Ascites control by TIPS is more successful in patients with a lower paracentesis frequency and is associated with improved survival

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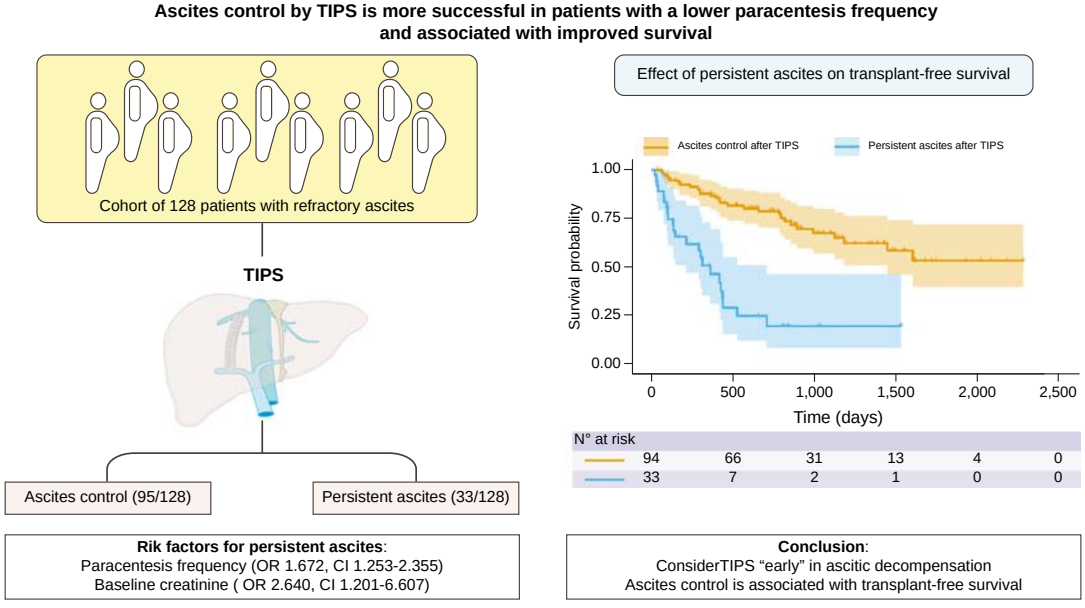
Graphical abstract



Highlights

- Ascites control post-TIPS is superior if the TIPS is placed at lower paracentesis frequency and creatinine levels.
- Transplant-free survival is decreased in patients with a failed ascites control post-TIPS.
- TIPS-placement should be considered "early" in ascitic decompensation.
- Close monitoring and prioritized organ allocation should be considered in patients with failed ascites control post-TIPS.

Lay summary

The insertion of a transjugular intrahepatic portosystemic shunt (TIPS) in patients with refractory ascites should be considered in patients with moderate decompensation and not as a last resort, as lower paracentesis frequency and creatinine levels pre-TIPS are associated with superior ascites control. In turn, failure to control ascites seems to be the only predictor of liver transplantation and death.

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Research Article

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Ascites control by TIPS is more successful in patients with a lower paracentesis frequency and is associated with improved survival

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Background & Aims: Refractory ascites is the main reason for the implantation of a transjugular intrahepatic portosystemic shunt (TIPS) in liver cirrhosis, but ascites control by TIPS fails in a relevant proportion of cases. Here, we investigated whether routine parameters pre-TIPS can predict persistent ascites after TIPS implantation and whether persistent ascites predicts long-term clinical outcome.

Methods: A detailed retrospective analysis of 128 patients receiving expanded polytetrafluoroethylene-covered stents for the treatment of refractory ascites was performed. Persistent ascites post-TIPS was defined as the prolonged need for paracentesis >3 months after TIPS. The influence of demographics, laboratory results, pre-TIPS heart and liver ultrasound results, and invasive hemodynamic parameters on persistent ascites was evaluated by univariable and multivariable logistic regression. Predictors of the composite endpoint liver transplantation/death were analyzed using a multivariable Cox regression.

Results: Ascites control post-TIPS was achieved in 95/128 patients (74%), whereas ascites remained persistent in 33/128 cases (26%). On multivariable analysis, a lower paracentesis frequency pre-TIPS (odds ratio 1.672; 95% CI 1.253–2.355) and lower baseline creatinine levels (odds ratio 2.640; CI 1.201–6.607) were associated with ascites control. Patients with persistent ascites post-TIPS had and impaired transplant-free survival (median 10.0 *vs.* 25.8 months), for which persistent ascites was the only independent predictor (hazard ratio 5.654; CI 3.019–10.59).

Conclusion: TIPS-placement in patients with lower paracentesis frequency and creatinine levels is associated with superior ascites control. Thus, TIPS implantation should be considered in moderate decompensation and not as a last resort. Persistent ascites post-TIPS seems to be the only predictor of liver transplantation and death.

