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ORIGINAL ARTICLE

Targeted decrease of portal hepatic pressure gradient improves ascites control after TIPS

Alexander Queck[1] | Louise Schwierz[2] | Wenyi Gu[1,3] | Philip G. Ferstl[1] | Christian Jansen[2] | Frank E. Uschner[1,3] | Michael Praktiknjo[2,3] | Johannes Chang[2] | Maximilian J. Brol[1,3] | Filippo Schepis[4] | Manuela Merli[5] | Christian P. Strassburg[2] | Jennifer Lehmann[2] | Carsten Meyer[6] | Jonel Trebicka[1,3,7]

[1]Department of Internal Medicine 1, University Hospital Frankfurt, Johann Wolfgang Goethe-University, Frankfurt am Main, Germany

[2]Department of Internal Medicine I, University Hospital Bonn, Bonn, Germany

[3]Department of Internal Medicine B, University of Münster, Münster, Germany

[4]Division of Gastroenterology, Azienda Ospedaliero-Universitaria di Modena and University of Modena and Reggio Emilia, Modena, Italy

[5]Gastroenterology, Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy

[6]Department of Radiology, University Hospital, University Bonn, Bonn, Germany

[7]European Foundation for the Study of Chronic Liver Failure, Barcelona, Spain

Correspondence
Jonel Trebicka, Department of Internal Medicine 1, University Hospital Frankfurt, Goethe University, Theodor Stern-Kai 7, D-60590 Frankfurt am Main, Germany.
Email: jonel.trebicka@kgu.de

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Abstract

Background: Ascites is a definitive sign of decompensated liver cirrhosis driven by portal hypertension. Although transjugular intrahepatic portosystemic shunt insertion (TIPS) is indicated for therapy of recurrent and refractory ascites, there is no evidence-based recommendation for a specific target of portal hepatic pressure gradient (PPG) decrease.

Methods: In this single-center, retrospective trial, we investigated the decrease of PPG in 341 patients undergoing TIPS insertion for therapy of refractory or recurrent ascites until 2015. During each procedure, portal and inferior vena cava pressures were invasively measured and correlated with patients' outcome and ascites progression over time, according to the prespecified Noninvasive Evaluation Program for TIPS and Follow-Up Network protocol (NCT03628807).

Results: Patients without ascites at 6 weeks after TIPS had significantly greater PPG reduction immediately after TIPS, compared to the patients with refractory ascites (median reduction 65% vs. 55% of pre-TIPS PPG; $p = 0.001$). Survival was significantly better if ascites was controlled, compared to patients with need for paracentesis 6 weeks after TIPS (median survival: 185 vs. 41 weeks; HR 2.0 [1.3–2.9]; $p < 0.001$). Therefore, higher PPG reduction by TIPS ($p = 0.005$) and lower PPG after TIPS ($p = 0.02$) correlated with resolution of severe ascites 6 weeks after TIPS. Multivariable analyses demonstrated that higher Child-Pugh score before TIPS (OR 1.3 [1.0–1.7]; $p = 0.03$) and lower serum sodium levels (OR 0.9 [0.9–1.0]; $p = 0.004$) were independently associated with ascites

Abbreviations: IVC, inferior vena cava; LVP, large-volume paracentesis; MELD, Model for End-Stage of Liver Disease; PHT, portal hypertension; PPG, portal hepatic pressure gradient; TIPS, transjugular intrahepatic portosystemic shunt insertion.

Alexander Queck, Louise Schwierz, Wenyi Gu, and Philip G. Ferstl indicates shared first authorship.

Jennifer Lehmann, Carsten Meyer, and Jonel Trebicka shared last authorship.

persistence 6 weeks after TIPS, whereas PPG reduction (OR 0.98 [0.97–1.00]; p = 0.02) was associated with resolution of ascites 6 weeks after TIPS.

Conclusion: Extent of PPG reduction and/or lowering of target PPG immediately after TIPS placement is associated with improved ascites control in the short term and with survival in the long term. A structured follow-up visit for patients should assess persistence of ascites at 6 weeks after TIPS.

