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Final Safety and Efficacy Results from a 106 Real-World Patients Registry with an Ascites-Mobilizing Pump

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List of Abbreviations

RA	refractory ascites
TIPSS	transjugular intrahepatic portosystemic stent shunt
HE	hepatic encephalopathy
LVP	large volume paracentesis
SoC	standard of care
QoL	quality of life
sCr	serum creatinine
SBP	spontaneous bacterial peritonitis
UTI	urinary tract infection
(S)AE	(serious) adverse event
PC	peritoneal catheter
HRS(-2)	hepatorenal syndrome (type 2)
SD	standard deviation
IQR	interquartile range
OLT	orthotopic liver transplantation
MELD	Model for end-stage liver disease
UNOS	United Network for Organ Sharing
DD	device deficiency

AKI	acute kidney injury
CI	confidence interval
MDR	multi-drug resistant

Conflict of Interest

GS has received support for the present manuscript, travel and meeting attendance, served as a speaker and participated in Advisory Boards for Sequana Medical. TB has received grants or contracts with Abbvie, BMS, Gilead, Humedics, Intercept, MSD/Merck, Merz, Novartis and Sequana Medical,received consulting fees from Abbvie, Alexion, Bayer, Eisai, Gilead, GSK, Intercept, Ipsen, Janssen, MSD/Merck, Novartis, Roche, Sequana Medical and Shionogi and served as a speaker for MedUpdate GmbH and the abovementioned except GSK, Roche and Shionogi, He has received support for travel and meeting attendance from Abbvie, Gilead, Intercept and Janssen. LS has received lecture honoraria from and participated in Advisory Boards of Sequana Medical. SZ has served as a speaker and a consultant to Abbvie, Gilead, Intercept, Janssen, Merck/MSD. SMP has served as a consultant to Sequana Medical, AbbVie, Gilead, Cambwick, and Intercept. FS has served as a speaker to Sequana Medical. CE has received research grants from Sequana Medical, the German Research Foundation (DFG) and the Berlin Institute of Health (BIH). AG has received consulting fees from Abbvie, Alexion, Bayer, BMS, CSL Behring, Eisai, Gilead, Intercept, Ipsen, Merz MSD, Novartis, Pfizer, Roche, Sanofi-Aventis and Sequana Medical, received support for meeting attendance and travel from Abbvie, Gilead, Intercept and Merz and participated on a Data Safety Monitoring Board or Advisory Board for Novartis. CT is a biostatistician contracted by Sequana Medical. JC is an employee of and holds shares and stock options of Sequana Medical. ADG has received a research grant from Sequana Medical. FL, JB, VV and VB have nothing to disclose.

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Ethics and patient consent

The protocol of this clinical study was approved by the respective ethics committees or institutional review boards as required by local law and regulations at all participating sites. All subjects or their legal guardian(s) had signed informed consent and the study was conducted in accordance with the Declaration of Helsinki and any other applicable national and international guidelines.

Data sharing

Data are not public but available from Jeroen Capel (Jeroen.Capel@sequanamedical.com) upon reasonable request.

ClinicalTrials.gov Identifier: NCT01532427

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Abstract

Background & Aims: Patients with cirrhotic refractory ascites ineligible for transjugular intrahepatic shunt (TIPSS) have limited treatment options apart from repeated large volume paracentesis. The alfapump® is an implantable device mobilizing ascites from the peritoneal cavity to the bladder, from where it can be excreted. The aim of this observational cohort study was to prospectively investigate safety and efficacy of the device in a real-world cohort with cirrhotic refractory ascites and contraindications for TIPSS.

Methods: A total of 106 patients received an implant at twelve European centers and were followed up for up to 24 months. Complications, device deficiencies, frequency of paracentesis, clinical status and survival were recorded prospectively.

Results: Approximately half of the patients died on-study, about a quarter were withdrawn due to serious adverse events leading to explant, a sixth were withdrawn due to liver transplant or recovery, and nine completed follow-up. The most frequent causes of on-study death and complication-related explant were progression of liver disease and infection. The device reduced the requirement for large volume paracentesis significantly, with more than half of patients not having required any post-implant. Survival benefits were not observed. Device-related reinterventions were predominantly caused by device deficiencies. A post-hoc comparison of the first 50 vs. the last 50 patients enrolled revealed a decreased reintervention rate in the latter, mainly related to peritoneal catheter modifications.

Conclusions: The device reduced paracentesis frequency in a real-world setting. Technical complications were successfully decreased by optimization of management and device modification (NCT01532427).

Keywords: ascites, alfapump; cirrhosis; large volume paracentesis; TIPSS

Lay summary

This study followed 106 patients with advanced liver disease as displayed by medically untreatable ascites for up to two years. Instead of standard treatment requiring repeated drainage of abdominal fluid via a needle, patients received an alfapump®, a device that moves the fluid to the bladder, from where it is cleared by urination. Technical and medical complications and overall outcome were analysed and are reported here.

Introduction

Ascites is the accumulation of fluid in the peritoneal cavity secondary to portal hypertension and compensatory circulatory reactions in patients with advanced liver cirrhosis. Five to ten per cent of patients with ascites develop refractory ascites (RA) per year (1,2), i.e., ascites which cannot be controlled any longer by standard treatment strategies such as dietary limitation of sodium uptake combined with high-dose diuretics. This is either because the highest-possible diuretic dose failed to prevent ascites re-accumulation or the patient developed adverse events contraindicating further use. Prognosis of RA is poor, with approximately a third of patients dying within 6 months (3) unless salvaged by liver transplant, which is currently the only curative treatment. Standard of care (SoC) for RA is repeated large volume paracentesis (LVP), defined by mobilization of >5000 ml of volume in one paracentesis, and albumin substitution to prevent circulatory dysfunction (4). Repeated LVP is relatively safe but represents a considerable burden in terms of healthcare resources and compromises quality of life of the patient due to discomfort and frequent hospitalization.