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Introduction

Liver cirrhosis is a major global health problem associated with high morbidity and mortality.[1,2] During its natural history, the formation of ascites is a key event in disease progression, which is related to a drastically decreased survival.[3,4] Ascites that cannot be mobilized successfully by diuretics or recurs early after paracentesis despite sufficient medical therapy is called refractory ascites,[5] and its management remains a serious clinical problem and matter of debate. Currently, large-volume paracentesis (LVP) with albumin substitution or the implantation of a transjugular intrahepatic portosystemic shunt (TIPS) are used for the treatment of refractory ascites. Several randomized controlled trials[6–11] and meta-analyses[12,13] have compared these approaches with regard to their effect on survival, showing an overall survival benefit in patients receiving a TIPS.[12] However, patient selection is crucial, as bilirubin levels >3 mg/dl and platelet count <75,000/μl,[14] older age, pre-TIPS hepatic encephalopathy (HE)[15] and cardiac impairment defined as an E/A ratio <1[16] are associated with a poor outcome after TIPS. Regarding the efficacy of TIPS-placement on ascites control, a recent meta-analysis reported a complete response in 51% of patients and a partial response (defined as not requiring extended paracentesis) in 68% of patients,[17] while a decreased survival in case of persistent ascites after TIPS-placement has been reported for a cohort of patients receiving bare metal stents.[18] The reason why ascites control fails in some patients after TIPS, despite a standardized patient selection following current guidelines, remains elusive. Thus, additional factors that improve patient selection need to be identified. In this study, we aimed to assess predictors of persistent ascites after TIPS by analyzing a wide range of demographic, laboratory, ultrasound and invasive hemodynamic variables. In addition, the effect of unsuccessful ascites control on transplant-free survival was assessed in our well-characterized cohort.

Key words: liver cirrhosis; hepatic venous pressure gradient; portal hypertension; refractory ascites; MELD score; transplant; decompensation; stents.

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Materials and methods

Patients

All patients receiving a TIPS for refractory ascites at the University Medical Center Hamburg-Eppendorf between January 2011 and

December 2016 were screened for this retrospective analysis. The following baseline parameters were collected: demographic data, a detailed disease history including the timepoint of the first ascitic decompensation and the monthly paracentesis frequency, medication pre-TIPS, and the results of the last analysis of the composition of the ascitic fluid. Before TIPS-placement, all patients received an echocardiography as well as a standardized abdominal ultrasound before and after TIPS. For this study, all echocardiograms and abdominal ultrasounds were re-evaluated and rescored if necessary. Available pre-TIPS CT scans/MRIs were additionally analyzed for collateral flow. Routine laboratory parameters including Child-Pugh score, model for end-stage liver disease (MELD) score and Chronic Liver Failure Consortium Acute Decompensation (CLIF-C AD) score were assessed at baseline and shortly after (mean 12 ± 18 days) TIPS-placement. Alcohol consumption post-TIPS was evaluated by review of the clinical records and defined as "any" alcohol consumption either reported by the patient or detected by alcohol markers (usually ethyl glucuronide in urine). Changes in cardiac function post-TIPS were systematically investigated by evaluation of available post-TIPS echocardiograms.

The following outcome parameters were retrospectively collected: the need for paracentesis after TIPS-placement, the number of TIPS revisions performed, dates of complicating events (bleeding, diagnosis of a hepatocellular carcinoma [HCC], spontaneous bacterial peritonitis [SBP]), the date of liver transplantation or death, and the date of the last clinical visit/contact. Patients that had not presented to our outpatient clinic for >6 months (cut-off date 01.01.2018) were followed up by phone. Persistent ascites was defined as the ongoing need for paracentesis >3 months after TIPS-placement as described before.[18] The study was approved by the local ethics committee (reference number PV5580) in accordance with the principles of the declaration of Helsinki.

TIPS procedure

All TIPS insertions were carried out by experienced interventional radiologists trained for this procedure. In order to optimize conditions, a paracentesis was performed before TIPS-placement. During the intervention, local anesthesia in combination with midazolame (Hofmann-La Roche, Basel, Switzerland) and piritramide (Hameln pharma plus GmbH, Hameln, Germany) was administered in most patients, but a minority received additional propofol sedation. The portosystemic pressure gradient (PSPG) was invasively acquired by measurement of the pressure gradient in the portal vein and the intra-abdominal portion of the vena cava. In all patients, a 10 mm expanded polytetrafluoroethylene (ePTFE) coated stentgraft (VIATORR®, W.L. Gore & Associates Inc., AZ) was used and dilated to 8 mm using an 8/40 mm balloon dilatation catheter (Boston Scientific, Marlborough, MA). If variceal flow was present after TIPS-placement, variceal embolization was additionally carried out using a 2:1 mixture of N-butyl cyanoacrylate (B. Braun Melsungen AG, Melsungen, Germany) and lipiodol (Guerbet, Villepinte, France).

Statistical analysis

Mean and median values with the corresponding standard deviation or interquartile range (IQR) were calculated for continuous data using Excel 2016 (Microsoft Inc., Redmond, WA) and SPSS Statistics Version 25 (IBM Corp., Armonk, NY), percentages and counts are given for categorical data. A univariable logistic regression was conducted to identify possible predictors of persistent ascites after TIPS-placement, followed by a multivariable logistic regression in which all parameters with a p value <0.1 in the univariable regression were included. The area under the receiver operating characteristic (AUROC) curve was calculated for metric variables selected by the multivariable logistic regression to determine an optimal cut-off point. Additionally, a multivariable Cox regression for covariate adjustment for the composite endpoint liver transplantation and death followed by a cause-specific analysis and a Fine and Grey competing risk regression model was carried out. For these analyses, variables that showed differences in the group-wise comparison (persistent ascites *vs.* ascites control after TIPS) or were considered relevant for patient outcome according to the literature were included as covariates. Given the exploratory character of these analyses, no adjustment for multiple testing was conducted and the significance level was set to be 0.05 for all calculations. Adjusted survival curves for the composite endpoint were calculated based on the multivariable Cox model adjusting for mean MELD, mean CLIF-C AD, and mean PSPG post-TIPS. Figure design and statistical testing was carried out using SPSS Version 25 and R Version 3.5.1 (R Core Team, 2018).