INTRODUCTION

Chronic liver disease of all etiologies leads to cirrhosis and development of portal hypertension (PHT).[1] The traditional hemodynamic hypothesis of ascites development associates PHT increase with progressive splanchnic vascular vasodilatation and consequent reduction of systemic effective arterial blood volume. This triggers the activation of neuro-endocrine systems to decrease water and sodium excretion at kidney level (i.e., increase in blood volume) and the consequent increase in cardiac output. This compensatory mechanism, in turn, aggravates PHT by raising the blood flow/pooling in the splanchnic vascular bed.[2] Following the vasodilatation hypothesis, refractory ascites[3] and acute kidney injury[4,5] hepatorenal syndrome (HRS), previously defined as type I HRS, are the extreme consequences of this circuital mechanism, which is aggravated by the gradual impairment of cardiac function (i.e., cirrhotic cardiomyopathy).[6,7]

Refractory ascites was defined by the International Ascites Club (IAC) in 1996 and 2003 and was based primarily on the absence of response to intensive diuretic therapy or the appearance of specific side effects of diuretics.[8,9] Transjugular intrahepatic portosystemic shunt insertion (TIPS) is the most effective procedure to treat ascites.[10–12] Indeed, TIPS placement results in a significant reduction in the number of large-volume paracentesis (LVP) or in the definitive control of ascites formation in patients with refractory ascites. Control of ascites is associated with improvement in survival in patients in the earlier stage of recurrent ascites.[12,13]

The difference between portal vein and inferior vena cava (IVC) blood pressures represents the most accurate method to calculate the porto-systemic pressure gradient (PPG).[14] While an immediate post-TIPS PPG < 12 mm Hg has been confirmed as protective from variceal rebleeding, a specific hemodynamic target is still controversially discussed in patients with ascites.[15,16]

Recently, we demonstrated that controlling of diameter of TIPS may improve response to ascites.[17] However, it is not clear which PPG target should be targeted.

The investigation of the effect of PPG reduction on patient outcome after TIPS implantation for recurrent and refractory ascites was the aim of this study.

METHODS

Study oversight

This is a retrospective analysis of prospective structured follow-up for patients receiving TIPS in a single tertiary center. Patients were recruited between March 1994 and July 2015 in the Department of Internal Medicine I, University of Bonn, Germany. The study protocol has been approved by the local ethics committee of the University of Bonn and the informed consent was waived (029/13). All authors had access to the study data and reviewed and approved the final manuscript.

Patients

A total of 341 patients with liver cirrhosis undergoing TIPS insertion for recurrent or refractory ascites were included in this study. Refractory ascites was defined according to the IAC criteria.[9] Recurrent ascites was defined as 3 times within 12 months.[13] The number of patients with varices or bleeding before TIPS is recorded in Table S1. Patients older than 18 years with clinical signs of liver cirrhosis and a multidisciplinary-confirmed indication for TIPS were included in our study. Exclusion criteria were the presence of systemic infection, recurrence of HE without an identifiable trigger, bilirubinemia >7 mg/dl, arterial pulmonary hypertension, or pregnancy. All patients signed and agreed to all procedures as declared in the study protocol.

Study design

Patients received TIPS insertion for ascites according to the German guidelines.[18,19] During the procedure, portal and IVC pressures were invasively measured with a pressure transducer system (Combitrans; Braun) and a multichannel monitor (Sirecust; Siemens). All patients received a structured follow-up period after TIPS as highlighted in the Noninvasive Evaluation Program for TIPS and Follow-Up Network study (NCT03628807). Here, outpatients follow-up schedules started 6 weeks after TIPS and included basic laboratory test, abdominal ultrasound, and physical visit by a physician on the TIPS team. Patients received further continuous monitoring until liver transplantation, death, or study discontinuation.

Statistical analyses

To check for normal distribution, Kolmogorov–Smirnov or D'Agostino and Pearson omnibus normality tests were performed. Parametric (unpaired *t* test) or nonparametric (Mann–Whitney) tests were applied accordingly. For analyses of paired observations, including Model for End-Stage of Liver Disease (MELD) score progression over time, paired *t* test (parametric) or Wilcoxon matched-pairs signed-rank test (nonparametric) was used. Independently associated variables of outcomes were assessed with logistic regression models. Significant variables with $p < 0.10$ in univariate analyses were selected into the multivariate model. For survival analyses, the log-rank (Mantel-Cox) test was used. For analyses regarding the follow-up, censored patients during the first 6 weeks were also excluded. Patients were censored in case of transplantation or loss to follow-up. *p* values < 0.05 were considered to be statistically significant. GraphPad Prism 9.0.0 for Windows (GraphPad Software, Inc.) or BIAS (version 10.08) for Windows was used for the performance of statistical analyses.