Alternatively, RA may be treated by insertion of a Transjugular Intrahepatic Portosystemic shunt (TIPSS), which releases some of the pressure in the portal venous system (3). However, TIPSS is only suitable for a subset of patients free from comorbidities such as congestive heart failure, pulmonary hypertension or cirrhosis-related complications, e.g., advanced stage and episodes of recurrent overt hepatic encephalopathy (HE) without an identifiable precipitating factor (3-5).

The alfapump® system (Sequana Medical N.V., Ghent, Belgium) is a subcutaneously implanted medical device consisting of a pump unit and two silicone catheters. It is designed to transport ascitic fluid from the peritoneal cavity into the bladder. Ascites

is excreted with urine, thereby reducing the requirement for paracentesis. Pump activity can be modified by the treating physician according to individual clinical needs (6). The device received European market approval in 2011 based on clinical data obtained in the PIONEER study (7) which included 40 patients followed up for mean 124±57 days. This current study was initiated in 2012 to prospectively collect clinical data related to safety and performance of the device in a cohort of patients ineligible for TIPSS in a real-world setting with a follow-up of up to 24 months or until withdrawal or death. Studies published in the meantime, including a meta-analysis and an interim analysis of this current registry comprising the first 56 patients, confirmed a significant reduction of LVP and paracentesis compared to the pre-implant period or SoC (8-11) and reported improvement of quality of life (QoL) (8,9,12) and nutritional status (8,9). However, despite modifications of the device and manufacturer's instructions, high rates of adverse events and technical issues requiring reintervention were observed (11). Frequent safety-related issues include deterioration of kidney function (acute kidney injury, increase in serum creatinine (sCr) (8,10,13)) and infections (pump pocket infections, spontaneous bacterial peritonitis [SBP], urinary tract infections [UTI]). Infections occurred at rates of 0.5 per patient in 12 months to 0.93 per patient in 6 months (9,14). The most important cause of reinterventions and explants, the latter required in approximately 20-30%, were infections and peritoneal catheter (PC) issues (10,11). Survival benefits compared to SoC were not observed (8). The primary objective of this study was to evaluate safety by prospectively recording device-related incidents in a real-world setting. The secondary objective was to evaluate clinical performance (post-implant paracentesis requirement, patients' clinical status by evolution of liver scores and relevant laboratory parameters). Here, final results from the full cohort of 106

patients included in this registry observed during six years are presented and discussed in relation to currently available clinical data.

Methods

Patients

Twelve European referral centers participated in this prospective observational cohort study. Patients with RA secondary to cirrhosis presenting contraindications to TIPSS (Table S1) received a treatment with the alfapump®. RA was defined as diuretic-resistant, diuretic-intractable or as early recurrent after paracentesis. Apart from RA, inclusion criteria were >18 years and written informed consent. Inability to operate the charging system and pregnancy were the only exclusion criteria.

Study treatment

Patients on treatment with the device were followed up to 24 months during 2012–2018 and information about paracentesis, deaths, incidents involving the device, pump-related surgical procedures and liver transplants were recorded prospectively. Blood chemistry, hematology data and AE information were collected as part of standard clinical practice.

Pre-implant management of candidates for device implantation was optimized with respect to nutritional support and screening/treatment of esophageal varices according to SoC. Paracentesis was performed one day pre-implant to void the abdominal cavity and to exclude SBP. Albumin was substituted according to current guidelines and local practice.

The implantation procedure is described in detail elsewhere (6,15). After implantation, administration of long-term antibiotic prophylaxis (e.g., norfloxacin, 400 mg/day or ciprofloxacin 750 mg/day) and discontinuation of diuretics was recommended but not mandatory. Patients were followed up weekly for the first month post-implant and per local clinical practice thereafter. Albumin was substituted as recommended according to current guidelines (e.g., for the prevention of post-

paracentesis circular dysfunction, hepatorenal syndrome [HRS] or in the context of SBP) and local practice at discretion of the investigator (4,10).

Ethics

This study was approved by the appropriate independent Ethical Committees and Institutional Review Boards of the participating centers and all patients gave written informed consent. This study complied with the declaration of Helsinki for human research ethics. It is registered on ClinicalTrials.gov (NCT01532427).

Definitions

Prospectively recorded incidents included both technical events and AE. Their causality relationship to the device were defined based on MEDDEV 2.12-1, rev 7 as events involving the device that at least potentially led to death or serious deterioration of health, i.e., requiring medical or surgical intervention and/or leading to (prolonged) hospitalization (see Table S2 for detailed definitions). AEs related to incidents were considered serious by default.

Reintervention was defined as surgical replacement or correction of at least one system component. Pump exchange comprised the exchange of the device with a new pump system. Explant was defined as complete surgical removal due to serious adverse event (SAE), transplantation or recovery.

Statistics

Data from hospital records and the manufacturer's technical database were analyzed. The follow-up schedule was at the discretion of the investigator and laboratory data that were closest to the indicated time points (baseline, 1, 3, 6, 12, 18 and 24 months) were analyzed. Results are reported as mean (± standard deviation [SD]) or as median (interquartile range [IQR]) unless stated otherwise. Data up to the last visit were used for patients lost to follow-up. No imputations for

missing data or any methods to address bias were applied. No formal sample size calculation was performed. The registry was closed once a predefined minimum of 100 patients with cirrhotic RA had been recruited. For the post-hoc analysis of the first vs. last 50 patients enrolled, parameters of interest were compared using Fisher's exact test for categorical parameters and two-sided independent sample t-test for continuous parameters (equal variance not assumed).

For survival analyses, Kaplan-Meier estimates were used. "Device survival" was defined as elapsed time from pump implantation to the time of explant for pump-related reasons. Pump replacement due to malfunction was counted as an event having occurred at time of replacement. Explant due to an SAE related to device deficiency was counted as an event having occurred at time of explant. Explants due to an SAE unrelated to the device were censored at time of explant. Explants due to orthotopic liver transplantation (OLT) or recovery (no further requirement of the pump) were not considered as events. Survival in the first vs. last 50 patients was compared using the Mantel-Cox test.

