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Transjugular intrahepatic portosystemic shunt and alfapump® system for refractory ascites in liver cirrhosis: Outcomes and complications

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Abstract

Background: Treatment of refractory ascites in liver cirrhosis is challenging. Transjugular intrahepatic portosystemic shunt and alfapump® have been proposed for the management, but few data comparing both exist.

Aims: The aim of this study was to evaluate the characteristics and outcomes of patients treated with transjugular intrahepatic portosystemic shunt and alfapump® for refractory ascites at our centre.

Methods: All consecutive patients were retrospectively reviewed for baseline characteristics, efficacy of treatment, complications and survival.

Results: In total, 19 patients with transjugular intrahepatic portosystemic shunt and 40 patients with alfapump® were included. Patients with transjugular intrahepatic portosystemic shunt had better liver function and less hepatic encephalopathy at baseline. Fifty-eight per cent of patients developed hepatic encephalopathy in the first six months after transjugular intrahepatic portosystemic shunt. In patients with alfapump®, renal function decreased and 58% developed prerenal impairment and 43% hepatorenal syndrome in the first six months. Alfapump® patients with new catheters required less reinterventions (26% versus 57% with old catheters, $p = 0.049$). Transplant-free survival at 1 year was 25% in alfapump® and 65% in transjugular intrahepatic portosystemic shunt. Hepatic encephalopathy predicted transplant-free survival in patients with alfapump® (hazard ratio 2.00, 95% confidence interval 0.99–4.02, $p = 0.05$). In a sensitivity analysis comparing patients with similar liver function, the rate of hepatorenal syndrome and prerenal impairment was higher in patients with alfapump® and these patients were hospitalised more frequently, whereas the rate of hepatic encephalopathy was similar in both treatment groups.

Conclusions: Both transjugular intrahepatic portosystemic shunt and alfapump® were effective treatments for refractory ascites in cirrhosis. Patients treated with transjugular intrahepatic portosystemic shunt had a better one-year transplant-free survival but had less negative prognostic factors at baseline. Selecting patients without hepatic encephalopathy prior to implantation of an alfapump® might improve transplant-free survival.

Keywords

Transjugular intrahepatic portosystemic shunt, automated low-flow ascites pump, liver cirrhosis, ascites

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Key summary

Established knowledge on this subject

- Alfapump® is effective in reducing need for paracentesis, but is associated with a high infection rate and renal dysfunction.
- Transjugular intrahepatic portosystemic shunt (TIPS) is a disease-modifying treatment, as it improves renal function. The influence on survival is controversially discussed.
- Currently, there are no studies directly comparing TIPS patients with alfapump® patients.

Significant findings of this study

- Patients treated with TIPS had better one- and two-year survival rates compared to alfapump®, but had less negative prognostic factors at baseline.
- The occurrence of hepatic encephalopathy was similar in both treatment groups.
- Hepatic encephalopathy predicted transplant-free survival in patients with alfapump®.
- Patients with alfapump® with new catheters developed less frequent complications due to alfapump®, especially catheter obstruction.

Introduction

Refractory ascites (RA) is a common complication in patients with advanced chronic liver disease. Prognosis after the onset of RA is poor, with one-year-mortality rate of approximately 50%.[1,2]

Treatment options consist in large volume paracentesis (LVP) with albumin infusion,[3] transjugular intrahepatic portosystemic shunt (TIPS),[4–7] automated low-flow ascites pump (alfapump®, Sequana Medical, Belgium),[8–12] indwelling peritoneal catheters[13,14] and liver transplantation (OLT), each with their inherent limitations. The efficacy of TIPS for RA has been demonstrated in several studies.[5–7,15] As compared to LVP, TIPS has been shown to reduce the risk of developing hepatorenal syndrome (HRS),[4] to increase the estimated glomerular filtration rate (eGFR)[16] and to improve survival when using polytetrafluoroethylene (PTFE)-covered stents.[4] However, patients with uncovered TIPS experienced hepatic encephalopathy (HE) more frequently than those treated with LVP and albumin.[4–7,15] In addition, TIPS is associated with an increased risk of liver failure and death in patients with high MELD score, and therefore it might not be a safe option in a relevant proportion of patients with RA.[17,18]

Recently, it has been reported that alfapump® may provide a good option as a bridge to OLT in RA, and improve quality of life due to a reduction in LVPs, although without survival benefit.[10]

The aim of our study was to assess the characteristics and outcomes of patients with cirrhosis receiving alfapump® or TIPS for RA at our centre, and to evaluate the efficacy and complications of these interventions.