RESULTS

Clinical and hemodynamic characteristics of patients at TIPS insertion

A total of 341 patients with a median age of 60 years underwent TIPS insertion for treatment of ascites. In most patients, chronic alcohol consumption was the reason for cirrhosis development (n = 241, 71%), followed by chronic viral hepatitis (n = 43, 13%). Median survival after TIPS insertion was 102 weeks, and 19 patients received liver transplantation over time (6%). At the time of TIPS insertion, HE was present in 65 patients (19%), and all patients presented grade 3 ascites, needing frequent LVP. Median MELD score of patients before TIPS was 12, and most of the patients were classified as Child-Pugh B (79%), presenting a median Child-Pugh score of 9. As expected, hypoalbuminemia (median 28 g/L) were observed (Table 1). Median portal pressure before TIPS was 28 mm Hg and decreased to a median of 21 mm Hg (−25%) ($p < 0.001$) after TIPS. Initial IVC pressure was 8 mm Hg and 13 mm Hg after TIPS (+50%) ($p < 0.001$). Median PPG levels before and immediately after TIPS insertion were 19 mm Hg and 8.0 mm Hg (−58%) ($p < 0.001$), respectively (Table 2).

Clinical characteristics of patients 6 weeks after TIPS

As expected, levels of sodium, albumin, and creatinine improved 6 weeks after TIPS insertion. In detail, median serum sodium levels increased from 135 mmol/L to 137 mmol/L ($p < 0.001$); median creatinine levels decreased from 1.3 mg/dl to 1.2 mg/dl (p = 0.0016); and median albumin levels increased from 28 g/L to 29.2 g/L (p = 0.055). The MELD score slightly increased from 12 to 14 at follow-up visit (p = 0.054), primarily due to bilirubin increase (before TIPS: median 1.2 mg/dl; follow-up: median 1.7 mg/dl; $p < 0.001$). Finally, HE improved through TIPS insertion. Although episodes of severe HE (grade ≥ 2) were present in 9% of the patients before TIPS, only 2% presented episodes of HE (grade ≥ 2) 6 weeks after TIPS ($p < 0.001$) (Table 1).

Impact of immediate PPG after TIPS insertion on ascites response

At the 6-week follow-up, ascites significantly improved through TIPS insertion ($p < 0.001$). Only 24% (n = 69) of the patients still needed LVP, whereas 29% (n = 83) presented with ascites only detectable by ultrasound. In 47% of the patients (n = 132) a complete resolution of ascites was achieved at 6 weeks after TIPS (Figure 1). Therefore, the median PPG reduction was 55% of initial PPG in patients with persistence of severe ascites, 58% in patients with ascites detected by ultrasound, and 65% in patients who resolved ascites at 6 weeks after TIPS. The percentage of PPG reduction was significantly higher if ascites resolved in comparison to patients with need for paracentesis, 6 weeks after TIPS (p = 0.001) (Figure 2A). Furthermore, significantly lower median PPG levels after TIPS were observed in patients with complete resolution of ascites compared to patients with refractory ascites, 6 weeks after TIPS (p = 0.002). In detail, median PPG after TIPS was 7 mm Hg in patients without ascites 6 weeks after TIPS, whereas median PPG of 8 mm Hg was observed in patients with mild or severe ascites 6 weeks after TIPS (Figure 2B). Moreover, significant differences could also be observed between patients with need of paracentesis and those with partial or complete control of ascites (Figure S1).

Multivariate logistic regression analysis was conducted to detect other predictors for therapy failure, assessed by persistence of severe ascites at 6 weeks

TABLE 1 General characteristics of patients undergoing TIPS insertion at baseline and at 6-week follow-up

