Hematology lab work was recorded at baseline (pre-TIPS) and at regular intervals after TIPS.

Results One hundred ninety-two patients (male: 72.4%, age: 56 ± 10 years; MELD: 12.1 ± 3.6) underwent TIPS implantation. Higher-grade ($\geq G2$) thrombocytopenia (PLT < 100 G/L) was present in 54 (28.7%), $\geq G2$ anemia (Hb < 10 g/dL) in 57 (29.7%), and $\geq G2$ leukopenia (WBC < 2 G/L) in 3 (1.6%) patients pre-TIPS, respectively. Resolution of $\geq G2$ thrombocytopenia, anemia, and leukopenia occurred in 24/55 (43.6%), 23/57 (40.4%), and 2/3 (66.7%), respectively. Similar results were also observed in the subgroup of patients without ‘bleeding’ TIPS-indication, with improvements of $G \geq 2$ thrombocytopenia and of $G \geq 2$ anemia in 19.8% and 10.2% of patients after TIPS, respectively.

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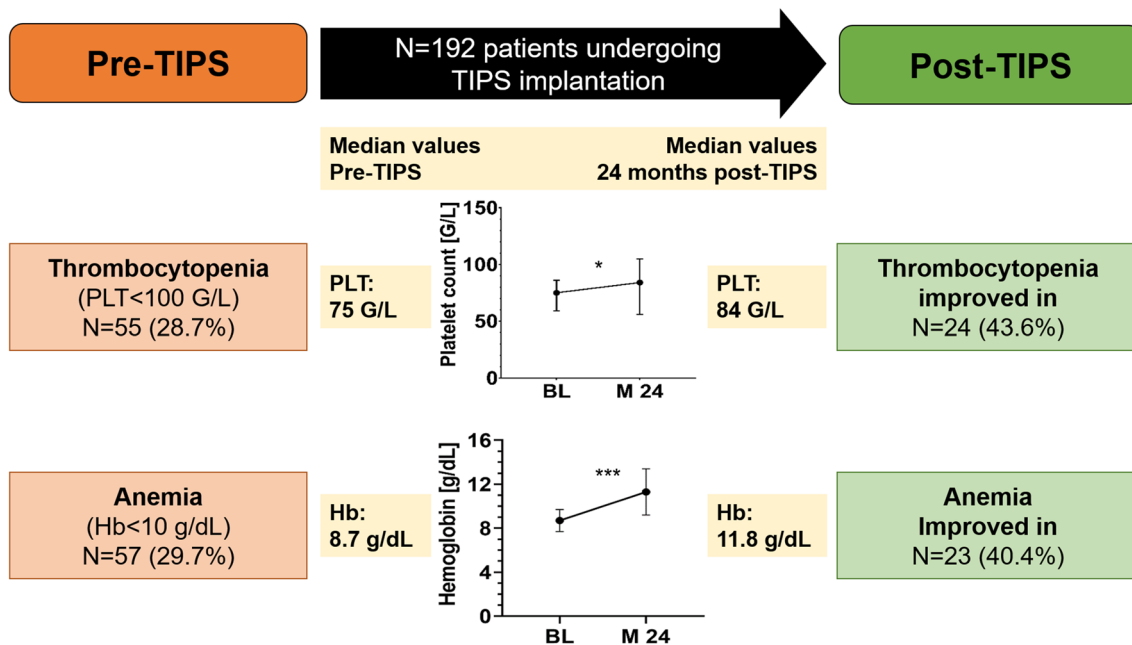
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Conclusions Thrombocytopenia, anemia, and leukopenia frequently improved after TIPS. Therefore, moderate- to higher-grade thrombocytopenia should not be regarded as a contraindication against TIPS, but rather be considered in case of severe thrombocytopenia—particularly prior to surgery or interventions.

Graphical Abstract



Keywords Hypersplenism · Thrombocytopenia · Anemia · TIPS · Portal hypertension · Cirrhosis

Abbreviations

PH	Portal hypertension
ACLD	Advanced chronic liver disease
TPO	Thrombopoietin
PLT	Platelet count
HVPG	Hepatic venous pressure gradient
TIPS	Transjugular intrahepatic portosystemic shunt
PTFE	Polytetrafluoroethylene
Hb	Hemoglobin
M	Month
G	Grade
LLN	Lower limit of normal
MELD	Model for end-stage liver disease
PG	Portal-systemic pressure gradient
SD	Standard deviation
IQR	Interquartile ratio
SEM	Standard error of the mean
WBC	White blood cell count
ALD	Alcohol-related liver disease
INR	International normalized ratio
FU	Follow-up
PS	Child's Pugh's Score
CRP	C-reactive protein

HE	Hepatic encephalopathy
OHE	Overt hepatic encephalopathy
OLT	Orthotopic liver transplantation