"Peritoneal catheter survival" was defined as time elapsed from catheter implantation to time of reintervention. Catheter revision or exchange and subject discontinuation from the study were counted as events that occurred at the time of reintervention, withdrawal or death as appropriate. Standard and modified catheter survival was compared using the Breslow (generalized Wilcoxon) test.

Statistical analyses were performed using SPSS Statistics v23.0 (IBM Corp, Armonk, NY). Graphs were generated using SPSS and Prism v9.1 (GraphPad Software, San Diego, CA).

Results

Patient disposition

Patients with refractory ascites secondary to cirrhosis or malignancy (n =110) from European countries (Switzerland: 52; Germany: 49; United Kingdom: 7; Spain: 2) were screened for this study. One patient failed screening because the RA was caused neither by cirrhosis nor malignancy. A total of 109 patients were enrolled and received an alfapump® implant. As just two patients with cancer as the sole cause of RA had been recruited and one cirrhotic patient had no data recorded post-baseline, data from 106 patients with liver cirrhosis were analyzed. Only 9 patients completed the study at 24 months. Premature discontinuations (91.5% of patients) were mainly due to SAEs and death, but also due to OLT and resolution of RA (See Figure S1 and Table S3).

Baseline Characteristics

Mean age at baseline was 61.4±8.7 years. Eighty patients were men and 26 were women (Table 1). Median Model for end-stage liver disease (MELD) (United Network for Organ Sharing [UNOS])- and Child Pugh scores were 12.5 (10.0–16.0) and 9.0 (8.0–10.0), respectively. Approximately three quarters of patients were Child-Pugh class B, whereas the remaining patients were Child-Pugh class C. The patients had suffered from RA for median 9.0 (6.0–15.00) months prior to device implantation and had required a median 2.30 (1.40–4.30) paracenteses (all volumes) per month over the previous three months.

Implantation procedure

All procedures except one were performed under general anesthesia. Median duration of surgery was 60.0 (50.0-70.0) minutes (N = 102) and median duration of hospitalization was 8.0 (4.0-13.0) days (N = 103). Albumin was administered as

required (Table S4). Perioperative antibiotic prophylaxis was given to 79 (74.5%) of patients. In total, 88 patients (83.0%) received long-term antibiotic prophylaxis (for details on regimens, see Table S5). Eighteen patients had no prophylactic regimen or unclear status.

Incidents

Overall, 163 incidents (adverse events in which contribution of the device could not be excluded) were recorded (1.5/patient). Fifteen patients did not suffer any incident. A total of 55 incidents (33.7%) were fatal. Main causes of on-study and post-withdrawal deaths were progression of liver disease and incidents involving infection (Table 2). Forty-eight incidents (29.4%) led to a medical or surgical intervention only and 52 (31.9%) led to hospitalization. The most frequently suspected causes of incidents were device deficiencies (DD; 61 events [37.4%]) and underlying disease (48 events [29.4%]; Table S6).

Infections

Eight infections occurred in 8/20 patients without documented antibiotic prophylaxis at the time of the incident. Thirty-three infections were reported in 24/88 patients on a prophylactic regimen, corresponding to 40.0% and 37.5% per patient, respectively. Notably, one of the latter patients was positive for human immunodeficiency virus and another was incompliant.

Renal safety

Eight events of acute kidney injury (AKI according to KDIGO criteria (16) increase in sCr by ≥26.5 µmol/L (0.3 mg/dL) within 48 h or by ≥50% from baseline within seven days) occurred in seven patients (Table S7). None occurred within seven days after implant. Two led to death and were associated with infection. One AKI event was concomitant with electrolyte imbalance, which occurred in association with

dehydration and could be managed by pump volume reduction. There were ten further cases of kidney failure in eight more patients, six of which resulted eventually in patient's death (Table S8). Six of these patients had a history of renal dysfunction and, according to the definition of hepatorenal syndrome of type 2 (HRS-2; (17)), four already presented HRS-2 before the implantation of the pump. All renal safety events recorded are summarized in Table S9. For detailed definitions of AKI, HRS-1 and HRS-2, see Table S2.

Device and procedure-related safety events

Seventy-eight device-related safety events in 44 patients (41.5%) were recorded, corresponding to 0.74/per patient. The PC was the most frequent cause of DD, followed by pump dysfunction (Table 3). Occlusion by biological material was the main cause of PC dysfunction. Displacement, disconnection and kinking also occurred with both catheters, but less frequently with the bladder catheter. The most important procedure-related safety event was implant site extravasation, in addition to one case each of wound dehiscence, post-procedural hemorrhage and seroma. Notably, long-term leakage of ascites did not occur in any patient, although short-term leakage was common.

Reinterventions and explantations.

In total, 108 surgical reinterventions were performed in 72 patients. This included 60 pump and/or catheter reinterventions and 48 complete explants (Table 4). Twenty-seven per cent of the explants were due to OLT, and 10% were due to recovery from RA. Most SAEs leading to explant were infections. Pump pocket infections and peritonitis were the most frequently recorded SAEs associated with explantation. Median duration of reintervention surgeries, including explants for OLT, was 45.0 (30.0–70.0) minutes.

Twenty-six of patients with explantation recovered fully and seven died secondary to the causative SAEs (Tables S9 and S10). Overall reintervention rate (except explantation for OLT or recovery) was 0.85/patient. Figure 1A presents post-implant pump system survival. Median and mean system survival were 13.1 months (95% confidence interval [CI] 10.8-15.4) and 13.4 months (CI 10.7–15.4), respectively.

Patient survival

Panel B of Figure 1 illustrates overall survival. Events include on-study and post-withdrawal deaths. All other patients were censored at withdrawal or study completion. Median and mean survival was 10.1 months (95% CI 4.9–15.3) and 13.4 months (95% CI 11.3–15.6), respectively. Thirty-four patients (31.5%) died within six months (29 on-study and five after SAE-related explant).