Parameter	Baseline (*n* = 341)	Follow-up at 6 weeks[a] (*n* = 284)	*p* value
Median (interquartile range) or number (percentage)			
General			
Age, years	60 (53–67)		
Etiology of cirrhosis:			
alcohol/viral/other	241/43/57 (71/13/16)		
Survival (95% CI), weeks	102 (69–134)		
Liver transplantation over time	19 (6)		
Clinical events			
HE			
Stage 0–1/2–4	310/31 (91/9)	277/7 (98/2)	<0.001
No/Yes	276/65 (81/19)	250/34 (88/12)	0.02
Ascites			
Stage 0/1–2/3	0/0/341 (0/0/100)	132/83/69 (47/29/24)	<0.001
Paracentesis			
No/Yes	0/341 (100)	215/69 (76/24)	<0.001
Scores			
MELD	12 (10–16)	14 (10–17)	0.054
Child-Pugh	9.0 (8.0–9.0)	8.0 (7.0–9.0)	<0.001
Child-Pugh class (A/B/C)	0/272/69 (0/79/21)	70/169/45 (25/59/16)	<0.001
Laboratory			
Sodium (mmol/L)	135 (132–138)	137 (134–140)	<0.001
Creatinine (mg/dl)	1.3 (1.0–1.8)	1.2 (0.9–1.5)	0.0016
Bilirubin (mg/dl)	1.2 (0.7–1.9)	1.7 (1.0–3.0)	<0.001
WBC (10^3/μl)	6.7 (4.9–9.0)	6.5 (4.8–8.4)	0.33
Albumin (g/l)	28 (23–34)	29.2 (25–34.4)	0.055
INR	1.2 (1.0–1.3)	1.2 (1.1–1.4)	0.007

Abbreviations: INR, international normalized ratio; MELD: Model for End-Stage Liver Disease; WBC, white blood cell count.

[a]Fifty-seven patients were censored during the first 6 weeks after TIPS. This group included 35 deaths, 4 with liver transplantation, and 19 without information of paracentesis.

TABLE 2 Portal hemodynamics of patients undergoing TIPS insertion for treatment of refractory ascites (*n* = 341 patients)

Parameter	Before TIPS	After TIPS	*p* value
Median (interquartile range)			
Portal hemodynamics			
PPG (mm Hg)	19 (16–23)	8 (5–10)	<0.001
Portal pressure (mm Hg)	28 (24–33)	21 (17–25)	<0.001
IVC pressure (mm Hg)	8 (5–12)	13 (9–17)	<0.001
Reduction of PPG by TIPS (%)	58 (47–72)		
Reduction of PP by TIPS (%)	25 (17–32)		
Increase of IVC pressure by TIPS (%)	50 (20–100)		

Abbreviations: IVC, inferior vena cava; PP, portal pressure.

after TIPS. Interestingly, the percentage of PPG decrease with response to TIPS (OR and 95% CI: 0.98 [0.97–1.00]; $p = 0.02$) was independently associated with persistence of severe ascites and need for paracentesis after being adjusted for Child-Pugh score and serum sodium levels before TIPS (Table 3 and Table S2).

Three different TIPS diameters were used in this study (8 mm, 10 mm, and 12 mm), with 10-mm stents being the predominant size. Therefore, 12-mm stents were used significantly more often in patients with persistent ascites 6 weeks after TIPS (ascites, $p = 0.01$; paracentesis, $p < 0.001$) (Figure S2).

Patients were further stratified into the different groups based on the percentage of PPG reduction at TIPS (Table 4). The reduction of 60% as the median was found to be the best cutoff with the highest net

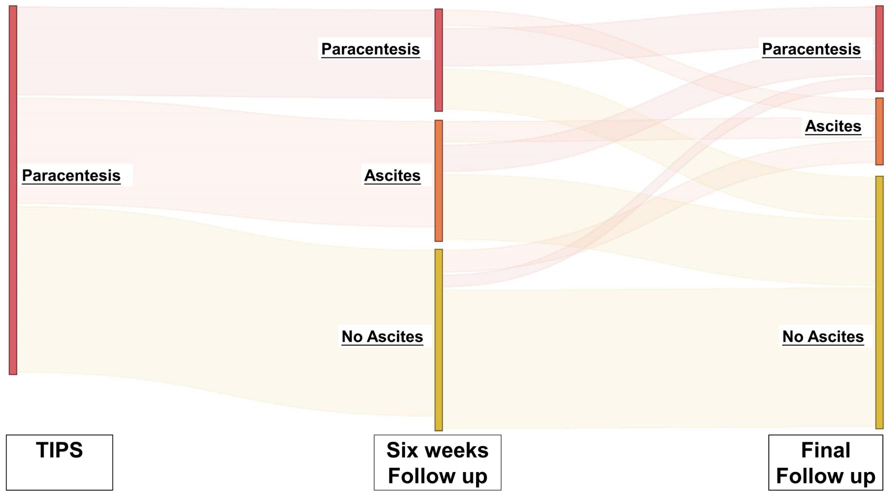


FIGURE 1 Sankey River diagram of the number of patients with or without different grades at different visits. Abbreviation: TIPS, transjugular intrahepatic portosystemic stent shunt.