Methods

Study design and patient population

The study was performed retrospectively at our tertiary, academic centre. TIPS is routinely performed since January 2015 at our centre, while alfapump® was first introduced in 2012. All patients diagnosed with RA (as defined by the current guidelines)[3] were considered for either TIPS, alfapump® or repetitive LVP. The allocation of treatment was determined by the treating hepatologist. The indication was determined according to the current guidelines at that time,[3] contraindications, current liver function and the patient's preferences. Patients who were treated with either TIPS or alfapump® at our centre and complied with the use of their data for research, were registered in a database. Written, informed consent was obtained from all registered patients. All registered patients with cirrhosis electively treated with TIPS or alfapump® for RA until August 2018 have been included in this study. The Canton of Bern Research Ethics Committee approved this study (KEK 2018-00487, approval date 27.03.2018). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

All patients were routinely checked up after the intervention every 3 months and clinically relevant data was stored in an electronic patient record. For the acquisition of the data in this study, patient records were retrospectively reviewed. Aside from baseline characteristics, variables were collected for every 6 months up to a maximum follow up of 24 months. Patients were followed up until February 2019, death, OLT, loss to follow-up or up to the maximum follow-up period. The results of this study were reported using

the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.[19]

Variables

Baseline characteristics included demographics, aetiology, laboratory values, anthropometric data, vital signs, comorbidities and cirrhosis-related complications prior to the intervention. Renal function was assessed as eGFR calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

Intervention-related complications occurring within 7 days of intervention (TIPS or alfapump®) were collected, including liver infarction, heart failure, wound dehiscence, ascites leak, infections and prerenal kidney impairment.

Laboratory values, anthropometric data, vital signs and clinically relevant events (number of paracentesis and litres of ascites removed, reinterventions, hospitalizations, infections, cirrhosis-related complications, liver unrelated events, death or OLT) were registered at the predefined timepoints. Reintervention was defined as a need for action due to dysfunction of the treatment (catheter obstruction, pump defect, TIPS dysfunction, etc.) or to adverse events such as overt hepatic encephalopathy (West Haven $\geq$2) and infections. All admissions to hospital were counted as hospitalization, thus including reintervention, liver-related illnesses as well as non-liver-related causes. HE, HRS, spontaneous bacterial peritonitis (SBP), variceal bleeding, portal vein thrombosis, hepatocellular carcinoma (HCC) and hydrothorax were recorded as cirrhosis-related complications. Liver-unrelated events consisted in pre-renal kidney impairment, ileus, heart failure, acute liver infarction, haematoma, ascites leakage and wound dehiscence.

Acute kidney injury (AKI) was defined by an increase in serum creatinine ($\geq$26.5 µmol/l) or a percentage increase of 50% as defined by current guidelines.[3] Whenever a prerenal impairment could not be treated with volume replacement therapy and albumin alone and it was necessary to treat the patient with terlipressin, the cause of kidney dysfunction was considered to be HRS.

TIPS and alfapump® implantation

LVP was performed with albumin replacement according to current guidelines prior to either TIPS or alfapump® interventions.[3]

The TIPS procedure was performed according to the international standards described in detail elsewhere.[20] All patients received ePTFE-covered stents (Viatorr, Gore); the TIPS procedure was performed under general anaesthesia and oro-tracheal intubation. After TIPS insertion, the stent was dilated to 8 mm. If no sufficient reduction in the portal pressure gradient (PPG) was noted (namely if the PPG remained >12 mm Hg), the stent was further dilated to 10 mm.

As for the implantation of alfapump®, detailed information can be found elsewhere;[11] in brief, peritoneal catheters were inserted in the umbilical region and pigtail catheters were placed in the bladder. The pump was placed in a subcutaneous pocket and connected to the catheters.