Results

Patient characteristics

In total, 222 patients receiving a TIPS for refractory ascites were identified, of which 131 patients had a complete documented work-up and were therefore included in this study. However, 1 patient was lost to follow-up and 2 patients suffered acute complications (fatal bleeding and immediate post-TIPS liver failure), resulting in a total of 128 patients in the final analysis. General characteristics are given in Table 1. The main etiology of liver disease was chronic alcohol abuse (92/128, 72%) and most patients presented with a liver cirrhosis Child-Pugh B (103/128, 80%). Before TIPS insertion, the mean PSPG amounted to 21.0 ± 4.5 mmHg (Table 2) and the mean MELD and CLIF-C AD score were 12.6 ± 3.8 and 50.8 ± 6.5 points, respectively (Table 3). During follow-up, a total of 95/128 patients (74%) showed ascites control, of which 58 patients (61%) needed no additional paracentesis at all, and ascites persisted in 33/128 patients (26%) with the ongoing need for paracentesis >3 months post-TIPS. A TIPS revision was carried out in 20/128 patients (15%), of which 14 (70%) underwent recanalization/dilatation and 6 (30%) a stent diameter reduction due to prolonged HE. In total, 11 patients (8%) underwent liver transplantation and 40 patients (31%) died during follow-up, resulting in an overall median transplant-free survival of 20.3 months (Table 1). None of the patients who underwent liver transplantation was prioritized on the waiting list due to refractory ascites.

Comparison of baseline characteristics between patients with ascites control and persistent ascites after TIPS

When stratifying the patient cohort according to ascites clearance, neither group differed with regard to baseline demographics and disease history including pre-TIPS medication (Table S1), but patients with ascites control after TIPS-placement had a lower paracentesis frequency pre-TIPS (2.2 ± 1.2 *vs.* 3.6 ± 2.2 per month, Table 1). Abdominal ultrasound studies at baseline indicated similar flow rates in the portal vein and the hepatic artery, but collaterals and shunts evaluated either by ultrasound or abdominal CT scan/MRI (additionally available in a subgroup of 36 patients) were more prevalent in patients with persistent ascites after TIPS (18/33, 55% *vs.* 28/95, 29% in patients with ascites control, Table 2). Baseline echocardiography including an assessment of the diastolic dysfunction, tricuspid annular plane systolic excursion, E/A, E/E', diameter of the right

Table 1. General characteristics.

	Complete cohort (n = 128)	Ascites control (n = 95)	Persistent ascites (n = 33)
Baseline parameters			
Sex (m/w) (n/%)	83 (64%)/45 (36%)	60 (58%)/35 (42%)	23 (70%)/10 (30%)
Age (years):	57.9 ± 9.7	57.6 ± 10.6	58.9 ± 6.2
BMI (kg/m^2):	24.3 ± 5.1	24.4 ± 5.0	24.0 ± 5.4
Etiology (n/%):			
ALD	92/72%	70/74%	22/66%
Viral	9/7%	5/5%	4/12%
NASH	8/6%	4/4%	4/12%
AIH/PSC	2/2%	1/1%	1/3%
ALD/viral	8/6%	7/7%	1/3%
Cryptogenic	9/7%	8/8%	1/3%
Child-Pugh Stage A/B/C (n)	0/103/24	0/75/19	0/28/5
Time lapse diagnosis cirrhosis – TIPS (mo)	37 ± 53	35 ± 38	44 ± 84
Time lapse first ascites – TIPS (wk)	30 ± 28	32 ± 28	27 ± 28
Paracentesis frequency (n/mo)	2.6 ± 1.7	2.2 ± 1.2	3.6 ± 2.2
History of SBP (n/%)	41/32%	31/33%	10/30%
History of HRS (n/%)	45/35%	30/32%	15/45%
HRS at TIPS-placement (n/%)	24/18%	17/18%	7/21%
Type I HRS (n/%)	7/29%	5/29%	2/29%
Type II HRS (n/%)	17/71%	12/71%	5/71%
History of upper GI bleeding (n/%)	27/21%	20/21%	7/21%
Variceal size	1.2 ± 0.8	1.2 ± 0.9	1.2 ± 0.9
Red spots (yes/no/unknown)	29/66/32	19/53/23	10/13/9
Outcome parameters			
Need of paracentesis after TIPS (n; yes/no)	70/58	37/58	33/0
TIPS revisions (n/%)	20/16%	8/8%	12/36%
Incidence of bleeding (n/%)	8/6%	5/5%	3/9%
Incidence of HCC (n/%)	11/8%	6/6%	5/15%
Incidence of SBP (n/%)	16/13%	4/4%	12/36%
Incidence of transplantations (n/%)	11/8%	4/4%	7/21%
Incidence of death (n/%)	40/31%	24/25%	16/48%
Transplant-free survival (mo. median w/IQR)	20.3 (24.4)	25.8 (25.5)	10.0 (11.4)

Baseline characteristics were comparable between groups, but patients with persistent ascites after TIPS had a higher paracentesis frequency at baseline. Values shown are mean ± SD or median with interquartile range for continuous data and counts and percentages for categorical data.
AIH, autoimmune hepatitis; ALD, alcoholic liver disease; BMI, body mass index; GI, gastrointestinal; HCC, hepatocellular carcinoma; HRS, hepatorenal syndrome; IQR, interquartile range; NASH, non-alcoholic steatohepatitis; PSC, primary sclerosing cholangitis; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt.

atrium and the left ventricular ejection fraction also yielded comparable results, but patients with ascites control after TIPS presented with a smaller left atrium (18.8 ± 5.1 *vs.* 21.8 ± 8.9 cm^2, Table 2). The composition of the ascitic fluid and routine laboratory parameters at baseline were similar between the group of patients with ascites control and persistent ascites, including MELD (12.3 ± 3.5 *vs.* 13.5 ± 4.4) and CLIF-C AD (50.3 ± 6.5 *vs.* 52.2 ± 6.4) scores (Table 3). However, patients with ascites control after TIPS presented with lower creatinine values at baseline (1.3 ± 0.5 *vs.* 1.7 ± 1.0 mg/dl).