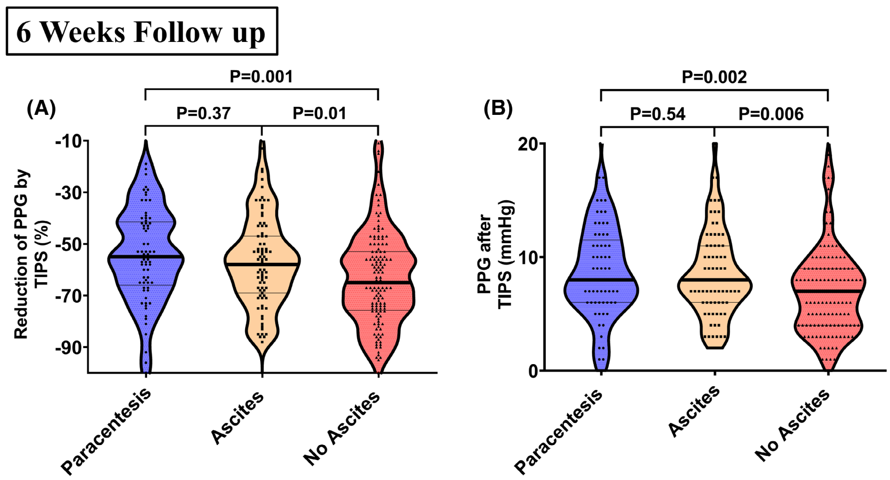


FIGURE 2 Violin plot with probability of density of the data using kernel density estimator. (A) Unpaired t-test was used to analyze ascites response at 6 weeks after TIPS dependent on portal hepatic pressure gradient (PPG) reduction by TIPS. Median PPG reduction was 55% in the group of patients with refractory ascites 6 weeks after TIPS (*n* = 69). Patients with ascites in ultrasound showed median PPG reduction of 58% (*n* = 83), and patients with no ascites at 6 weeks after TIPS of 65% (*n* = 132). (B) Mann–Whitney test was used to analyze ascites response at 6 weeks after TIPS in dependency of post-TIPS PPG. Median PPG after TIPS was 8 mm Hg in the group of patients with refractory ascites 6 weeks after TIPS (*n* = 69). Patients with ascites in ultrasound showed median PPG of 8 mm Hg (*n* = 83), and patients with no ascites at 6 weeks after TIPS of 7 mm Hg (*n* = 132).

TABLE 3 Logistic regression of factors associated with need for paracentesis at 6-week follow-up after TIPS insertion due to refractory ascites

	Univariable model			Multivariable model[a]		
	OR	95% CI	*p* value	OR	95% CI	*p* value
PPG reduction percentage by TIPS	**0.98**	0.97–1.00	0.01	**0.98**	0.97–1.00	0.02

Note: PPG reduction used the relative value calculated as follows: ("PPG after TIPS" – "PPG before TIPS")/"PPG before TIPS." Bold indicates *p* value < 0.01.
[a]The model was adjusted by Child-Pugh score, WBC count (per µl), and sodium (mmol/L).

reclassification index (Table S3 and Figure S3). Of note, the target PPG after TIPS was also significantly lower in the patient groups with higher percentual PPG reduction (target PPG < 12 mm Hg = 79% and <10 mm Hg = 62% in the group of PPG reduction <60% of initial PPG compared with target PPG < 12 mm Hg = 99% and <10 mm

Hg = 96% in the group of PPG reduction ≥ 60% of initial PPG; $p < 0.001$). Not surprisingly, only 2% of patients achieved a 60% reduction of PPG but still had a PPG higher than 10 mm Hg (Figure S4). No significant differences were found in baseline MELD and Child-Pugh score, respectively (Table 4; Table S1). Additionally, no significant differences were observed regarding presence of refractory ascites or HE. Except for higher baseline level of albumin in patients with PPG reduction below 60% (median 28.9 vs. 27.3 g/L; $p = 0.004$), baseline biochemical parameters were not significantly different at TIPS insertion. After TIPS insertion, ascites improved in both groups significantly ($p < 0.001$). Interestingly, ascites resolved in 39% of the patients with lower PPG reduction (below 60%), compared to 54% in patients with higher PPG reduction (60% or above). Ascites was detected by ultrasound in another 31% of the patients with lower PPG reduction, compared to 27% of the patients with higher PPG reduction. Persistent severe ascites was seen in 30% of the patients with lower PPG reduction, compared to 19% of the patients with higher PPG reduction. Therefore, significant superior ascites control was achieved in patients with higher PPG reduction ($p = 0.006$). The frequency of HE episodes did not increase in 6 weeks or last follow-up (Table S4), and no significant differences were observed between both patient groups 6 weeks after TIPS (Table 4). Moreover, in patients with higher PPG reduction, albumin levels significantly increased already at 6 weeks after TIPS ($p < 0.001$), whereas no differences were observed in serum albumin levels of patients with lower PPG reduction. No differences between these two groups were