Statistics

Patients lost to follow-up were censored alive at the last day of presentation and patients with OLT were censored dead at the time of OLT. There was a total of five patients treated both with alfapump® and TIPS. Patients were analysed in the group to which they were originally assigned (intention-to-treat analysis). Whenever a variable was not available in all patients, the number of patients indicating the variable was provided.

Categorical variables were compared by Chi-square test (χ^2 test). Continuous variables were reported as median and interquartile range or as mean and standard deviation depending on the distribution of data and compared by unpaired *t*-test and Mann-Whitney-U test. Comparison of transplant-free survival between both groups was done using Kaplan-Meier curves and Log-rank test. Univariate Cox regression was used to determine predictive factors for survival and expressed as hazard ratio (HR) with 95% confidence interval (CI).

Three subgroup analysis were performed. The first two compared patients with a similar range of MELD-Na score (MELD-Na below 15; first subanalysis) and Child-Pugh score (below 10 points; second subanalysis). The third subgroup analysis was done from 2015, when the improved alfapump® catheters were implemented in our center.

All statistical analyses were performed using IBM SPSS Version 25.0 (Chicago, Illinois, USA) software. For all analyses, a *p*-value of <0.05 was considered to be statistically significant.

Results

Study population

Sixty patients were registered in the database between 2012–2018. One patient treated with alfapump® had to be excluded, as no follow-up data were available. Fifty-nine patients were analysed, 19 with TIPS and

40 with alfapump®. Patient's characteristics at baseline are displayed in Table 1. Patients with alfapump® had a worse liver function as compared to TIPS as well as a higher proportion of HE ($p = 0.02$) and SBP ($p = 0.06$). Patients with TIPS showed a higher rate of hydrothorax ($p = 0.02$).

Outcome in patients with TIPS

TIPS was effective in reducing the need for paracentesis, as 11 patients (58%) did not require any paracentesis at all in the first six months after intervention. Only three (16%) patients required more than two paracenteses. Overall, two TIPS had to be closed due to intractable HE, and three TIPS patients had an alfapump® implanted. The reason for the implantation of an alfapump® was HE in one patient and TIPS dysfunction in two patients. In the first six months, three patients required a reintervention. Fifty-six per cent of patients were hospitalised at least once in the first 6 months for a median hospitalization time of 1 day (0–9). Need for hospitalization, LVP and reintervention at 1 and 2 years may be seen in the Supplementary Material Tables 1 and 2.

Laboratory values are displayed in Supplementary Material Table 3. While bilirubin rose significantly, renal function improved steadily in the TIPS group. In the first 6 months, 5.3% experienced HRS and 21% prerenal kidney injury. Fifty-eight percent of TIPS patients developed at least one episode of HE and 26% severe infection. Ileus was observed in 11.1%. All complications are listed in Supplementary Material Table 4.

Five patients in the TIPS group died (26%) during follow-up, all of them in the first 6 months, and two

Table 1. Overall analysis – baseline characteristics of the study population.