Efficacy

The frequency of any volume paracentesis decreased 9.9fold and the monthly volume evacuated by paracentesis 12.2fold. (Figure 2, Table S11). Post-implant frequency of LVP was mean 0.14±0.23/month. Fifty-four per cent of patients remained LVP-free over the entire study period (Figure 2). Most of the 239 reported post-implant paracenteses were related to device-associated problems, followed by reasons related to the patient's medical condition, i.e., paracentesis performed in an emergency condition or following temporary reduction of the daily pumped volume, or inappropriate pump settings or charging. The cause of about a fifth of paracenteses remained unknown (Table S12).

Forty-four patients (41.5%) received albumin in the context of paracentesis at least once and six (5.7%) never. As albumin use and reporting thereof was not mandated by the study protocol, the status of 56 (52.8%) patients remained unknown (see also Table S4).

Prognostic scores and laboratory parameters

The evolutions of MELD [UNOS] and Child-Pugh scores are presented in Table S13. Mean changes from baseline in liver scores, plasma creatinine, total bilirubin, serum albumin, and INR over the study period are presented in Figure 3 and Table S14.

MELD score increased steadily in the short-term patients (<9 months) and also within the first month in the long-term survivors (≥9 months), but then decreased to near baseline levels.

Mean Child-Pugh score increased steadily in the short-term patients but remained stable for the first six months post-implant in the long-term patients and improved thereafter.

Mean serum bilirubin concentrations improved transiently in the short-term survivors at three months but had deteriorated again at six months. In the long-term survivors, mean bilirubin concentrations remained below baseline.

Mean serum albumin concentrations decreased steadily compared to baseline until six months post-implant in the short-term survivors. A less pronounced decrease in albumin concentrations was observed in the long-term patients followed by increase thereafter.

Mean plasma creatinine increased steadily in both groups, with a markedly steeper increase in the short-term patients. A comparison of patients with a history of renal issues and those without revealed higher creatinine values in the former throughout the study, with the same dynamics of steep increase within one month post-implant and stabilization after 3 months as observed in the short-term vs. long-term survivors (Figure 3F, Figure S2).

Post-hoc analysis: Impact of device modifications

During the study period the manufacturer made adjustments to the device design, software and patient management instructions to address issues with post-implant paracentesis requirement and reinterventions. To reduce clogging, a new type of PC was introduced (18), which ten patients in this study received initially and a further six as replacements. The modified catheter is a pig-tail peritoneal dialysis catheter (Medionics PSNA-100; Medionics International, Markham, Canada) with smaller diameter of openings that connects to the standard PC. To capture effects of the modifications, a post-hoc analysis of the first 50 vs. the last 50 patients enrolled in this study was performed. Baseline characteristics were not significantly different between the two groups, except for the type of RA, which was likely caused by the fact that this information was not available for 64% of patients in the first group (Table S15). Notably, a difference in overall reintervention rate was observed (Table 5). Whereas overall survival (Figure 1C), number of explants due to SAE or DD, exchanges or explants due to DD only and number of explants were similar between the two patient groups, there was a difference in number of PC issues, mainly driven by a significant reduction of PC occlusion events. All of these involved the standard PC. In three procedures, the standard PC was exchanged for the modified catheter. None of the modified PCs became deficient, indicating longer survival (Figure 1D).

Discussion

This study represents the largest cohort of real-world patients with the longest available follow-up available so far (Mean observation time: 267±222 days). Patient selection was kept minimal to obtain a cohort reflective of patients seen in everyday clinical practice. Alcohol was the dominant etiology for liver cirrhosis, followed by

hepatitis C and NASH. Advanced disease in this study population is reflected by high proportions of patients with prior events of HE, HRS-2 and SBP.

SAE were the most frequent reason for study discontinuation. Of the patients with SAE, 54% recovered fully, whereas 21% deceased.

Five patients recovered and no longer required the device or paracenteses. Twelve per cent of the patients withdrew to receive a liver graft, demonstrating that the device may be used to control ascites in patients awaiting OLT.

Six-month known mortality in this study was 31.3%, which is in line with previous observations for patients treated with paracentesis (3).

Full post-marketing surveillance registry cohort survival increased by approximately 18 days compared to the first 56 patients reported (10). At that time, three of the first 56 patients had not yet completed the study. In addition, improved patient management might have contributed to increased survival. Concerns about device-related AKI were raised by previous studies, reporting multiple episodes in 7/10 patients (13) and significantly more events vs. SoC (8), particularly in the first week post-implant, most of which, however, were asymptomatic (grade 1). In this study, AKI occurred in 6.6% of patients, and none of the events started within seven days post-implant, which is consistent with observations from the MOSAIC study (9,19), suggesting that risk can be mitigated by careful adjustment of daily pump volume and perioperative albumin replacement. However, asymptomatic AKI events may have been missed due to lack of mandatory sampling in the immediate post-operative period.

Prolonged leakage of ascites from the PC insertion site was a risk identified in the registration trial (7) but only occurred in one patient.

Device-related infections were another concern that, in this study, occurred at a slightly higher frequency in patients without record of long-term antibiotic prophylaxis, which highlights the benefits of this measure under alfapump® therapy. However, the number of patients without reported prophylaxis was small and complete listing of concomitant medication was not mandated. Long-term antibiotic prophylaxis in patients with advanced liver disease has been debated, as a greater risk of infections with multi-drug resistant (MDR) germs was feared. Two recent studies, however, showed that infections with MDR were not more frequent in patients receiving quinolone antibiotics (20), even in regions with a high prevalence (21). While there were no significant survival benefits, bacterial infections were reduced (20), which is relevant for alfapump® therapy as infections were a frequent cause of explant.

Overall, device-related events affected two thirds of patients. Whereas pump and PC issues occurred in about a quarter of patients each, bladder catheter-related deficiencies and charging problems were rare.