Introduction

The development of portal hypertension (PH) in advanced chronic liver disease (ACLD) accounts for severe complications in patients with cirrhosis [1], such as development of ascites or variceal bleeding. PH-induced splanchnic venous congestion may also cause splenomegaly [2–4]. Splenomegaly has a prevalence of 50%–100% in cirrhosis depending on the underlying etiology [2] and is often complicated by hypersplenism-associated cytopenia [5]. Hypersplenism mostly induces thrombocytopenia; however, anemia and leukopenia may also occur [6, 7]. Patients with cirrhosis and PH may also present with non-hypersplenism associated causes for cytopenia [6, 8–10], such as iron deficiency due to gastrointestinal blood loss or malnutrition [6, 11, 12], or deprived levels of thrombopoietin (TPO) due to hepatic insufficiency [13]. Since platelet count (PLT) indirectly correlates with severity of PH, i.e., hepatic venous pressure

gradient (HVPG), PLT is widely recognized as a valuable marker for noninvasive assessment of PH [14–16].

Both refractory ascites and severe/recurrent variceal bleeding can be effectively treated by placing a transjugular intrahepatic portosystemic shunt (TIPS) [1, 14, 17–19]. TPO agonists may be used to increase the PLT count before invasive procedures [20]. Moreover, splenectomy and other interventions such as partial splenic artery embolization or liver transplantation have shown to improve thrombocytopenia in distinct patient collectives [5, 13, 21, 22]. However, the effect of TIPS on cytopenia has not yet been fully characterized. Prior studies have yielded controversial results regarding improvement of thrombocytopenia after TIPS implantation [23–25], and data on the course of anemia or leukopenia after TIPS are scarce.

Methods

Study Design and Patient Cohort

This retrospective cohort study was conducted at two tertiary care centers in Vienna, Austria. We assessed whether TIPS implantation improves hypersplenism-associated cytopenia (thrombocytopenia, anemia, leukopenia) in consecutive patients undergoing TIPS implantation between 1999 and 2017 fulfilling the following inclusion criteria: (i) diagnosis of cirrhosis (ii) indication for TIPS due to refractory ascites or variceal hemorrhage (iii) age > 18 years, (iv) implantation of a polytetrafluoroethylene (PTFE)-covered TIPS and (v) available hematology lab reports prior to TIPS (baseline) and at least at one follow-up visit between 3 and 24 months after TIPS placement. Patients with hepatocellular carcinoma, other malignancies, or primary hematologic disorders were excluded from analysis.

Data Acquisition

Clinical and epidemiological data were extracted from medical histories, and laboratory data from the respective digital patient management systems. TIPS intervention data were collected from the respective intervention reports of each study center, while spleen diameter was assessed by local radiologists specifically for this study (see below).

Parameters

We recorded hemoglobin (Hb) values, platelet count, and white blood cell count (WBC) at the following time points: at baseline (0–10 days prior to TIPS implantation), and at approx. 3 months (M3; \pm 3 weeks), 6 months (M6; \pm 6 weeks), 12 months (M12; \pm 10 weeks), and

24 months (M24; \pm 20 weeks) after TIPS implantation, where available.

Alterations in blood cell counts were graded as follows:

Thrombocytopenia:

- o No thrombocytopenia (grade, G0) at $PLT \geq 150$ G/L;
- o G1: PLT 100–149 G/L;
- o G2: PLT 50–99 G/L;
- o G3: $PLT < 50$ G/L,
- Anemia:
- o No Anemia (G0): Hb at or above the lower limit of normal (LLN: male: ≥ 13.5 g/dL, female: ≥ 12.5 g/dL);
- o G1: Hb 10.0 g/dL—LLN;
- o G2: Hb 7.5–10.0 g/dL;
- o G3: Hb < 7.5 g/dL.
- Leukopenia:
- o No Leukopenia $WBC \geq 4.00$ G/L;
- o G1: 2.00–3.99 G/L;
- o G2: 1.00–1.99 G/L;
- o G3: < 1.00 G/L.

MELD was calculated as previously described [26].

TIPS-Procedure

TIPS stent graft implantations were performed according to standard operating procedures as previously described [17–19, 27, 28]. Portosystemic pressure gradient (PPG) was measured by radiologists intra-procedurally by subtracting the pressure within the right atrium from the directly measured portal vein pressure prior to TIPS dilatation. Afterward, patients were surveilled during routine clinical visits with routine blood draws (including complete blood counts) every 3–6 months after TIPS insertion.

Measurement and Dynamics of Splenomegaly

When available, spleen size was assessed by an experienced radiologist at the largest cranial-caudal diameter at level of the hilus in coronary reconstruction in cross-sectional imaging at the following time points: at baseline (within 3 months prior to TIPS), within 12 months (short-term follow-up), and later than 12 months (long-term follow-up) after TIPS implantation. A spleen diameter of > 11 cm was regarded as splenomegaly. Changes in spleen diameter by $\pm > 2.0$ cm or by > 10% were considered relevant increases/decreases.