Characteristic	TIPS	Alfapump®	*p*-Value
	($n = 19$)	($n = 40$)	
Age, years	60.6 ± 8.8	59.3 ± 9.3	0.63
Gender (male), *n* (%)	12 (63.2)	29 (72.5)	0.47
Main aetiology, *n* (%)			
Alcohol	16 (84.2)	25 (62.5)	0.09
NASH	1 (5.3)	4 (10)	0.54
Viral	–	7 (17.5)	0.05
Other	2 (10.5)	4 (10)	0.95
Active drinking, *n* (%)	1 (5.6)	3 (7.7)	0.77
Complications prior to intervention, *n* (%)			
Varices	15 (88.2)	32 (84.2)	0.70
Variceal bleeding	6 (31.6)	13 (32.5)	0.94
Portal vein thrombosis	5 (27.8)	8 (20)	0.51
Hepatocellular carcinoma	1 (5.6)	7 (17.5)	0.22
Hepatorenal syndrome	4 (22.2)	6 (15)	0.50
Spontaneous bacterial peritonitis	2 (11.1)	14 (35)	0.06
Hepatic encephalopathy	3 (15.8)	19 (47.5)	**0.02**
Hydrothorax	4 (21.1)	1 (2.5)	**0.02**
Labour parameters			
Sodium, mmol/l	137.3 ± 3.5	135.5 ± 4.5	0.09
Potassium, mmol/l	4.2 ± 0.64	4.3 ± 0.53	0.35
GFR, ml/min	55.8 ± 20.4	57.6 ± 23.2	0.78
Albumin, g/l	28.6 ± 4.9[a]	27.9 ± 5[b]	0.64
Bilirubin, µmol/l	14.2 ± 9.4	39 ± 28	**0.00**
AST, U/l	37.2 ± 11.1	56.4 ± 37.3[c]	**0.02**
ALT, U/l	22.8 ± 9.6	30.7 ± 18.3[c]	0.07
White blood cell count, G/l	6.6 ± 2.35[d]	6.6 ± 2.72[e]	0.98
Haemoglobin, g/l	97.8 ± 10.8[d]	92.4 ± 17.1[f]	0.27
Platelets, G/l	162.3 ± 67.1[d]	127.5 ± 77.6[f]	0.18
INR	1.19 ± 0.19	1.28 ± 0.22	0.09
Scores			
MELD-Na	12.6 ± 5.1	15.9 ± 5.6	**0.04**
Child Pugh	8.33 ± 0.6	9.05 ± 1.6	0.07

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GFR: glomerular filtration rate; INR: international normalised ratio; NASH: non-alcoholic steato-hepatitis; TIPS: transjugular intrahepatic portosystemic shunt.
[a]Available in $n = 14$; [b]available in $n = 29$; [c]available in $n = 28$; [d]available in $n = 12$; [e]available in $n = 24$; [f]available in $n = 2$.

underwent liver transplantation. Median follow-up period in patients with TIPS was 16.7 months (3–24). Seven patients finished the 24-month period without OLT and two patients were lost to follow-up. Three patients were alive at the end of the study period in February 2019 but did not have the maximum follow-up of 24 months. Most TIPS patients died of non-cirrhosis-related causes (see Supplementary Material Table 5). Actuarial transplant-free survival at 6 and 12 months was 72% and 65% respectively (Figure 1).

Outcome in patients with alfapump®

Alfapump® reduced the need for paracentesis markedly: 17 patients (43%) no longer needed paracentesis in the first 6 months and only six patients (15%) needed more than two paracenteses. Eighty-five per cent of alfapump® patients were admitted to hospital post-alfapump® implantation at least once for a median hospitalization time of 19 days (4–33).

The alfapump® had to be surgically revised at least once in 30% of patients and completely removed in 30%. In nine alfapump® patients, an obstruction of the catheter occurred and 11 suffered from infection. Two alfapump® patients received TIPS during the follow-up, one due to portal vein thrombosis and HRS, the other due to a dysfunction of alfapump®. In the first six months, 43% underwent a reintervention whereof 18% due to catheter obstruction and 18% due to infections. Since the introduction of the new improved catheters there was a lower need of reintervention (26% vs 57% with old catheters, $p = 0.049$), mainly due to a decreased rate of catheter obstruction (5% vs 18%, $p = 0.05$).

Within the alfapump® group, eGFR decreased on average 13±22 ml/min in the first 6 months ($p = 0.08$) (Supplementary Material Figure 1 and Supplementary Material Table 6). HRS occurred in about 43% of alfapump® patients and prerenal kidney impairment in 58% respectively. Further complications consisted of infections and HE (55% and 58% respectively in the first 6 months).