Hemodynamic parameters, laboratory and abdominal ultrasound follow-up in patients with ascites control or persistent ascites after TIPS

Baseline portal and central venous pressure values with the corresponding PSPG before TIPS-placement were similar in both groups (Table 2). A stent was successfully placed in all patients, resulting in a decrease of mean PSPG values from 21.0 ± 4.5 to 8.7 ± 2.9 mmHg in the whole cohort. Patients with ascites control after TIPS showed a trend towards lower post-TIPS PSPG values compared to patients with persistent ascites (8.4 ± 2.8 mmHg *vs.* 9.4 ± 2.8 mmHg) and a higher absolute decrease in PSPG brought about by the intervention (ΔPSPG 12.9 ± 4.1 *vs.* 10.5 ± 4.1 mmHg). During angiography, collateral flow before TIPS-creation was present in 27/128 (21%) of patients with a higher prevalence in the group of patients with ascites control (22/95, 23% *vs.* 5/33, 15%), and an additional variceal embolization was only carried out in 6 patients.

The follow-up abdominal Doppler ultrasound was performed after a median of 3 days (IQR 1) following TIPS-placement. Portal venous flow increased significantly from 19.1 ± 5.4 to 37.3 ± 13.3 cm/sec, accompanied by an increase in hepatic arterial flow

Table 2. Abdominal imaging, echocardiography and invasive pressure measurement results.

	Complete cohort (n = 128)	Ascites control (n = 95)	Persistent ascites (n = 33)
Abdominal imaging*			
Porto-systemic collaterals (n/%)	40/31%	24/25%	16/48%
Shunt within the liver (n/%)	3/2%	2/2%	1/3%
Spleno-renal shunt (n/%)	3/2%	2/2%	1/3%
Portal venous flow pre-TIPS (cm/sec)	19.1 ± 5.4	18.9 ± 5.7	19.6 ± 4.6
Portal venous flow post-TIPS (cm/sec)	37.3 ± 13.3	38.3 ± 13.5	34.3 ± 12.5
Δportal venous flow (cm/sec)	17.8 ± 14.4	18.8 ± 14.5	15.1 ± 14.0
Hepatic arterial flow pre-TIPS (cm/sec)	66.2 ± 36.5	64.9 ± 35.2	69.7 ± 40.6
Hepatic arterial flow post-TIPS (cm/sec)	89.9 ± 37.3	92.9 ± 37.6	83.9 ± 26.8
Spleen size pre-TIPS (mm)	143 ± 30 x 55 ± 15	143 ± 28 x 55 ± 15	142 ± 35 x 57 ± 16
Intra-TIPS flow (cm/sec)	115 ± 33	116 ± 32	111 ± 35
Intrahepatic flow post-TIPS (retro-/antegrade, n)	116/2	88/0	28/2
Intrahepatic flow velocity post-TIPS (cm/sec)	20.5 ± 8.0	20.5 ± 8.0	20.6 ± 8.3
Echocardiography			
Diastolic dysfunction grade 0/I/II (n)	69/54/3	53/38/2	16/16/1
TAPSE (mm)	25.2 ± 4.9	25.1 ± 4.5	25.3 ± 5.8
E/E‘	8.6 ± 2.6	8.5 ± 2.4	8.8 ± 3.2
E/A	1.1 ± 0.4	1.1 ± 0.5	1.1 ± 0.4
Right atrial diameter (cm^2)	14.9 ± 4.4	14.6 ± 4.4	15.6 ± 4.4
Left atrial diameter (cm^2)	19.6 ± 6.5	18.8 ± 5.1	21.8 ± 8.9
LVEF (%)	64.0 ± 6.2	64.0 ± 6.4	63.8 ± 5.7
Heart rate (bpm)	78 ± 12	78 ± 12	81 ± 13
Mean arterial pressure (mmHg)	80 ± 10	80 ± 9	79 ± 11
Invasive hemodynamic variables			
Collaterals detected by angiography (n/%)	27/21%	22/23%	5/15%
Spleno-renal shunt (n/%)	3/2%	3/3%	0/0%
Additional embolization performed (n)	6	6	0
Portal pressure pre-TIPS (mmHg)	30.0 ± 5.7	30.1 ± 5.6	29.8 ± 6.3
Central venous pressure pre-TIPS (mmHg)	9.1 ± 4.6	8.9 ± 4.6	9.6 ± 4.6
PSPG pre-TIPS (mmHg)	21.0 ± 4.5	21.4 ± 4.4	19.9 ± 4.7
Portal pressure post-TIPS (mmHg)	20.0 ± 5.7	19.4 ± 5.7	21.7 ± 5.3
Central venous pressure post-TIPS (mmHg)	11.7 ± 4.8	11.5 ± 4.8	12.3 ± 5.0
PSPG post-TIPS (mmHg)	8.7 ± 2.9	8.4 ± 2.8	9.4 ± 2.8
PSPG >10 mmHg post-TIPS (n/%)	29/23%	19/20%	10/30%
PSPG >12 mmHg post-TIPS (n/%)	13/10%	8/8%	5/15%
ΔPSPG (mmHg)	12.3 ± 4.2	12.9 ± 4.1	10.5 ± 4.1

Baseline and follow-up ultrasound results were comparable between the groups. On echocardiography, patients with ascites control had a smaller left atrium. Invasive pressure measurements revealed that patients with ascites control had a trend to lower post-TIPS portal pressure values and a stronger decrease in PSPG (ΔPSPG). Values shown are mean ± SD or counts. *An additional imaging modality was available in 36 patients (CT scan: 34 patients; MRI: 2 patients. 11 CT and both MRI scans were performed in patients with persistent ascites after TIPS). Bpm, beats per minute;LVEF, left ventricular ejection fraction; PSPG, portosystemic pressure gradient; TAPSE, tricuspid anular plain systolic excursion; TIPS, transjugular intrahepatic portosystemic shunt.