TABLE 4 Influence of PPG reduction by TIPS on patient characteristics

	PPG reduction by TIPS			
	<60% of initial PPG		**≥60% of initial PPG**	
Parameter	**Baseline (*n* = 174)**	**Follow-up at 6 weeks[b] (*n* = 144)**	**Baseline (*n* = 167)**	**Follow-up at 6 weeks[b] (*n* = 140)**
Median (quartile) or absolute (percentage)				
Clinical events				
HE				
0–1/2–4	154/20 (89/11)	139/5 (97/3)$^{+++}$	156/11 (93/7)	138/2 (99/1)$^{+++}$
Ascites				
0/1–2/3	0/0/174 (0/0/100)	56/45/43^{+++} (39/31/30)	0/0/167 (0/0/100)	76/38/26^{+++}/** (54/27/19)
Diuretics[a]	83 (76)		96 (73)	
Scores				
MELD	12 (9.0–17)	13 (10–17)	12 (10–16)	14 (10–17)
Child-Pugh score	9 (8.0–9.0)	8.0 (7.0–9.0)$^{+++}$	9 (8.0–9.0)	8.0 (6.0–9.0)$^{+++}$
Child-Pugh class: A/B/C	3/134/37 (2/77/21)	31/88/25^{+++} (22/61/17)	2/133/32 (1/80/19)	39/81/20^{+++} (28/58/14)
Laboratory				
Sodium (mmol/L)	135 (131–138)	137 (133–140)$^{++}$	136 (132–139)	137 (134–140)$^{++}$
Creatinine (mg/dl)	1.3 (1.0–1.8)	1.2 (0.9–1.5)$^{+}$	1.3 (1.0–1.8)	1.2 (0.9–1.5)$^{+}$
Bilirubin (mg/dl)	1.2 (0.7–1.9)	1.7 (1.0–2.7)$^{+++}$	1.1 (0.7–1.9)	1.7 (1.0–3.3)$^{+++}$
WBC (10^3/µl)	6.7 (5.0–9.0)	6.6 (4.8–8.6)	6.4 (4.8–9.0)	6.4 (4.8–8.4)
Albumin (g/L)	28.9 (24.4-35.0)	28.5 (25.0–34.0)	27.3** (20.9–32.1)	29.3^{+++} (25.1–34.8)
INR	1.2 (1.0–1.3)	1.2 (1.1–1.4)	1.2 (1.1–1.3)	1.2 (1.1–1.4)$^{+}$
PPG after TIPS				
Median, mm Hg	10 (8.0–12)	5.0 (4.0–7.0)***		
≤10, n	108 (62)	160 (96)		
≤12, n	137 (79)	165 (99)		
>12, n	37 (21)	2 (1)		

Note: ***p*** <0.05 and ****p*** <0.01 between the two different PPG reduction groups at the same timepoint (either baseline or follow-up). $^{+}p < 0.05$, $^{++}p < 0.01$, and $^{+++}p < 0.001$ between the same PPG reduction group, but at different timepoints (baseline vs. follow-up).

[a] A total of 241 patients had recorded information regarding treatment of diuretics.

[b] Fifty-seven patients were censored during the first 6 weeks following TIPS. This group included 35 deaths, 4 with liver transplantation, and 19 without information of paracentesis.

seen at 6 weeks after TIPS regarding the MELD and Child-Pugh score (Table 4).

Finally, persistent need for paracentesis at 6 weeks after TIPS predicted poor survival outcome of patients, compared to patients with ascites resolution ($p < 0.001$). Significant survival differences could also be found between the group of patients need for paracentesis and patients with only ascites ($p = 0.003$) (Figure 3 and Figure S5). If combining the group of no ascites together with ascites without paracentesis, a significantly better survival could still be found in the non-paracentesis group ($p < 0.001$) (Figure S1C). Therefore, median survival of patients 185 weeks (patients without ascites), 128 weeks (patients with ascites only detectable by ultrasound), and 41 weeks (patients with persistent need for paracentesis), respectively. Moreover, the decade of TIPS insertion did not significantly influence patient survival (Figure S6). However, the covered TIPS improved more short-term survival than the non-covered TIPS (Figure S7).