Twenty-four alfapump® patients (60%) died in the 24 months of follow-up and 11 (28%) received an OLT. Alfapump® patients were followed up for a median of 4.1 months (1.4–11). After 24 months, three patients were alive and had not undergone OLT. Two patients were lost to follow-up. Transplant-free survival was 36% and 25% at 6 and 12 months respectively (Figure 2). Comparing alfapump® patients according to the presence or absence of HE prior to the intervention showed better survival of alfapump® patients

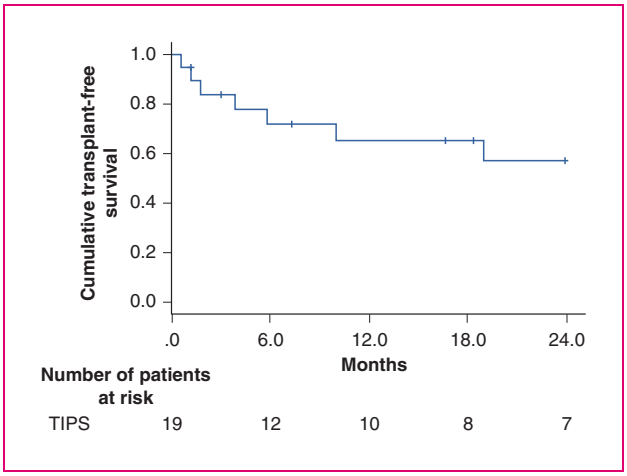

Figure 1. Transplant-free survival of patients with TIPS.

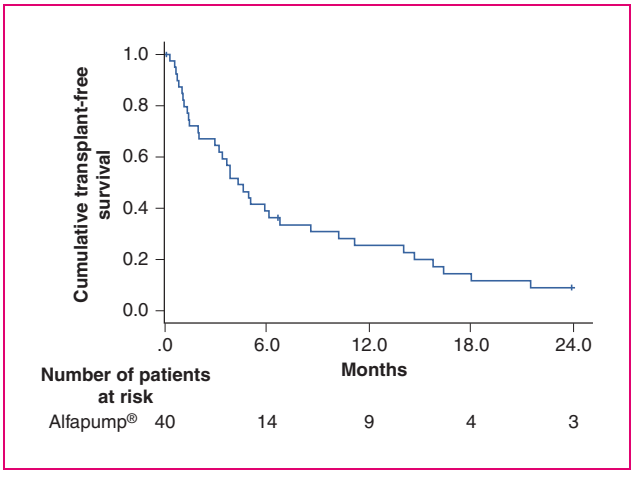

Figure 2. Transplant-free survival of patients with alfapump®.

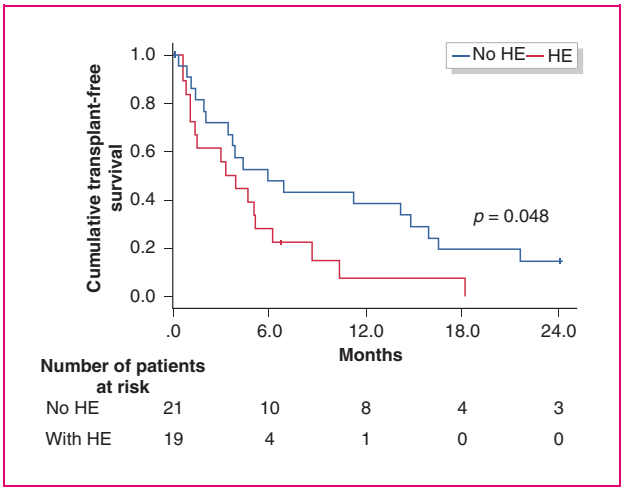

Figure 3. Transplant-free survival of patients with alfapump® with versus without prior history of hepatic encephalopathy (HE).

without HE (Figure 3). In univariate analysis, prior history of HE was a significant predictor of mortality or OLT after the intervention (HR 2.00, 95% CI 0.99–4.02, $p = 0.05$), see also Table 2. Comparing transplant-free survival of alfapump® patients with new versus old catheters, Kaplan-Meier curves seem to diverge, but the difference was not statistically significant at any timepoint (see Supplementary Material Figure 2).

Sensitivity analysis: comparison of TIPS and alfapump® in patients with similar liver impairment

TIPS patients were compared to either alfapump® patients with a MELD-Na score below 15 ($n = 20$) or, in a second analysis, with a Child-Pugh score below 10 ($n = 26$). Patient characteristics are displayed in Supplementary Material Tables 7 and 8. However, the subgroups still differed in some relevant aspects: TIPS patients had a worse kidney function at baseline whereas alfapump® patients more often had a variceal bleeding, an SBP or a HE prior to the intervention.