(Table 2). All but 2 patients presented with a retrograde intrahepatic portal venous flow, intra-TIPS flow amounted to a mean of 115 ± 33 cm/sec, and all flow parameters were comparable between the groups (Table 2).

After a mean of 12 ± 18 days, a routine laboratory follow-up was carried out. In the whole cohort, bilirubin increased significantly (from 1.4 ± 0.9 to 1.9 ± 1.2 mg/dl) after TIPS, whereas creatinine values decreased to a significant extent (from 1.4 ± 0.7 to 1.1 ± 0.4 mg/dl), resulting in stable MELD and CLIF-C AD scores. Changes in laboratory parameters were also comparable between the groups of patients with ascites control and persistent ascites after TIPS (Table 3).

Predictors of persistent ascites after TIPS-placement

Variables from all pre-TIPS assessments were first analyzed with an univariable logistic regression model, but only the pre-TIPS paracentesis frequency, the left atrial diameter, baseline creatinine values, PSPG post-TIPS and the absolute PSPG decrease (ΔPSPG) had a p value <0.1 and were therefore included in the multivariable regression model (Table 4). On multivariable

Table 3. Baseline analysis of the ascitic fluid and routine laboratory parameters and short-term follow-up of MELD and CLIF-C AD scores

	Complete cohort (n = 128)	Ascites control (n = 95)	Persistent ascites (n = 33)
Baseline analysis of ascites			
Protein content (g/L)	14.9 ± 8.1	15.6 ± 8.8	13.2 ± 5.4
Albumin (g/L)	11.3 ± 5.8	11.7 ± 6.8	10.3 ± 1.3
Glucose (mg/dl)	135.5 ± 44.1	132.6 ± 37.8	142.7 ± 56.7
LDH (mg/dl)	58.4 ± 28.2	59.9 ± 31.4	54.3 ± 15.7
Baseline laboratory parameters			
Bilirubin (mg/dl)	1.4 ± 0.9	1.4 ± 0.9	1.2 ± 0.1
GOT (U/L)	47.4 ± 23.6	46.4 ± 23.2	50.4 ± 24.9
GPT (U/L)	25.5 ± 14.7	23.6 ± 14.0	31.1 ± 15.3
g-GT (U/L)	146.4 ± 135.2	131.2 ± 103.3	190.1 ± 196.3
AP (U/L)	162.1 ± 203.4	162.0 ± 231.0	162.3 ± 90.6
Albumin (g/L)	26.4 ± 5.4	26.4 ± 5.3	26.4 ± 5.9
Platelets (1,000/μl)	158 ± 84	152 ± 73	175 ± 110
INR	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.1
Fibrinogen (g/L)	3.3 ± 1.2	3.4 ± 1.2	3.3 ± 1.4
Potassium (mmol/L)	4.6 ± 0.6	4.3 ± 0.6	4.5 ± 0.6
Sodium (mmol/L)	134.6 ± 4.5	134.5 ± 4.6	134.7 ± 4.2
Creatinine (mg/dl)	1.4 ± 0.7	1.3 ± 0.5	1.7 ± 1.0
C-reactive protein (mg/L)	15.6 ± 13.4	15.1 ± 13.0	17.0 ± 14.4
White blood cell count (1,000/μl)	6.5 ± 2.6	6.5 ± 2.5	6.8 ± 2.8
MELD score	12.6 ± 3.8	12.3 ± 3.5	13.5 ± 4.4
CLIF-C AD score	50.8 ± 6.5	50.3 ± 6.5	52.2 ± 6.4
Child-Pugh score (points)	8.8 ± 0.9	8.9 ± 1.0	8.7 ± 0.8
Follow-up laboratory parameters			
Time after TIPS-placement (d)	12 ± 18	13 ± 20	11 ± 12
Bilirubin (mg/dl)	1.9 ± 1.2	1.8 ± 1.2	1.9 ± 1.3
Creatinine (mg/dl)	1.1 ± 0.4	1.1 ± 0.3	1.3 ± 0.5
MELD score	12.8 ± 3.7	12.4 ± 3.1	13.8 ± 4.9
CLIF-C AD score	50.6 ± 6.0	49.9 ± 5.5	52.5 ± 6.8

Baseline diagnostic of ascites and laboratory parameters were comparable between groups. However, patients with ascites control presented with lower creatinine values. On follow-up, bilirubin increased and creatinine decreased in both groups, resulting in stable MELD and CLIF-C AD scores. Values shown are mean ± SD.
CLIF-C AD score, chronic liver failure consortium – acute decompensation score; INR, international normalized ratio; MELD, model for end-stage liver disease; TIPS, transjugular intrahepatic portosystemic shunt.

analysis, the paracentesis frequency pre-TIPS (odds ratio [OR] 1.672; 95% CI 1.253–2.355), ΔPSPG (OR 1.164; CI 1.027–1.340) and baseline creatinine values (OR 2.640; CI 1.201–6.607) were identified as independent predictors of persistent ascites after TIPS. However, an additional AUROC calculation showed a poor discriminating power of baseline creatinine with an area under the curve of 0.661 and an optimal cut-off value of 1.5 mg/dl with a mediocre sensitivity (0.758) and a poor specificity (0.515, see Fig. S1 and Table S2).