Sub-analyses

We also evaluated the course of blood cell counts after TIPS implantation according to etiology of liver disease (alcoholic liver disease, ALD vs. viral etiology vs. other etiologies)

and in a sub-group of patients undergoing TIPS without a bleeding-related indications.

Statistics

All statistical analyses were performed using Microsoft Excel (Microsoft Office 2016, Microsoft Corporation/Impressa Systems, Santa Rosa, California, USA), GraphPad Prism 9.0.0 (Prism 9, GraphPad Software, LLC, San Diego, California, USA) and SPSS Statistics V.26 (IBM SPSS Statistics for Windows, Version 26.0.0.0., IBM Corp., Armonk, NY, USA). Categorical variables are presented as absolute numbers (percentage) of patients with a certain characteristic. Metric variables were tested for normal distribution using the Kolmogorov–Smirnov-test. Normally distributed variables are presented as mean \pm standard deviation (SD) and skewed variables as median (interquartile range, IQR) unless otherwise specified. Changes in blood counts over time were assessed by paired t-test or the Wilcoxon matched-pairs signed rank test, wherever applicable. Spearman's rank correlation coefficient was calculated when assessing correlations between two metric variables. In case of missing values, patients were excluded for the respective analyses.

We further calculated multivariable regression models to evaluate independent predictors for improvement of moderate-to-high grade cytopenia. We entered age, etiology of liver disease (ALD vs. non-ALD etiology), MELD/MELD-Na, in addition to any variable with a p value ≤ 0.100 in univariate analysis into a step-wise backwards binomial logistic regression analysis. To assess risk factors for mortality, we computed multivariable Cox regression analyses, where patients were censored at day of liver transplant or last follow-up, and death was regarded an event. Two-sided p values were calculated, and significance level was set at $p < 0.05$.

Ethics

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in a priori approval by the human research committees of the Medical University of Vienna (1760/2014) and the City of Vienna (MA15, 14-264-VK). The need for written consent was waived.

Results

Study population (Fig. 1, Table 1, Table 2)

237 patients met the inclusion criteria. 45 patients were excluded due to primary hematologic disorders and malignancies. The final study population comprised 192 patients undergoing PTFE-TIPS implantation ($n = 109$, 56.8% for ascites; $n = 83$, 43.2% for variceal bleeding). Mean MELD was 12.1 ± 3.6 , and most patients had Child–Pugh class B (63.5%) or class C (29.7%) cirrhosis. Among 67 patients with cross-sectional imaging readily available, almost 90% presented with splenomegaly > 11 cm prior to TIPS implantation.

In total, thrombocytopenia was prevalent in 56.8% of patients and anemia in 89.1%, while less than 20% presented with leukopenia. Moderate-to-severe (G2/G3) thrombocytopenia was present in 28.7%, G2/G3 anemia in 29.7%, and G2 leukopenia in three patients (1.6%). No patient was diagnosed with G3 leukopenia at baseline.

Effect of TIPS on Thrombocytopenia

Median platelet count at baseline was 131 G/L (*see online source Table-S1*). Mild thrombocytopenia (G1) was present in 54 (28.1%) patients, while 46 patients (24.0%) were diagnosed with moderate (G2) and 9 patients (4.7%) with severe (G3) thrombocytopenia (Table 2). Improvement of PLT was more pronounced, the lower the pre-TIPS PLT: While only 16.7% of patients with G1 thrombocytopenia improved to G0, 43.6% of patients with G2/G3 thrombocytopenia improved by ≥ 1 stage (Fig. 1); conversely, 48.1% of patients with G1 thrombocytopenia worsened by ≥ 1 grade, but only 10.9% with G2/3 thrombocytopenia (vs. G1: $p = 0.002$).

In patients with G1 thrombocytopenia pre-TIPS, PLT decreased after TIPS implantation at M3, but increased again to values similar to the pre-TIPS level at M24 (Fig. 2a and b). Importantly, after TIPS implantation, PLT levels remained stable in patients with moderate (G2) thrombocytopenia at baseline, but severe (G3) thrombocytopenia improved significantly and sustainably to G2 (*see also online sources Table S1, Figure SF1*).

Effect of TIPS on Anemia

Mean baseline hemoglobin was 10.8 ± 1.9 g/dL (Table-S1). In total, 114 patients (59.4%) were diagnosed with mild (G1) anemia, 52 patients (27.1%) with moderate (G2) and 5 patients (2.6%) with severe (G3) anemia prior to TIPS (Fig. 2c). In patients with mild (G1) anemia, despite a slight drop at M3 by < 1 g/dL that recovered at M6, Hb remained