Table 2. Univariate regression analysis in the alfapump® population.

Factors influencing transplant-free survival	Hazard ratio (95% CI)	*p*-Value
New catheters	0.72 (0.36–1.43)	0.35
HE prior to intervention	2.00 (0.99–4.02)	**0.05**
SBP prior to intervention	1.50 (0.74–3.03)	0.26
MELD-Na	1.03 (0.96–1.10)	0.37
Child Pugh	1.05 (0.85–1.28)	0.67

CI: confidence interval; HE: hepatic encephalopathy; SBP: spontaneous bacterial peritonitis.

Comparison of TIPS patients with the liver-function-adjusted alfapump® patients during the first six months is displayed in Table 3. In both sensitivity analyses, hospitalizations and reinterventions were less frequent in patients with TIPS. HRS and prerenal impairment were significantly more frequent in patients with alfapump®, whereas HE occurred equally frequent in both treatment groups. There was a trend towards a higher infection rate in patients with alfapump®.

Cumulative transplant-free survival after 12 months was 65% in the TIPS group versus 23% in alfapump® patients with MELD-Na score below 15 ($p = 0.02$, Supplementary Material Figure 3) and 26% in alfapump® patients with Child-Pugh score below 10 ($p = 0.01$, Supplementary Material Figure 4).

Discussion

Currently, there is no randomized controlled trial (RCT) directly comparing alfapump® patients with TIPS. The aim of this study was to analyse the characteristics and outcome of patients with cirrhosis and refractory ascites treated with TIPS or alfapump® at our centre.

As the use of TIPS is limited by circumstances potentially affecting the outcome, we expected differences between the two study populations. Indeed, alfapump® patients had worse liver function at baseline as indicated by higher MELD-Na and Child-Pugh scores, and a higher rate of HE prior to the intervention.

While both treatments showed similar efficacy rates, they differed in terms of complications. TIPS patients experienced AKI less frequently than alfapump® patients, both due to pre-renal kidney failure

Table 3. Sensitivity analysis – transjugular intrahepatic portosystemic shunt (TIPS) versus alfapump® subgroups with better liver function.

	TIPS	Comparison to alfapump®			
	Overall population ($n = 19$)	Alfapump® with Child-Pugh score <10 ($n = 26$)		Alfapump® with MELD-Na score <15 ($n = 20$)	
	Frequency, *n* (%)	Frequency, *n* (%)	*p*-Value	Frequency, *n* (%)	*p*-Value
Need for LVP	8 (42.1)	12 (48)	0.70	11 (57.9)	0.33
Hospitalizations	10 (55.6)	21 (80.8)	0.07	17 (85)	**0.046**
Reintervention	3 (15.8)	12 (46.2)	**0.03**	9 (45)	**0.048**
HE	11 (57.9)	14 (53.8)	0.79	10 (50)	0.62
HRS	1 (5.3)	10 (38.5)	**0.01**	8 (40)	**0.01**
Prerenal impairment	4 (22.2)	16 (61.5)	**0.007**	13 (65)	**0.006**
Infections	5 (26.3)	13 (50)	0.11	11 (55)	0.07

HE: hepatic encephalopathy; HRS: hepatorenal syndrome; LVP: large volume paracentesis.

($p = 0.01$) and HRS ($p = 0.01$), which was considered whenever a pre-renal kidney impairment could not be treated with volume replacement therapy and albumin alone, and required terlipressin. Although Bureau et al. described AKI occurring mainly during the first seven days,[10] only two out of 23 patients experienced AKI in the immediate post-interventional period in our study. Our findings are consistent with another study[9] indicating that AKI also occurs over a longer-term period. Indeed, the renal function of alfapump® patients, evaluated as CKD-EPI-eGFR, decreased about 22 ml/min in the first six months in our study. This corroborates a meta-analysis indicating a rise in creatinine of 23 μmol/l in patients with alfapump®.[21] We observed a trend towards a higher rate of bacterial infection in alfapump® vs TIPS (55% versus 26%, $p = 0.07$), which might have contributed to the higher AKI and HRS rate. As our patients only received albumin in cases of LVP with more than 5 l extracted, the loss of proteins through the urinary output might also have led to the high rate of HRS and pre-renal impairment as well as the worsening eGFR, which had already been suggested by Solà et al.[9] In contrast to alfapump® patients, the eGFR increased in patients with TIPS. Our findings are consistent with other studies, as improved kidney function[16,22] and lower rates of HRS[4] after TIPS have been repeatedly reported. Contrary to AKI, we observed a higher rate of ileus in patients with TIPS, especially in patients with umbilical hernias.