Persistent ascites after TIPS predicts liver transplantation and death

During follow-up, 8 patients (6%) suffered from portal hypertensive bleeding complications, HCC developed in 11 patients (8%) and 16 patients (13%) were treated for SBP. After stratification for ascites control, the event rate for HCC and bleeding was similar between groups, but more patients with persistent ascites developed SBP (4/95, 4% *vs.* 12/33, 36%, Table 1). Patients with ascites control after TIPS presented with a lower event rate of liver transplantations or death (28/95, 29% *vs.* 23/33, 70%), corresponding to a longer transplant-free survival (median 25.8 *vs.* 10.0 months, Table 1 and Fig. 1). In a multivariable Cox regression including baseline creatinine, baseline MELD score, baseline CLIF-C AD score, post-TIPS PSPG values and group stratification according to ascites control or persistent ascites after TIPS, only persistent ascites was identified as an independent predictor of the composite endpoint liver transplantation/death (hazard ratio [HR] 5.654; CI 3.019–10.59; Table 5), which was confirmed both in the cause-specific analysis (not shown) and the Fine and Grey competing risk regression for each endpoint (death or liver transplantation). In the cause-specific analysis, the baseline CLIF-C AD score was also predictive of the endpoint "death" (HR 1.068; CI 1.01–1.13; $p = 0.02$; data not shown), whereas baseline MELD score was an additional independent predictor of the endpoint "liver transplantation" (HR 1.323; CI 1.024–1.71; $p = 0.03$; data not shown). In the Fine and Grey competing risk regression, baseline CLIF-C AD score was an additional independent predictor of death (HR 1.058; CI 1.001–1.12; see Table 5).

Table 4. Uni- and multivariable logistic regression to identify independent predictors of persistent ascites after TIPS

		95% CI		
Parameter	**Odds ratio**	**Lower**	**Upper**	***p* value**
Univariable logistic regression				
Timelapse first ascites – TIPS implantation	0.994	0.975	1.010	0.478
Paracentesis frequency pre-TIPS	1.631	1.262	2.192	<0.001
Portal venous flow pre-TIPS	1.021	0.944	1.101	0.593
Spleen size	0.999	0.985	1.012	0.861
Intra-TIPS flow	0.995	0.982	1.007	0.400
E/E‘	1.043	0.882	1.229	0.618
E/A	1.081	0.402	2.642	0.867
Right atrial diameter	1.055	0.958	1.164	0.274
Left atrial diameter	1.072	1.004	1.159	0.055
Mean arterial pressure	0.991	0.950	1.033	0.662
Ascitic protein content	0.957	0.900	1.012	0.156
Baseline bilirubin	0.820	0.490	1.277	0.412
Baseline creatinine	2.255	1.246	4.657	0.015
Baseline CLIF-C AD score	1.046	0.983	1.115	0.158
Baseline MELD score	1.084	0.977	1.204	0.126
Baseline Child-Pugh score	0.852	0.544	1.312	0.473
PSPG post-TIPS	1.131	0.983	1.312	0.090
ΔPSPG	1.173	1.056	1.319	0.005
Multivariable logistic regression				
Paracentesis frequency pre-TIPS	1.672	1.253	2.355	0.002
Left atrial diameter	1.048	0.956	1.155	0.322
Baseline creatinine	2.640	1.201	6.607	0.023
PSPG post-TIPS	1.082	0.903	1.307	0.396
ΔPSPG	1.164	1.027	1.340	0.024

All parameters with a *p* value <0.1 in the univariable analysis were included in the multivariable logistic regression. The paracentesis frequency pre-TIPS, baseline creatinine and the absolute decrease in PSPG values (ΔPSPG) could be identified as independent predictors of persistent ascites.
CLIF-C AD score, chronic liver failure consortium – acute decompensation score; MELD, model for end-stage liver disease; PSPG, portosystemic pressure gradient; TIPS, transjugular intrahepatic portosystemic shunt.

Evolution of the underlying liver disease and follow-up echocardiography and angiography after TIPS

The development of the underlying liver disease may affect ascites control and prognosis of patients with decompensated liver cirrhosis. Chronic alcohol abuse, viral liver disease or the combination of both were the main etiologies of liver cirrhosis in this cohort (Table 1). Data on alcohol consumption after TIPS-placement were available in 77/92 (84%) patients with alcoholic liver disease (ALD) and in 104/128 (81%) patients irrespective of disease etiology (Table S3). When stratified according to ascites clearance, the rate of post-TIPS alcohol consumption was similar for patients with ALD (19/70, 27% in the ascites control group *vs.* 7/22, 31% in patients with persistent ascites) and for all patients irrespective of disease etiology (22/95, 23% *vs.* 8/33, 24%). All 3 patients with a chronic hepatitis B infection were already under treatment before TIPS-placement, and in case of chronic hepatitis C virus (HCV) infection, 2/15 patients were treated before TIPS, 1/15 patients was treated after TIPS and 12/15 patients did not receive antiviral therapy and therefore had a stable underlying liver disease.

A total of 52 out of 128 patients underwent follow-up echocardiographies, of which 32 were performed in patients with ascites control and 20 in patients with persistent ascites. When stratified according to ascites clearance, changes in cardiac parameters were similar between groups, especially an increase in atrial diameters (Table S4). A deterioration of diastolic dysfunction defined as a diastolic dysfunction grade II or III was observed in 5/32 (16%) patients with ascites control and 2/20 (10%) patients with persistent ascites after TIPS. In patients with ascites control, 1 patient with a diastolic dysfunction II° developed an additional moderate tricuspid insufficiency, 2 patients developed either a moderate mitral or tricuspid insufficiency and 1 patient developed pulmonary arterial hypertension. In patients with persistent ascites after TIPS, 1 patient developed a moderate tricuspid insufficiency and 2 patients presented with cardiac failure due to a newly developed dilatative cardiomyopathy and a high-grade tricuspid insufficiency.