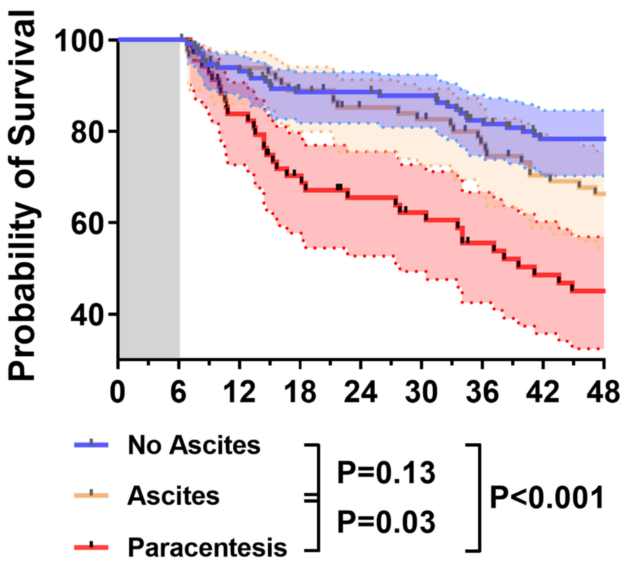
DISCUSSION

In this study, we show that (i) PPG reduction of less than 60% from the initial value was independently associated with persistence of ascites requiring paracentesis at 6 weeks after TIPS, and (ii) persistence of severe ascites requiring paracentesis at 6 weeks after TIPS is associated with poorer outcome.

Treatment of ascites using TIPS is still debated and challenging. Refractory ascites predisposes to hepatorenal syndrome (type 1), spontaneous bacterial peritonitis, and strongly impacts survival.[20] Even though LVP with albumin administration represents the first-line therapy for ascites, TIPS insertion showed survival and ascites control improvement both in recurrent and refractory ascites.[12] Therefore, TIPS is recommended by the European Association for the Study of the Liver guidelines as therapy for these complications of portal hypertension.[11] These recommendations are reinforced by our data. Forty-seven percent of patients resolved, and another 29% presented ascites only at ultrasound already 6 weeks after TIPS. Only in 24% of patients was ascites not resolved by TIPS at the 6-week follow-up, which was a predictor of mortality. This finding is important, as it classifies a subpopulation of patients with TIPS who require more assistance, including possible transplant option.

Persistence of ascites after TIPS was not solely associated with the magnitude of portal hypertension such as PPG, but also with severity of disease assessed by Child-Pugh score and lower sodium levels. Because hyponatremia is especially a frequent finding in end-stage liver cirrhosis[21] and is associated with in-hospital mortality of patients with cirrhosis,[22] one may hypothesize that patients may benefit from TIPS for treatment of ascites in earlier stages of cirrhosis, when hyponatremia is not yet present. Of note, Bureau et al. showed survival benefit of TIPS for treatment of recurrent ascites.[13] In addition, Piecha et al. recently illustrated improved ascites control after TIPS in patients with lower paracenteses rates before TIPS.[23] Our data confirm these studies and suggest 6 weeks after TIPS as an important timepoint to check for response and stratify care of patients with TIPS for ascites.

In our study we intended to find a cutoff for PPG target after TIPS, as the decline of the portal pressure after TIPS could be interpreted by the PPG reduction, reducing the complications of PHT, especially ascites. Therefore, independent association of target PPG < 10 mm Hg and resolution of ascites 6 weeks after TIPS was observed. Moreover, this real-life large study also shows that the probability of ascites resolution is much higher if PPG reduction exceeded 60% of PPG before TIPS. Not only were ascites controlled and albumin levels increased, but patient outcome also improved. As expected by the previous studies analyzing PPG for variceal development and bleeding, in these patients, the target PPG was also significantly more often below 12 mm Hg and in most of the patients even



132	132	124	117	116	114	106	98	98
83	83	78	73	67	65	58	53	49
69	69	57	46	41	38	33	29	27