The device efficiently reduced paracentesis frequency and volume of ascites evacuated per month (9.9fold and 12.2fold, respectively). A formal p-value denoting statistical significance was not calculated due to uncertainties affecting both the pre-implant values, which were based on estimates made at baseline, and the post-implant values, which may be underestimated due to underreporting of paracenteses performed outside the study centers. Nevertheless, the effect of alfapump® implantation is regarded as clinically relevant. The proportion of patients who remained LVP-free post-implant was lower than the 62% calculated in a recent meta-analysis of 206 RA patients treated with the device from seven studies and case

series (including 56 patients from this cohort) (11), but slightly higher than observed in a clinical trial comparing covered TIPSS to LVP treatment (51.7%) (22).

The usual discontinuation of albumin substitution after implantation of the device might explain the transient drop in serum albumin observed. A separate analysis comparing patients withdrawn prior to vs. after nine months suggests that improvement after six months reflect a selection of patients with a better evolution. Differential development of bilirubin, INR and creatinine in short-term vs. long-term survivors was observed, with the latter increasing in both groups, but to different extents. This is in line with previous observations demonstrating a steady decrease of glomerular filtration rate over six months in ten patients treated with the device (13), while no significant differences regarding sCr change from baseline were observed with device vs. SoC treatment (8). The reason for the individually different response of creatinine levels to device treatment remains elusive, but those with increase may have had more advanced liver disease and a propensity to develop HRS-2.

In a post-hoc analysis comparing the first 50 vs the last 50 patients, less reinterventions were observed in the latter group. Notably, the number of patients with catheter-related issues dropped by more than 50% in the patients enrolled later. The modified catheter appeared to be less prone to obstruction, thus contributing to the reduction in catheter-related issues. However, as the sample size is small, these results should be considered exploratory.

Results from this registry may be generalized since it included real-world patients not highly selected. Nevertheless, the study has several limitations. First, it is based on data collected longitudinally from real-life cases with no standardized protocol and patients selected and managed according to local practices, hence selection bias

cannot be excluded. Second, due to absence of randomization, direct comparison with other treatments is impossible. Third, the analysis of data is limited to the collected parameters.

This real-life prospective cohort confirms that the alfapump® effectively controls ascites in the majority of patients, hereby reducing the need for repeated paracentesis. However, complications occurred frequently, which partly reflects the underlying advanced liver disease and partly technical problems with the device. Importantly, the number of technical complications were by and large reduced in the second half of the cohort, reflecting an improved system and better management. Future focus should be the identification of the ideal patient for treatment with the device, real-life QoL effects and better characterization of the impact on nutritional status. In addition, the combination of alfapump® with hernia repair, which resulted in better outcome of the latter in a small feasibility study (23), and bridging to OLT (24) should be further explored.

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Tables

Table 1: Baseline Characteristics. IQR, interquartile range; MELD, model of end-stage liver disease**;** SD, standard deviation; UNOS, United Network of Organ Sharing.

Number included in analysis	106
Median age, years (range)	60.0 (44-83)
Male gender (%)	75.5
Body mass index (kg/m^2), mean (SD) [N=100]	25.8 (5.0)
Type of refractory ascites (N [%]) [N=73]	
Diuretic-resistant	50 (47.2)
Diuretic-intractable	23 (21.7)
Etiology of liver cirrhosis (N [%])	
Alcohol	71 (67.0)
Hepatitis C	8 (7.5)
Non-alcoholic steatohepatitis (NASH)	6 (5.7)
Cryptogenic	5 (4.7)
Hepatitis C virus (HCV) and alcohol	3 (2.8)
Alcohol and NASH	2 (1.9)
Cardiac	2 (1.9)
Hepatitis B virus and alcohol	2 (1.9)
Autoimmune hepatitis (AIH)	1 (0.9)
Drug-induced	1 (0.9)
HBV	1 (0.9)
HBV and AIH	1 (0.9)

HBV and NASH	1 (0.9)
HCV and HBV and Alcohol	1 (0.9)
Other	1 (0.9)
Medical History of interest (N [% of 106])	
Renal dysfunction†, N =101	47 (44.3)
Hepatic encephalopathy‡, N =103	42 (39.6)
Grade ≥2	21 (19.8)
Grade 1	4 (3.8)
Grade not specified or missing	17 (16.0)
Hepatorenal syndrome, N = 99	32 (30.2)
Spontaneous bacterial peritonitis, N=102	31 (29.2)
Hepatocellular Carcinoma, N=106	8 (7.5)
Urinary tract infection, N=83	14 (13.2)
Child Pugh Score (N=106)	
Mean (SD)	8.8 (1.3)
B (7-9 points) (N [%])	77 (72.6)
C (10-15 points) (N [%])	29 (27.4)
MELD score (UNOS) (N=100)	
Mean (SD)	13.2 (4.4)
Blood values at baseline	
Bilirubin (μmol L^{-1}), mean (SD)	37.7 (42.6)
Median (IQR)	25.5 (18.0-41.0)
Creatinine (μmol L^{-1}), mean (SD)	110.4 (45.1)
Median (IQR)	97.0 (86.0-121.0)
Albumin (g/L), mean (SD)	30.7 (5.7)

Median (IQR)	31.0 (27.0-34.0)
INR, mean (SD)	1.27 (0.22)
Median (IQR)	1.23 (1.10-1.39)

† Investigator's assessment based on patient file; no further details available

‡grading according to West Haven Criteria

Table 2: Causes of death in known mortality

	Total N	% of deaths	N pump *in situ*	N Post-explant
Progressive chronic liver disease	15	27.2	15	
Sepsis/infection	12	21.8		5
Sepsis	5†	9.0	5	
Abdominal sepsis and multi-organ failure	1	1.8	1	
Peritonitis	2	3.6		2
Pump pocket infection	1	1.8		1
Pump pocket infection and sepsis	1	1.8		1
Sepsis and ileus	1	1.8	1	
Small bowel perforation with sepsis/peritonitis	1	1.8		1
Hemorrhage	7‡	12.7	6	1
Hepatocellular carcinoma	3	5.4	3	
Renal failure	3	5.4	3	
Cardiac disorders	2§	3.6	2	
Progressive chronic liver disease and infection	2¶	3.6	1	1
Acute-on-chronic liver failure	1	1.8	1	