HE was frequent in both groups, more frequent than reported elsewhere for TIPS[23] as well for alfapump®,[21] without differences among treatment. As HE is a clinical diagnosis, the assessment of HE often varies between different studies. However, most of the episodes were West Haven grade 2 and could be treated easily. The lack of difference could be potentially due to several factors, including the use of covered TIPS stents[22–24] associated with lower rates of HE,[2,15,25–28] and by the high rate of infection and AKI – common triggers of HE – in the alfapump® patients. Anyhow, our alfapump® patients were likely more prone to HE, due to their high frequency of HE pre-alfapump® and worse liver function at baseline. Importantly, we found that HE prior to intervention might be associated with decreased survival of alfapump® patients. This data suggests that patients who had experienced HE have worse outcomes, and this should be considered as a subset of patients with RA less likely to benefit from alfapump®.

As for procedure-related factors that could impact the prognosis, we observed a lower rate of early catheter obstruction requiring reintervention with new alfapump® catheters. Although not statistically significant, the Kaplan-Meier curves of alfapump® patients with new versus old catheters seem to diverge. However, this more likely reflects an improved management of patients with an alfapump® than a catheter-related survival benefit.

In terms of survival, transplant-free survival at 1 year was higher in TIPS patients than in alfapump® patients with low MELD-Na score or low Child-Pugh scores. Sixty per cent of alfapump® patients died within 24 months and this underlines the poor prognosis of patients with RA even after achieving a reduced need of LVP. Although quality of life was not assessed directly, the frequent hospitalizations in patients with alfapump® might pose a problem in this respect.

This study has limitations related to the low number of cases, to the retrospective study design, to the different degree of liver failure of patients treated with TIPS versus those with alfapump® and the indication bias. In addition, the strength of the evidence provided by such a study is much less than that afforded by a direct comparison of the two treatments through a trial. Therefore, these results should be interpreted with caution.

Despite these limitations, our study confirmed that in the setting of RA both methods are effective in reducing the need of LVP. Moreover, TIPS improves renal function, likely because it corrects key pathophysiological factors in HRS,[16,22] while alfapump® is associated with worsening of renal function. TIPS is associated with good one-year survival[4,15] and with rates of HE that although high, were not greater in the alfapump® group. This, however, should be considered in the light of the more advanced degree of liver failure in the alfapump® treated patients. The fact that HE predicted mortality in patients undergoing alfapump® treatment lead us to speculate that selecting for alfapump® treatment only patients without previous HE would perhaps impact positively on survival in patients with RA. This point could not be assessed in patients treated with TIPS, since most TIPS patients had no previous HE.

Our data suggest that patients with RA and relatively preserved liver function and without negative prognostic indicators for TIPS will probably benefit from TIPS, whereas alfapump® may be the only alternative to large volume paracentesis in those with advanced liver failure, contraindications or negative prognostic factors for TIPS.

Declaration of conflicting interests

V Will, SG Rodrigues and A Berzigotti have no conflict of interest to declare. G Stirnimann has received a speaker's fee and consultancy fee from Sequana Medicals. A De Gottardi has received speaker's fees from Sequana Medicals. J Bosch has received a speaker's fee from Gore.

Ethics approval

The Canton of Bern Research Ethics Committee approved this study (KEK 2018-00487). By their approval, they ensured that the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

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Informed consent

Written, informed consent was obtained from all patients participating in the study.

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Supplemental material

Supplemental material for this article is available online.

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