FIGURE 3 Log-rank test (Mantel-Cox) was used to analyze survival differences dependent on ascites progression (three groups) after TIPS insertion at 6 weeks. Probability of survival is presented in patients' percentage with 95% CI ($n = 284$ patients). Median survival of 41 weeks for patients with the need for paracentesis at 6 week follow-up, 128 weeks with ascites in ultrasound, and 185 weeks with absence of ascites at follow-up.

below 10 mm Hg. This is known to be beneficial for the treatment of variceal bleeding and supports our study and the solidity of the data.[14,24]

A frequent question is the post-TIPS follow-up, which is not standardized yet. In this study, outpatient follow-up visit was scheduled at 6 weeks after TIPS. At this timepoint we could clearly stratify the course following TIPS. This is an easy tool to detect patients at high risk of unstable course of disease. Importantly, patients with ascites, who require paracentesis at 6 weeks after TIPS, are such patients. This study suggests that even in patients with uncomplicated TIPS insertion, a short-term follow-up 6 weeks after TIPS should be scheduled to be able to predict their course of disease.

Additionally, the follow-up for complications of HE is also of great importance. Our study revealed a slight improvement of HE after TIPS insertion, which was possibly due to decreased bacterial translocation after TIPS, an improvement of nutritional status, and the administration of albumin, rifaximin, and lactulose for the patients. As expected in our results, TIPS insertion increases effective arterial blood volume and reduces the complications from PHT as well as the neurohormonal activation, leading to improvement serum sodium, creatinine, and albumin. Despite the high mortality and the long follow-up, only about 6% of the patients received liver transplant during follow-up in our cohort. On the one hand, many of these patients had alcohol-related cirrhosis. On the other hand, many of them had a MELD score < 15.

This study has limitations. The retrospective design of our analyses may lead to some bias. In addition, immediate post-TIPS PPG may vary over time, and the study included a long inclusion period over two decades, which may have induced bias due to the change in type and quality of the stents, as well as the standard of care and procedure. However, our results show no survival differences between the two decades. Finally, the study did not distinguish between recurrent and refractory ascites. Therefore, prospective trials analyzing this PPG reduction target in ascites need to confirm our results.

PPG reduction ≥ 60%, and/or target PPG < 10 mm Hg after TIPS for the therapy of ascites appears to improve ascites control and therefore patient outcome. Structured follow-up visits 6 weeks after TIPS can be useful in identifying patients with increased mortality.

AUTHOR CONTRIBUTIONS

Study concept and design: Jonel Trebicka. Data acquisition: Jonel Trebicka, Alexander Queck, Louise Schwierz, Jennifer Lehmann, Carsten Meyer, Christian Jansen, Frank E. Uschner, Philip G. Ferstl, Michael Praktiknjo, Johannes Chang, Maximilian J. Brol, Filippo Schepis, Manuela Merli, and Christian P. Strassburg. *Analysis*: Jonel Trebicka and Alexander Queck. *Data interpretation*: Jonel Trebicka, Alexander Queck, and Wenyi Gu. *Manuscript draft*: Jonel Trebicka, Alexander Queck, and Wenyi Gu. *Critical revision of the manuscript for important intellectual content*: Jonel Trebicka, Alexander Queck, Louise Schwierz, Jennifer Lehmann, Carsten Meyer, Wenyi Gu, Christian Jansen, Frank E. Uschner, Philip G. Ferstl, Michael Praktiknjo, Johannes Chang, Maximilian J. Brol, Filippo Schepis, Manuela Merli, and Christian P. Strassburg. *Statistical analysis*: Jonel Trebicka, Alexander Queck, and Wenyi Gu. *Funding obtainment*: Jonel Trebicka, Alexander Queck, Louise Schwierz, Jennifer Lehmann, and Carsten Meyer. *Technical or material support*: Jonel Trebicka, Alexander Queck, Louise Schwierz, Jennifer Lehmann, and Carsten Meyer. *Study supervision*: Jonel Trebicka, Louise Schwierz, Jennifer Lehmann, and Carsten Meyer.

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CONFLICT OF INTEREST

Philip G. Ferstl consults for SNIPR Biome and Cytosorbents. Carsten Meyer consults for W.L. Gore and Sirtex Medical.

ORCID

Michael Praktiknjo https://orcid.org/0000-0001-7033-9956
Manuela Merli https://orcid.org/0000-0003-3173-9767
Jonel Trebicka https://orcid.org/0000-0002-7028-3881

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SUPPORTING INFORMATION

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

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