During follow-up, 12 TIPS revisions were performed in patients with persistent ascites, including 3 TIPS reductions and 9 dilatations without an improvement of ascites. Reasons why the other patients were not considered for a stent dilatation include HE (4 patients), fear of exhaustion of cardiac reserve (3), blood stream infection (2), liver transplantation shortly after TIPS-placement (2), late-onset recompensation with diuretics (1) and an unstructured follow-up (9).

Discussion

Despite careful patient selection, ascites persists in a relevant proportion of patients receiving a TIPS for refractory ascites. In this study, we demonstrate that lower pre-TIPS paracentesis

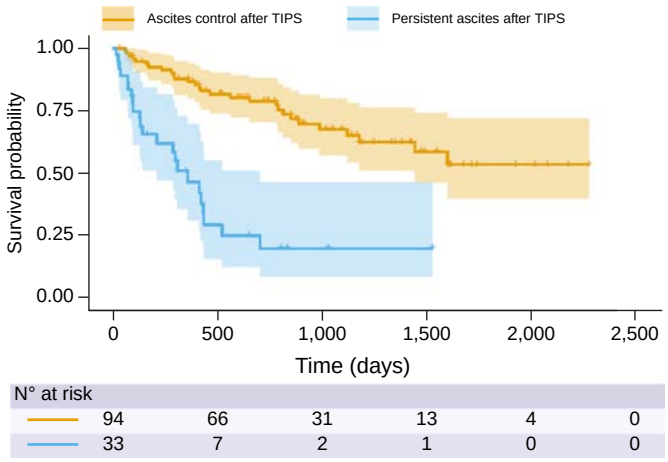

Fig. 1. Adjusted survival curves based on the multivariable Cox regression for the composite endpoint comparing the groups "ascites control" *vs.* "persistent ascites". Adjustment was carried out for mean PSPG post-TIPS, mean MELD and mean CLIF-C AD scores.CLIF-C AD score, chronic liver failure consortium – acute decompensation score; MELD, model for end-stage liver disease; PSPG, portosystemic pressure gradient; TIPS, transjugular intrahepatic portosystemic shunt.

frequency and creatinine levels are associated with superior ascites control and that TIPS-non-response with persistent ascites predicts impaired transplant-free survival.

As patients were selected according to widely accepted recommendations, the patient cohort presented in this study is rather homogeneous and baseline characteristics including MELD and Child-Pugh scores and pre- and post-TIPS ultrasound, laboratory and PSPG values are comparable to the published literature.[6,8,14,15,19,20] All TIPS-placements were technically successful with an adequate decrease in portal pressure, leading to ascites control in 74% and persistent ascites with the ongoing need for paracentesis >3 months after TIPS in 26% of patients, which is also in line with previous reports.[17]

On multivariable analysis, paracentesis frequency pre-TIPS, baseline creatinine and the absolute decrease of PSPG (ΔPSPG) were independent predictors of persistent ascites post-TIPS. However, the clinical importance of the difference in ΔPSPG is questionable, as it only amounted to approximately 1.5 mmHg with a lower limit of the odds ratio close to 1. To our surprise, the post-TIPS PSPG was not associated with ascites control in our cohort, even though some patients presented with post-TIPS PSPG values >12 mmHg which is not considered optimal. In this context, the timing of the PSPG measurement immediately after TIPS-creation could have influenced our results, as values change over time.[21] Furthermore, recent studies[22,23] have reported a passive dilatation of the TIPS-stent after its placement, which might also contribute to further changes in PSPG values. Therefore, defining an optimal PSPG cut-off for patients with refractory ascites remains a matter of debate,[24] especially in light of the potentially deleterious effect of overly aggressive pressure reduction.[25]

Similar to our results, several other studies have reported that higher creatinine values at baseline are associated with an unfavorable outcome after TIPS for refractory ascites.[6,19,26] However, guiding therapeutic decisions based on creatinine values alone is difficult, as a TIPS itself improves renal function,[15] as also seen in our cohort, so that renal insufficiency/hepatorenal syndrome (HRS) can be considered an indication for TIPS itself.[27] Importantly, the rate and type of HRS was similar between groups in our cohort, which otherwise would have been an important confounder, as the type of HRS has also been shown to have an impact on post-TIPS survival.[28,29]

Besides lower creatinine values, a lower pre-TIPS paracentesis frequency was also identified as an independent predictor of ascites control post-TIPS. Taking these 2 findings together, our data support the idea that a TIPS should be inserted "early" in ascitic decompensation and not be reserved for patients with an extremely high paracentesis frequency.[30] Even though there are a multitude of reasons for renal impairment in liver cirrhosis, long-term diuretic therapy with a consecutive increase in creatinine values is a key contributor. Therefore, an "early" TIPS in refractory ascites may help to break the vicious circle of attempting to increase diuretics to mobilize ascites, causing further renal impairment which in turn makes pharmaceutical control of ascites impossible. This approach is also supported by the latest

Table 5. Multivariable Cox regression and Fine and Grey competing risk regression to identify variables associated with the endpoints liver transplantation and death

		95% CI		
Parameter	**Hazard ratio**	**Lower**	**Upper**	***p* value**
Multivariable Cox regression				
Baseline creatinine	0.716	0.390	1.315	0.281
Baseline MELD score	1.113	0.992	1.250	0.069
Baseline CLIF-C AD score	1.043	0.992	1.096	0.098
PSPG post-TIPS	0.952	0.854	1.062	0.382
Persistent ascites after TIPS	5.654	3.019	10.59	<0.001
Fine and Grey competing risk regression – endpoint death				
Baseline creatinine	0.757	0.410	1.398	0.37
Baseline MELD score	1.075	0.945	1.223	0.27
Baseline CLIF-C AD score	1.058	1.001	1.12	0.047
PSPG post-TIPS	1.014	0.901	1.142	0.82
Persistent ascites after TIPS	2.426	1.208	4.871	0.013