Complications after orthotopic liver transplantations	1	1.8	1	
Multiple Organ Dysfunction	1	1.8	1	
Progressive chronic liver disease with hepatorenal syndrome – acute kidney injury	1	1.8	1	
Sigmoid perforation††	1	1.8	1	
Stroke	1	1.8	1	
Unknown	5	9.0	5	
Total	55	100	48	7

† Pneumogenic (2), cholangitis (1), not specified or unknown (2)

‡ gastrointestinal bleeding (4), gastrointestinal bleeding with subsequent acute-on-chronic liver failure (1), Procedural (Post-transjugular intrahepatic shunt insertion) (1), bleeding (1), subarachnoid hemorrhage (1)

§ cardiac failure, cardiac tamponade

¶ end-stage liver disease, urinary tract infection, pump pocket infection and abdominal abscess (1), end-stage liver disease and pump pocket infection (1)

†† unrelated to surgery

Table 3: Summary of device deficiencies and procedure-related events

Device deficiencies and procedure related events	Events n	Patients N (%)
Total device deficiencies	78	44 (41.5)
Pump dysfunction	33†	27 (25.5)
- clogging	13	11 (10.3)
- communication	5	4 (3.8)
- charging	5	5 (4.7)
- humidity	3	3 (2.8)
- faulty sensors	2	2 (1.8)
- unknown/not specified	7	6 (5.6)
Peritoneal catheter	39	24 (22.6)
- occlusion	32	21 (19.8)
- dislocation	3	3 (2.8)
- disconnection	3	2 (1.8)
- kinking	1	1 (0.9)
Bladder catheter	5	5 (4.7)
- occlusion	1	1 (0.9)
- displacement	1	1 (0.9)
- damage	1	1 (0.9)
- kinking	2	2 (1.8)
Charging system	7	6 (5.6)
- Docking station dysfunction	1	1 (0.9)
- insufficient charging	6	5 (4.7)
Procedure related events	5	5 (4.7)

- implant site extravasation	3	3 (2.8)
- wound dehiscence	1	1 (0.9)
- post-procedural hemorrhage	1	1 (0.9)
- seroma	1	1 (0.9)

† numbers below do not add up because more than one device deficiency description may have been given per reported event

Table 4: Reasons for pump explantation

Adverse event/device deficiency		30
Infection		23
Pump pocket infection	*8*	
Peritonitis	*6*	
Sepsis or suspicion of infection	*2*	
Bacterascites	*1*	
Bacterascites and pump pocket infection	*1*	
Enterococcus faecium infection, site not specified	*1*	
Perforated diverticulum	*1*	
Peritonitis and pump pocket infection	*1*	
Sepsis and pump pocket infection	*1*	
Urinary tract infection	*1*	
Macroscopic hematuria		3†
Renal insufficiency/failure		2
Ascites leakage		1
Clogged pump, occluded peritoneal catheter and pump pocket erosion		1
Other		18
Orthotopic liver transplantation		13
No longer required		5‡

† One patient had recovered (hepatitis C virus) and did not need the device any longer

‡ Patients withdrawn early (4), explant after study completion (1)

Table 5: Results of post-hoc analysis first 50 vs. last 50 enrolled patients.

	First 50	Last 50	p-Value
Mean overall survival† (95% -‡) (months)	14.0 (11.0–17.1)	13.1 (10.1–16.2)	0.668§
Median overall survival† (95% CI) (months)	12.1 (8.2–16.0)	7.6 (0–18.7)	
Number of reinterventions (in n patients)	55 (30)	33 (26)	0.546¶
Reinterventions, mean per patient	1.1	0.7	*0.032*††
Time to first reintervention, mean (months)	5.7	7.1	0.311††
Number of device deficiencies with peritoneal catheter issues (in n patients)	28 (16)	8 (7)	0.056¶
Number of device deficiencies with peritoneal catheter occluded (in n patients)	25 (15)	7(6)	*0.048*¶
Number of device deficiencies with peritoneal catheter dislocated (in n patients)	2 (2)	1(1)	1.000¶
Number of device deficiencies with peritoneal catheter kinked	1 (1)	0 (0)	1.000¶
Number of pump exchanges/explants (in n patients)	31 (24)	25 (21)	0.688¶
Pump exchanges/explants, mean per patient	0.6	0.5	0.385††

Time to first pump exchange/explant‡‡, mean (months)	9.6	8.7	0.622††
Number of exchanges/explants due to device deficiency (in n patients)	16 (14)	13 (12)	0.820¶
Exchanges/explants due to device deficiency, mean per patient	0.3	0.3	0.565[c]
Time to first exchange/explant due to device deficiency, mean (months)	11.4	9.5	0.460††
Patients explanted, n	16	12	0.504[d]
Time to explant, mean (months)	9.3	7.1	0.332††
Time to first therapeutic paracentesis, mean (months)	3.0	3.7	0.531††

† including death on-study/withdrawal/study completion/post-withdrawal death

‡ confidence interval

§ Log rank (Mantel-Cox) test

¶ 2-sided Fisher's exact test for categorical parameters

†† 2-sided independent sample t-test for continuous parameters (equal variance not assumed)