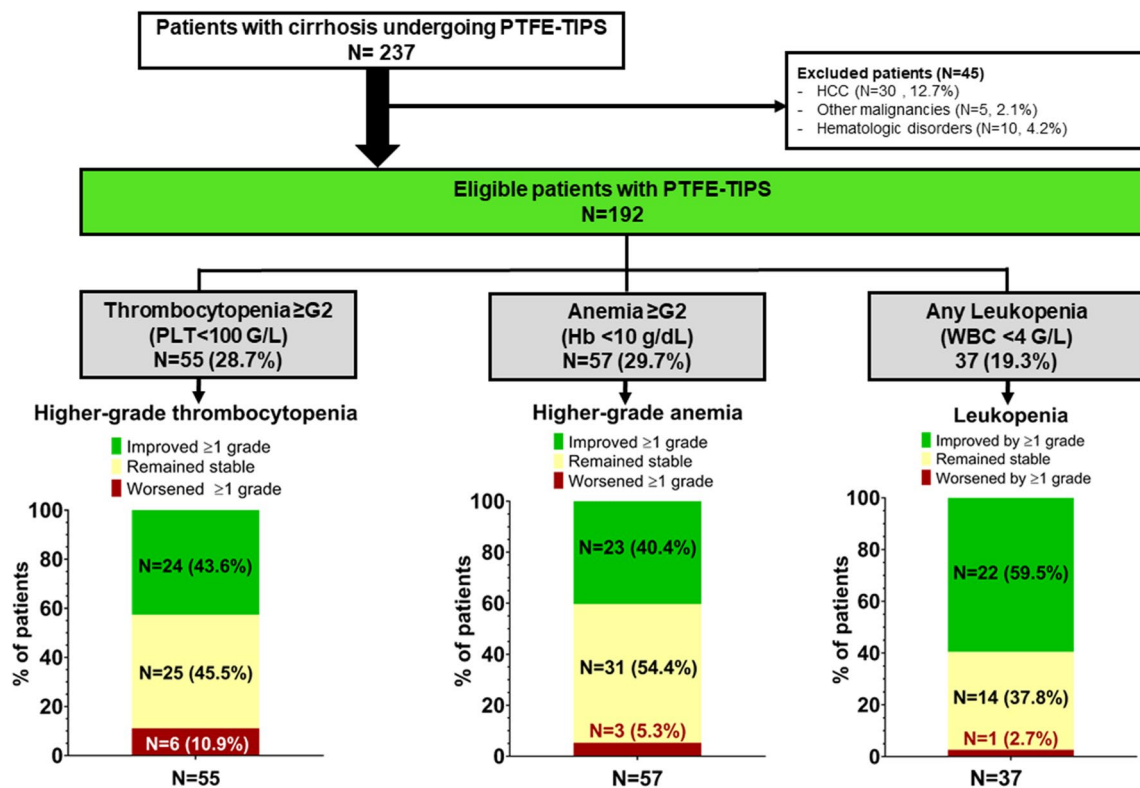


Fig. 1 Patient Flowchart. *Abbreviations:* PTFE, polytetrafluoroethylene; TIPS, transjugular intrahepatic portosystemic shunt; HCC, hepatocellular carcinoma; LLN, lower limit of normal; WBC, white blood

cell count. Lower Limit of normal (LLN) of hemoglobin: males: 13.5 g/dL, females: 12.5 g/dL

mostly stable (Fig. 2c and d). Among patients with G2/3 anemia, Hb levels significantly and permanently improved by ≥ 1 grade in 40.4% of patients (Fig. 1, 2c and d). The proportion of patients with G2/3 anemia improved from approx. 30% at baseline to 24% at 12 months.

Changes in White Blood Cell Count (WBC) After TIPS Implantation

Leukopenia (WBC < 4G/L) was uncommon in patients undergoing PTFE-TIPS implantation, as only 17.7% were diagnosed with G1 (WBC: 2–3.99G/L), 1.5% (3 patients) with G2 (WBC: 1-2G/L) and no patient with G3 leukopenia (WBC: < 1G/L) at baseline. Approximately 60% of patients with leukopenia improved by ≥ 1 grade after TIPS, while G1 leukopenia worsened to G2/3 in one patient (Fig. 1). Overall, WBC increased significantly after TIPS implantation, and normalized in most patients in under a year (Table ST1, Fig. 2e–f).

Course of Splenomegaly After TIPS and Correlation to Blood Counts

Pre-TIPS cross-sectional images were reviewed in 133 patients. The median pre-TIPS spleen diameter was 14.5 cm (IQR: 12.5–16.25), as 115/133 (86.5%) showed pre-TIPS splenomegaly. 85 patients underwent a follow-up cross-sectional imaging scan that covered data on spleen diameter: 38 patients had a second “short-term” imaging scan within 12 months (median 4.0 months, IQR 1.3–7.3 months) with a “short-term” post-TIPS spleen diameter of 14.0 cm (*p* = 0.347), and 55 patients had a “long-term” (> 12 months after TIPS; median 43.7 months, IQR 19.0–70.7 months) follow-up imaging showing a median “long-term” post-TIPS spleen diameter of also 14.0 cm (*p* = 0.251).