In the multivariable Cox regression, persistent ascites was the only parameter predictive of the composite endpoint liver transplantation/death. In the competing risk analysis, baseline CLIF-AD scores showed an additional predictive value for death in this cohort.
CLIF-C AD score, chronic liver failure consortium – acute decompensation score; MELD, model for end-stage liver disease; PSPG, portosystemic pressure gradient; TIPS, transjugular intrahepatic portosystemic shunt.

prospective, randomized trial comparing TIPS to LVP[8] in patients with only recurrent ascites and a limited paracentesis frequency, which demonstrated a survival benefit in TIPS-treated patients. Therefore, we suggest that a TIPS should be considered early in patients with a stable underlying liver disease whose kidney function is beginning to be impaired, whereas in patients with an HCV-associated liver cirrhosis, treatment of the underlying disease with direct-acting antivirals should be considered first[31] to improve liver function.

Furthermore, our data clearly indicate that patients with persistent ascites after TIPS have a decreased transplant-free survival. Interestingly, neither the MELD nor the CLIF-C AD score was predictive of the composite endpoint transplantation and death, and neither score changed to a statistically significant extent on short-term follow-up (even though these scores can be inaccurate on short-term follow-up due to procedure-related changes in *e.g.* bilirubin). In this regard, our study highlights another issue regarding patient selection for TIPS and a possible liver transplantation. While patients with persistent ascites after TIPS have an impaired transplant-free survival, this is not adequately reflected by current clinical scores used for organ allocation in some countries, like the MELD score, especially as its main driver – serum creatinine – may improve after TIPS-placement. Therefore, prioritized organ allocation for patients with persistent ascites after TIPS awaiting liver transplantation should be systematically evaluated and considered as a standard strategy.

Despite a thorough analysis, we did not find any additional predictive marker among the routinely assessed parameters that may help in the patient selection for TIPS. In this present study, the CLIF-C AD score that has shown to improve the prediction of prognosis in acutely decompensated patients[32] has been evaluated in TIPS patients for the first time. However, it did not yield any further predictive power despite incorporating age and white blood cell count – factors that have been described as relevant for patient outcome after TIPS.[33–35] Considering the impact of systemic inflammation on patient outcome after TIPS,[33] further prospective studies are warranted to dissect the crosstalk between portal hypertension and immunity. In this context, elastography techniques to measure liver and spleen stiffness may also help to anticipate patient outcome after TIPS-placement, as both parameters quickly respond to pressure changes[36–38] and a beneficial effect of a decrease in liver stiffness after TIPS or non-selective betablocker treatment have been reported.[39,40]

The strength of this study lies within the exhaustive in-depth analysis and a highly standardized patient selection and treatment, particularly the exclusive use of ePTFE-covered stentgrafts. However, it also has several limitations, like its retrospective nature, a limited sample size and a high confidence interval on multivariable analysis due to the limited number of events. In this context, recompensation after TIPS itself poses a potential bias as it allows for a more aggressive treatment of potentially life-limiting liver-related and unrelated medical conditions. In addition, not all patients with persistent ascites post-TIPS underwent a stent re-dilatation for various reasons, even though some of these patients might arguably have benefited from a further stent dilatation. Another limitation is, that due to the study design, the evaluation of alcohol consumption only represents an approximation, as no details on drinking habits (*e.g.* amount consumed, frequency, *etc.*) can be provided. On the other hand, the data at hand indicate that most patients remained under stable conditions with respect to their underlying liver disease, which is important as interventions like alcohol withdrawal and viral eradication have a direct impact on liver function and portal hypertension.[41] Similarly, the data of follow-up echocardiography and the association of spontaneous shunts on TIPS function can only be regarded as preliminary. Even though changes in cardiac parameters were similar between groups and cardiac failure was only observed in 2 patients in this cohort, the limited availability of follow-up echocardiograms preclude a generalization, so that post-TIPS heart failure might have been overlooked as a factor contributing to the persistence of ascites. In addition, abdominal imaging pre-TIPS revealed a higher number of shunts in patients with persistent ascites post-TIPS, which is in line with a previous report on the association of spontaneous shunts and outcome in patients in liver cirrhosis.[42] However, as only a fraction of patients were evaluated by a CT or MRI scan, and as more collaterals were detected in patients with ascites control during angiography, these results cannot be generalized. However, the association between spontaneous shunts and post-TIPS outcome should be investigated in prospective studies if possible.

In conclusion, our results suggest that TIPS-placement should not be restricted to patients with a high paracentesis frequency and renal impairment, but that it should already be considered early during ascitic decompensation in patients with refractory ascites and a lower paracentesis frequency. Persistent ascites after TIPS is associated with a poor prognosis, so that prioritized liver transplant allocation should be considered.

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Conflicts of interest

JK and DB have served as speakers for W.L. Gore & associates in the past. JK has served as an advisory board member for Novartis. The other authors have nothing to disclose regarding the work under consideration for publication.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

FP: design of the study, data acquisition, statistical analysis and interpretation of the data, and writing the paper. UK: data acquisition, interpretation of the data, and critical reading. AKO: statistical analysis and critical reading. DS: data acquisition and critical reading. AD: interpretation of the data and critical reading. TH: interpretation of the data and critical reading. CS: data acquisition and critical reading. HI: interpretation of the data and critical reading. DB: interpretation of the data and critical reading. AWL: interpretation of the data and critical reading. CS: interpretation of the data and critical reading. JK: conception and design, writing the paper, critical reading, and final approval.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhepr.2019.04.001.

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