‡‡except for orthotopic liver transplantation or no more need

Figure Legends

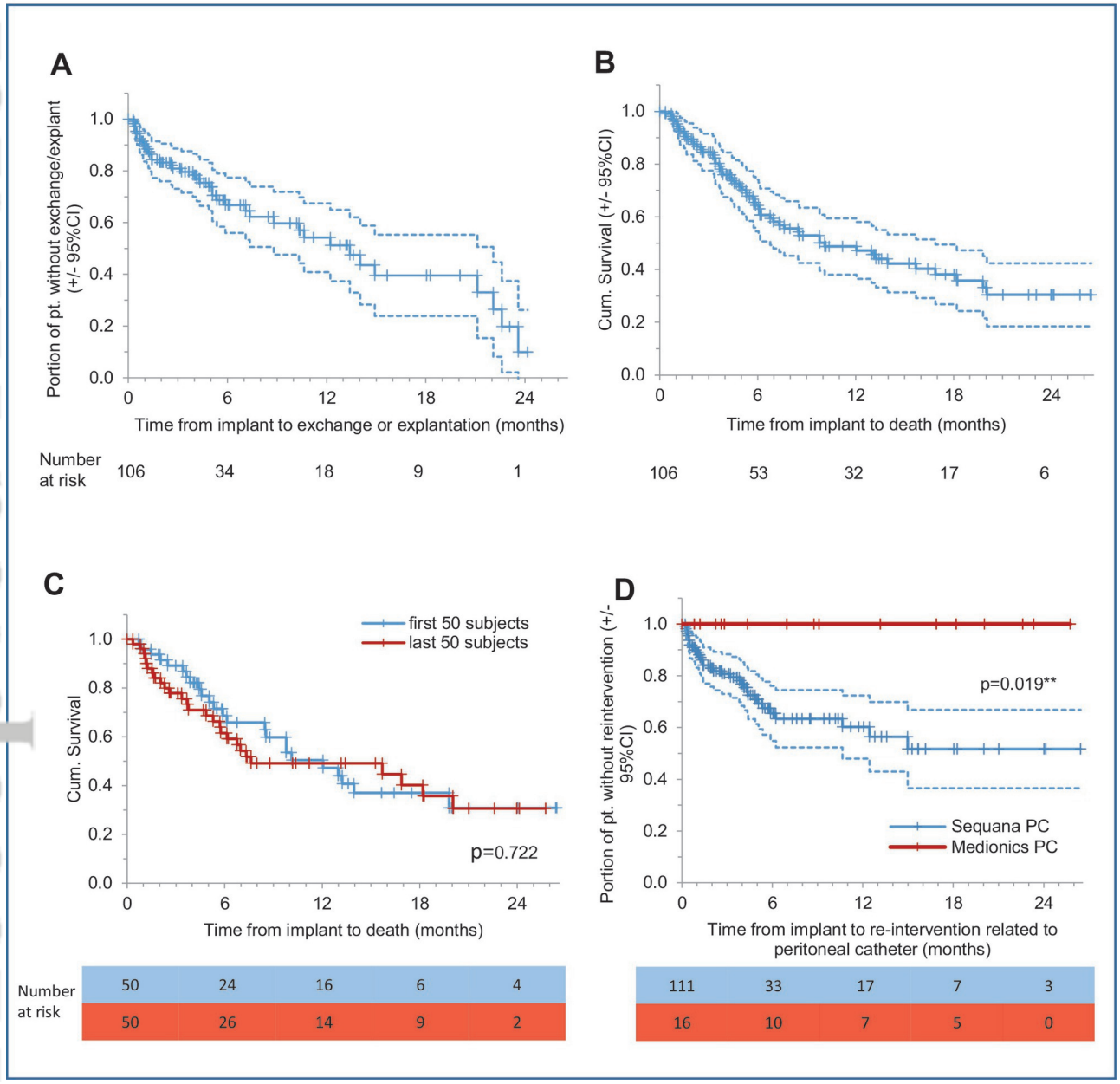
Figure 1. Survival of patients and device components. (A) Time to first pump exchange or explant due to device deficiency. Death, withdrawal for reasons unrelated to the device and explants due to orthotopic liver transplantation or resolution of ascites were censored at the time of explant or death as appropriate. **(**B**)** Overall survival including known deaths after pump explant. Withdrawal and study completion were censored at the time of explant. (C) Survival of the first 50 (blue) vs. the last 50 patients enrolled (red) including known deaths after pump explant, withdrawal and study completion. The p-value was calculated using the Mantel-Cox test. (D) Time to peritoneal catheter deficiency in the standard (blue, n=111) vs. modified catheter (red; n=16), showing a significantly longer lifetime for the latter. The p-value was calculated using the Breslow (Generalized Wilcoxon) test. All panels: Vertical lines indicate censoring of patients at risk. Dashed lines represent 95% confidence interval boundaries.

Figure 2. Paracentesis (A) Pre- vs. post-implant paracentesis frequency per month and (B) volume of ascites (L) evacuated per month 3 months pre-implant vs. post-implant. Note that pre-implant values are estimates based on data collected at the baseline visit and that post-implant values may be underestimated because not all paracenteses may have become known. Hence, a formal p-value was not calculated. Mean is indicated with +. Bars represent median and interquartile range; whiskers indicate 5^{th} and 95^{th} percentile. (C) Large volume paracentesis (>5 L) post-implant.

Figure 3. Mean changes of liver scores and lab values of interest from baseline. (A) Model of end-stage liver disease (MELD) score (United Network of

Organ Sharing [UNOS]), (B) Child Pugh Score, (C) serum albumin, (D) total bilirubin and (E) international normalized ratio (INR), (F) serum creatinine vs. baseline over time. Blue: Total patient population. Red: Short-term patients (withdrawn at <9 months [9M]). Green: Long-term patients (withdrawn at ≥9 months or completed study. The 9M threshold was chosen arbitrarily but later found empirically to be clinically and economically meaningful. Error bars represent two standard errors (SE).