Although greater pre-TIPS spleen diameter correlated with the presence of thrombocytopenia (splenomegaly > 11 cm: 66.1% vs. no splenomegaly ≤ 11 cm): 16.7%; *p* = 0.001, see Table-ST3) as well as with improvement of platelet count after TIPS (median spleen diameter in patients with post-TIPS increase in PLT by > 20%: 15.5 cm (IQR: 13.2–18.8 cm); stable PLT: 14.6 cm (IQR: 13.0–16.5 cm); decrease in PLT by > 20%: 14.0 cm (IQR: 12.0–15.2 cm);

Table 1 Patient characteristics

Patients receiving PTFE-TIPS	192 (100%)
Male (<i>n</i> , %)	139, 72.4%
Age (years; $\mu \pm$ SD)	56.0 \pm 10.0
Etiology (<i>n</i>, %)	133, 69.3%
Alcoholic liver disease	17, 8.9%
Viral	16, 8.3%
Alcoholic and viral liver disease	6, 3.2%
Autoimmune and/or cholestatic	1, 0.5%
Nonalcoholic steatohepatitis	16, 8.3%
Cryptogenic	3, 1.6%
Other	
Main indication for TIPS (<i>n</i>, %)	109, 56.8%
Refractory/recurrent ascites	83, 43.2%
Variceal bleeding:	
Child–Pugh Score^a (median, IQR)	9 (8–10)
Child A (<i>n</i> , %)	11, 5.7%
Child B (<i>n</i> , %)	122, 63.5%
Child C (<i>n</i> , %)	57, 29.7%
MELD (points; $\mu \pm$ SD)	12.1 \pm 3.6
MELD-Na (points; $\mu \pm$ SD)	15.9 \pm 4.6
PPG (mmHg; $\mu \pm$ SD)	19.9 \pm 5.6
Pre-TIPS	7.6 \pm 3.5
Post-TIPS	– 12.4 \pm 4.9
Reduction by TIPS	

^aData for CTP assessment was not available in *N*=2 patients.

^bCross-sectional imaging-based pre-TIPS spleen diameter assessment was available in 67 patients.

p = 0.0093), these effects were not observed for Hb and WBC.

Predictive Factors for Improvement of Thrombocytopenia and Anemia After TIPS

In a sub-analysis (Table ST2), we evaluated potential predictive indicators for improvement of advanced (G2/G3) thrombocytopenia and anemia after TIPS implantation. Variceal bleeding as indication for TIPS did not impact on the likelihood of post-TIPS improvement of thrombocytopenia, and

neither did PPG nor liver function tests (*p* > 0.05 in univariate analysis). Only severity of thrombocytopenia (G3 vs. G2; *p* = 0.007) predicted improvement of thrombocytopenia in univariate analysis. In the multivariable model, G3 thrombocytopenia emerged as strong predictor (OR = 32.000, *p* = 0.003) for improving thrombocytopenia with TIPS; similarly, in a different model using PLT as a parameter instead of thrombocytopenia grade, higher PLT emerged as an independent negative predictor for improvement of PLT (OR: 0.683, *p* = 0.028), indicating higher response rates with lower platelet values.

Pre-TIPS variceal bleeding (*p* = 0.001), low baseline Hb (*p* = 0.026) and lower MELD-Na were associated with improvement of anemia in univariate analysis (Table-S2B). In the multivariable model only variceal bleeding as TIPS-indication (OR 5.585, *p* = 0.022) and low baseline hemoglobin count (per g/dL: OR 0.352, *p* = 0.020) remained independent predictors for improvement of anemia.

Sub-analysis of Patients Receiving TIPS for Ascites

Similar results on improvements of thrombocytopenia and anemia were seen in the subgroup of patients receiving PTFE-TIPS for ascites who do not hold the potential bias related to significant bleeding-induced cytopenia (see online sources Table-ST4, Figures-SF2).

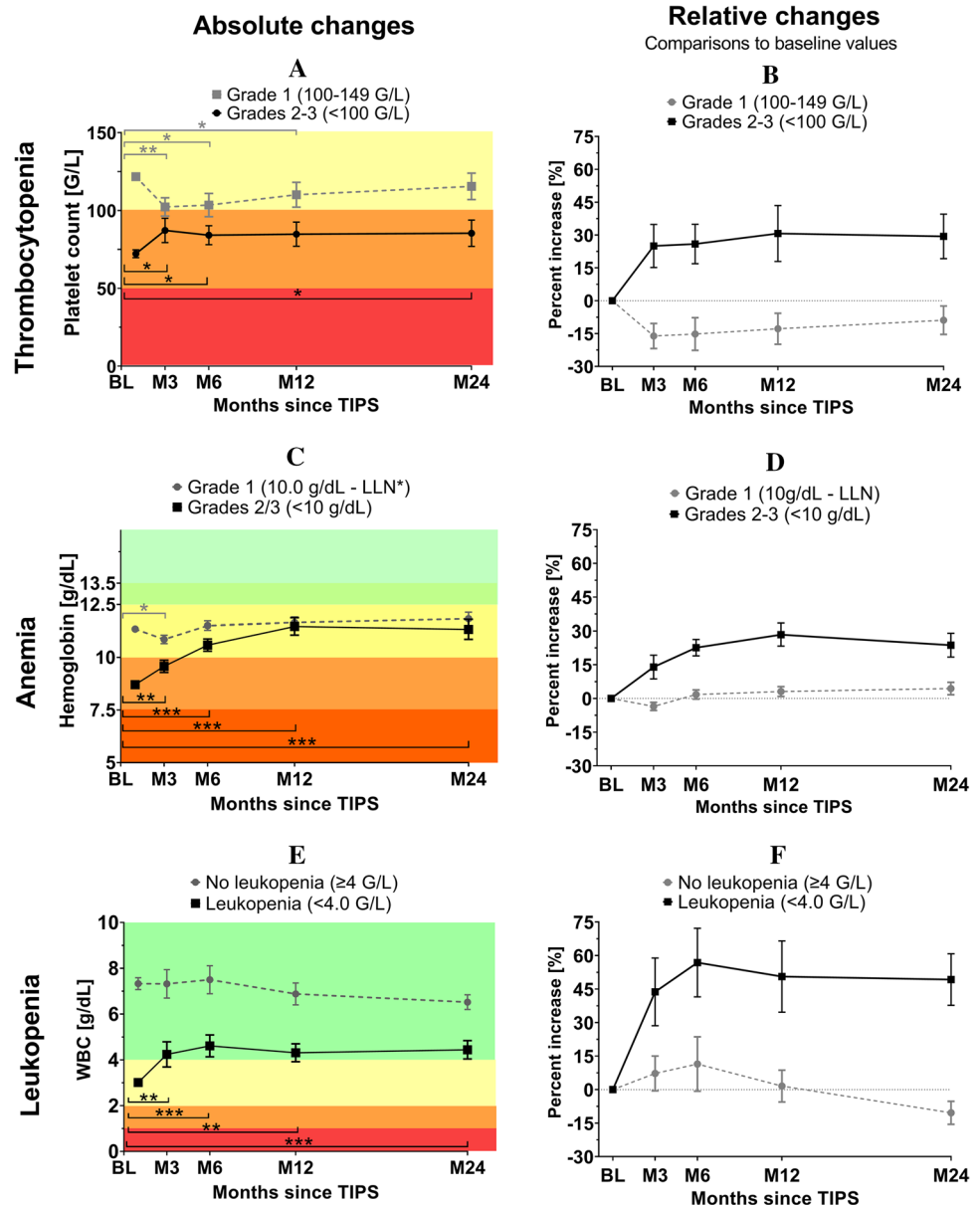
Sub-analysis According to Etiology

When stratifying patients according to their etiology of liver disease, advanced thrombocytopenia was numerically more prevalent in viral hepatitis than in ALD or other etiologies (52.9% vs. 26.8% vs. 23.1%, respectively, *p* = 0.063). However, there was no difference with regards to G2/3 anemia at baseline (*P* = 0.724). The course of G2/3 thrombocytopenia after TIPS implantation did not differ between etiologies, and G2/3 anemia improved significantly after TIPS regardless of etiology.

Table 2 Prevalence of cytopenias in patients undergoing TIPS implantation

Nr. of patients	192 (100%)
Platelet count (G/L; median, IQR)	131, 94–198
Mild thrombocytopenia (G1: 100–149 G/L; <i>n</i> , %)	54, 28.1%
Moderate/severe thrombocytopenia (G2/G3: \leq 100 G/L; <i>n</i> , %)	55, 28.7%
Hemoglobin (g/dL; $\mu \pm$ SD)	10.8 \pm 1.9
Mild anemia (G1: Hb: 10-m \leq 13.5/f: \leq 12.5 g/dL; <i>n</i> , %)	114, 59.4%
Moderate/severe anemia (G2/G3: Hb < 10 g/dL; <i>n</i> , %)	57, 29.7%
White blood cell count (G/L; median, IQR)	5.90, 4.37–7.65
Mild leukopenia (G1: 2–4 G/L; <i>n</i> , %)	34, 17.7%
Moderate/severe leukopenia (G2/G3: < 2 G/L; <i>n</i> , %)	3, 1.6%
Bicytopenia (<i>n</i>, %)	75, 39.1%
Pancytopenia (<i>n</i>, %)	32, 16.7%

Fig. 2 Improvement of thrombocytopenia, anemia and leukopenia over time. **a, c, e**: absolute and **b, c, f**: relative changes in **a, b**: platelet count (PLT); **c, d**: hemoglobin and **e, f**: white blood cell count (WBC) over time, stratified by severity of the underlying cytopenia. Denotations: *: $p < 0.05$, **: $p < 0.01$; ***: $p < 0.001$



Discussion

To our knowledge, our study is first to investigate the effects of TIPS on all three hematopoietic cell lines in patients who received PTFE-covered stents. Thrombocytopenia and anemia were prevalent in most patients prior to TIPS, and higher-grade (i.e., G2/3) thrombocytopenia and anemia significantly improved consistently after the procedure. While mild and moderate leukopenia also tended to improve after TIPS, the respective patient numbers were low and thus, no strong conclusion can be drawn in this regard.