Figure 1: Patient and system component survival



liv_15337_figure 1 survival graphs.eps

Figure 2: Paracentesis

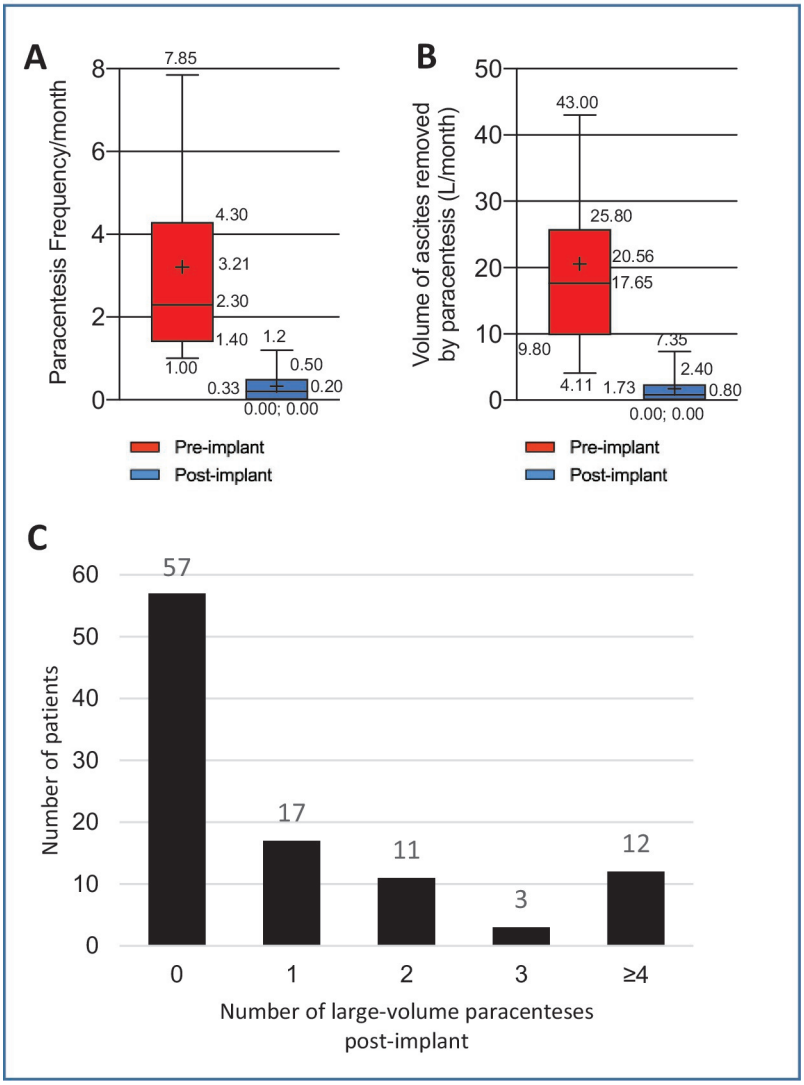


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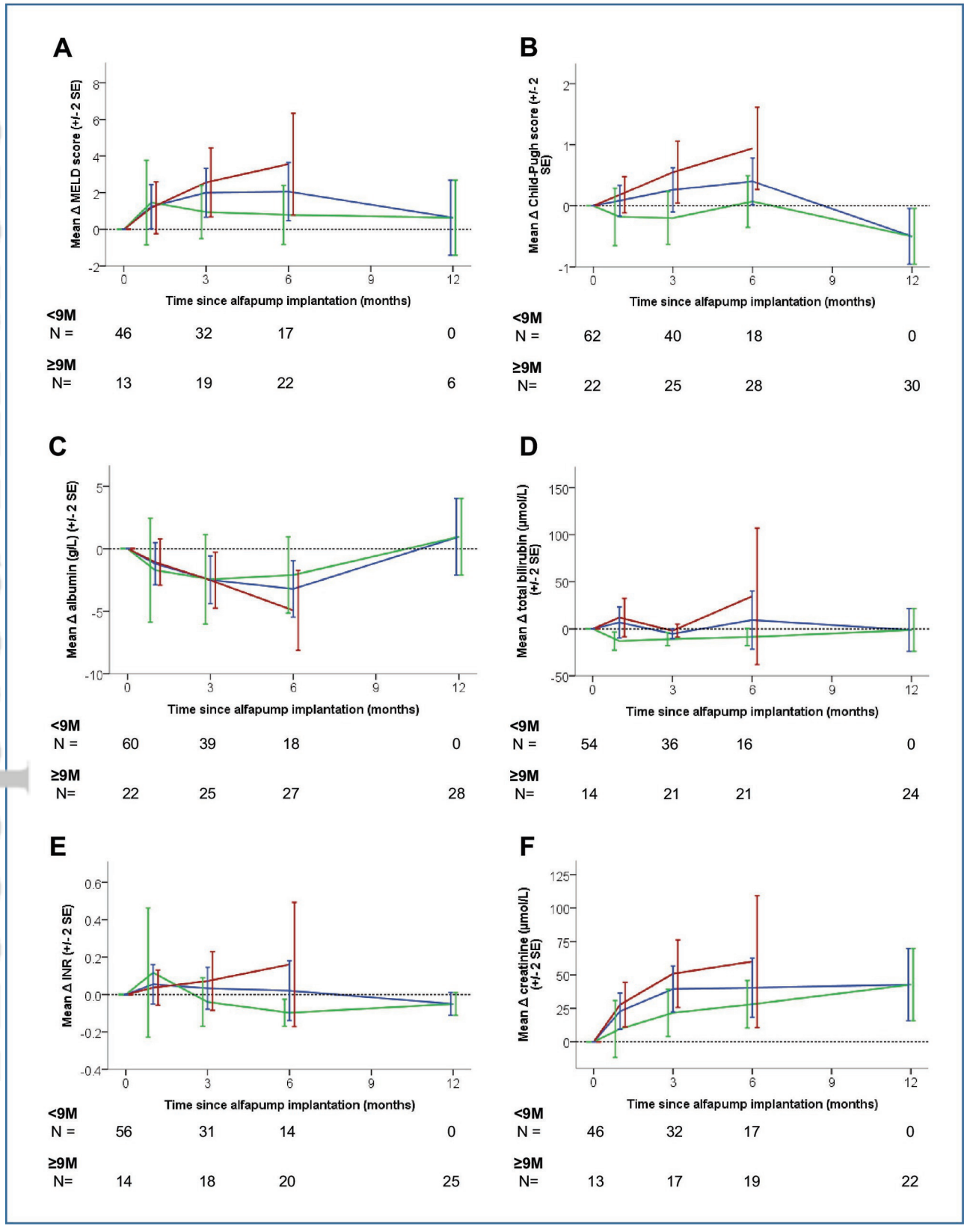
Figure 3: Evolution of liver scores and lab values over time



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