In 1999, Gschwantler et al. [23] reported an improvement of PLT after TIPS implantation in comparison to a control group of patients who did not undergo TIPS. In their longitudinal prospective study, median PLT of

the 55 included patients who underwent TIPS implantation increased by approximately 20% over the first year after TIPS, while PLT of the 110 controls significantly decreased. Moreover, PLT of patients with < 100G/L at baseline increased by > 25%, but none normalized. Masoud et al. [24] also reported significant increases in PLT after TIPS, averaging +22% in a total of 74 patients undergoing TIPS implantation and reporting higher increases (+36%) in patients with moderate thrombocytopenia and highest increases (+55%) in patients with severe thrombocytopenia at baseline. We observed similar effects of PTFE-TIPS on PLT in our study with a comparable increase in PLT of +19.8% in patients with G2/G3 thrombocytopenia (up to +75.6% at M12 in patients with G3 thrombocytopenia). Besides the grade

of thrombocytopenia at baseline, Massoud et al. [24] did not identify any meaningful predictor for improvement of thrombocytopenia after TIPS.

In contrast, Barney et al. [25] did not report a significant increase in PLT levels after TIPS but a slight improvement in Hb [25]. Although their findings are indeed in line with the results from our general study population, by stratifying patients according to cytopenia severity, we found that PLT tended to decrease in patients with $PLT \geq 100$ G/L, but increased in patients with lower baseline values, especially in the relevant sub-groups of patients with G3 thrombocytopenia and anemia at baseline. Unfortunately, the study by Barney et al. [25] lacked sub-analyses and included patients with HCC, and thus, the beneficial effect of TIPS on hematology may have been masked by their pooled analysis. Ultimately, the improvement of higher-grade thrombocytopenia after TIPS implantation may suggest that severe thrombocytopenia should actually *not* be regarded as a contraindication for TIPS implantation (as previously proposed) [1]. In contrast, Barney et al. [25] did not report a significant increase in PLT levels after TIPS but a slight improvement in Hb [25]. Although their findings are indeed in line with the results from our general study population, by stratifying patients according to cytopenia severity, we found that PLT tended to decrease in patients with $PLT \geq 100$ G/L, but increased in patients with lower baseline values, especially in the relevant sub-groups of patients with G3 thrombocytopenia and anemia at baseline. Unfortunately, the study by Barney et al. [25] lacked sub-analyses and included patients with HCC, and thus, the beneficial effect of TIPS on hematology may have been masked by their pooled analysis. Ultimately, the improvement of higher-grade thrombocytopenia after TIPS implantation may suggest that severe thrombocytopenia should actually *not* be regarded as a contraindication for TIPS implantation (as previously proposed).

Studies in liver-transplanted patients reported a significant reduction in spleen volume in patients with pre-transplant splenomegaly, although normalization of spleen volume was rare [29–31]. A recent study by Liu et al. [32] investigated the effects of TIPS implantation on thrombocytopenia and splenomegaly (spleen volume) in 104 patients mostly (mostly 95%) with variceal bleeding as TIPS-indication. The authors found an impressive correlation between improvement of platelet count and a decrease in splenic volume after TIPS [32] which, however, was likely affected by the underlying acute bleeding events.

Regrettably, we did not routinely measure spleen elastography nor assessed erythropoietin or thrombopoietin prior to TIPS implantation. Therefore, our retrospective study design did not allow to decipher the underlying pathophysiology responsible for the improvement of cytopenias after TIPS, such as a decrease in splenic congestion or amelioration of hyporegenerative anemia/thrombocytopenia. However, at

our study centers, only patients who are decompensated with a history of recent or recurrent variceal bleeding and/or intractable/refractory ascites are referred to TIPS implantation. In case of clinical re-compensation (e.g., diuretic control of ascites [33] and/or a single variceal bleeding episode with an uncomplicated clinical course under secondary prophylaxis in a low-risk setting) in patients who present with low benefit/risk ratio (e.g., $HVPG \leq 12$ mmHg), we consider the TIPS intervention to no longer be indicated. As a result, all patients included into this study presented with CSPH at time of TIPS placement, which is why we highly suspect PH and associated splenomegaly to be the major drivers in the pathogenesis of hypersplenism and cytopenia in our patient collective.

Hepatic decompensation, development of acute-on-chronic liver failure and mortality have all been linked to systemic inflammation (e.g., caused by bacterial translocation, ongoing viral infection, or alcohol intoxication) in patients with CLD [33–39]. Thus, it is to be expected that patients in need for TIPS implantation would present with elevated inflammation markers prior to TIPS, and that decompression of portal pressure would improve systemic inflammation and reduce the risk of further complications such as ACLF and mortality [40]. These effects have indeed been demonstrated both by prescription of non-cardioselective beta-blockers [36, 41] and by TIPS implantation in patients with increased risk of PH-associated complications and death [28, 42–45]. While decompression of PH by TIPS might ameliorate inflammation in some patients (by limiting bacterial translocation) and reduce splanchnic venous vascular shear stress [42], some patients do experience a further increase in splenic stiffness (which is considered a marker for portal hypertension and inflammation) after TIPS that is associated with poor post-procedural outcome and increased mortality [46]. Additionally, mechanical hemolysis of erythrocytes and platelets may impede hematologic improvement or actually worsen blood cell counts in patients undergoing TIPS, as was demonstrated by Ansari-Gilani et al. [47] who reported improvement in platelet counts only in patients with G2-3 thrombocytopenia and patent TIPS according to Doppler sonography. Mechanical destruction of blood cells could be the cause for the decline in blood cell counts in our patients without apparent hematologic hypersplenism (i.e., no or G1 cytopenias).

Since pre-TIPS blood counts can be considerably influenced by bleedings events, either directly due to blood loss/iron deficiency or indirectly by infection/inflammation-associated acute phase reactions [48], we also performed sub-analyses in patients who only presented with ascites as the sole indication for TIPS. The results were similar to those of the entire study cohort, with continuous improvement of

higher-grade anemia and normalization of leukopenia after TIPS [48].

In 2011, Bureau et al. [49] recommended TIPS implantation in patients with a baseline PLT count of > 75 G/L and a bilirubin level of < 50 $\mu\text{mol/mL}$, since according to their data, lower PLT values were associated with increased post-TIPS mortality. We were not able to verify this finding in our cohort; in our multivariable model (*data not shown*), surprisingly, neither thrombocytopenia nor any of the MELD components (INR, bilirubin, creatinine) emerged as predictors for mortality after TIPS, but pre-TIPS PPG, ascites as indication for TIPS and low WBC count ($p < 0.010$). Contrariwise, cytopenia improvement did not appear to influence post-TIPS mortality, either. We hypothesize that (baseline) leukopenia is associated with more severe portal hypertension-associated hypersplenism than thrombocytopenia, considering that only patients with radiologically evident splenomegaly had $\text{WBC} < 4$ G/L. On the other hand, leukopenia was very rare in our cohort, as leukopenia may be masked by chronic liver injury-associated inflammation (which in itself may be associated with increased mortality) [36, 50].

Strengths of our study include the large sample size compared to previous studies and the detailed stratification of patients according to severity of thrombocytopenia and anemia. In addition, our study is the first to systematically focus on all three types of hematopoietic cell lines and their longitudinal course after TIPS implantation.

Nonetheless, our study has some limitations: First, due to its retrospective nature, some blood count results were missing. Second, we may have introduced a selection bias by not including patients with a follow-up of < 3 months (our first follow-up time point); moreover, selection bias may have aggravated over time due to loss of follow-up and mortality. Third, the stratified analysis is prone to a phenomenon termed *regression toward the mean*. Fourth, we had to merge G2/G3 thrombocytopenia/anemia and all grades of leukopenia for several analyses, which precluded us to evaluate the effects of TIPS in detail within the distinct groups. Finally, the study lacks a matched control group of patients without TIPS.

In conclusion, thrombocytopenia with $\text{PLT} < 100$ G/L, anemia with $\text{Hb} < 10$ g/dL, and leukopenia improved sustainably after covered TIPS. This underlines the role of advanced PH and PH-associated hypersplenism on high-grade cytopenia in cirrhosis. Therefore, we recommend that higher-grade anemia and thrombocytopenia not be regarded as absolute contraindications for TIPS implantation, but to be considered in the individual benefit/risk ratio assessment when screening for TIPS, especially in patients who are scheduled to undergo major interventions or surgery (e.g., liver transplantation) who might actually profit from pre-surgical TIPS.

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Declarations

Conflict of interest Mattias Mandorfer served as a speaker and/or consultant and/or advisory board member for W.L. Gore and Associates. Thomas Reiberger received grant support and speaking honoraria from W.L. Gore and Associates. Maria Schoder served as a speaker and/or consultant and/or advisory board member for W.L. Gore and Associates.

Ethics approval This study was conducted in accordance with the Declaration of Helsinki and its later amendments. It was approved by the Ethics Committees of the Medical University of Vienna (1760/2014) and of the City of Vienna (MA15, 14–264-VK). This research study was conducted retrospectively from data obtained for clinical purposes, and all the procedures being performed were part of the routine care. Due to the retrospective nature of the study, the need for informed patient consent was waived by the local Ethics Committees.

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