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Meta-Analysis

Current treatment options of refractory ascites in liver cirrhosis – A systematic review and meta-analysis

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ABSTRACT

Background: Refractory ascites is a severe complication of liver cirrhosis and treatment options consist in large volume paracentesis, transjugular intrahepatic portosystemic shunt, alfapump®, peritoneovenous shunt and permanent indwelling peritoneal catheter.
Aim: Our aim was to assess the efficacy, mortality and complications of each treatment.
Methods: We performed a systematic review using Pubmed and Embase. Frequencies were summarized with Comprehensive Meta-Analysis Software.
Results: Seventy-seven studies were included. In patients with transjugular intrahepatic portosystemic shunt, 1-year mortality was 33% (95% CI 0.29–0.39, I^2=82.1; τ^2 = 0.37; p<0.001) with lower mortality in newer studies (26% vs. 44%). At 6 months, mortality in patients with alfapump® was 24% (95% CI 0.16–0.33, I^2=0.00; τ^2 = 0.00; p = 0.83), 31% developed acute kidney injury (95% CI 0.18–0.48, I^2=44.0; τ^2 = 0.22; p = 0.15). Mortality at 12 months was 44% (95% CI 32%-58%, I^2=76.7, τ^2 = 0.44, p<0.001) in peritoneovenous shunts and 45% (95% CI 38%–53%, I^2=61.4, τ^2 = 0.18, p = 0.003) in large volume paracentesis, respectively. Overall mortality in patients with permanent indwelling catheters was 66% (95% CI 33%-89%, I^2=82.5, τ^2 = 1.57, p = 0.001).
Discussion: Mortality in patients with transjugular intrahepatic portosystemic shunt was lower in newer studies, probably due to a better patient selection. Acute kidney injury was frequent in patients with alfapump®. Permanent indwelling catheters seemed to be a good option in a palliative setting.

1. Introduction

Refractory ascites (RA) is a severe condition in liver cirrhosis predisposing to complications such as hepatic encephalopathy (HE) and is associated with poor survival [1]. The therapy of RA consists in large volume paracentesis (LVP) with albumin substitution [2], transjugular intrahepatic portosystemic shunt (TIPS) [3–7], automated low-flow ascites pump (alfapump®) [8], peritoneovenous shunt (PVS) [9] and permanent indwelling peritoneal catheter (PIPC) [10,11]. However, liver transplantation (OLT) [12] remains the best long-term curative option. Currently, LVP and albumin is the first line therapy of RA. The substitution of albumin is essential in preventing paracentesis-induced circulatory dysfunction (PICD), which is the main complication of LVP [2].

There is evidence that LVP is inferior to TIPS concerning survival in selected patients [3,7]. Selection criteria is essential, as patients with low platelet count and low hemoglobin might develop early liver failure [13]. A drawback of TIPS is the higher risk of developing HE [3–7].

For patients not qualifying for TIPS, alfapump® is a bridging option to OLT. Alfapump® is effective in treating RA, but up to 30% of patients develop acute kidney injury (AKI) and infections are quite frequent [8,14]. PIPC is used in a palliative setting when ambulant treatment is preferred against frequent LVP at the hospital [10,11]. However, the development of spontaneous bacterial peritonitis (SBP) is a major drawback of PIPC [10,11]. PVS plays a minor role in the treatment of refractory ascites due to a higher risk of disseminated intravascular coagulation (DIC), sepsis and heart failure [13].

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There is a growing number of observational studies reflecting the real-life efficacy and complication rate. The aim of this study was to provide an update on the treatment of RA in liver cirrhosis by assessing the efficacy, mortality and complications of the different treatment options.

2. Methods

2.1. Search strategy and eligibility criteria

The design and execution of this systematic review was adapted according to MOOSE [15] and PRISMA [16] guidelines. The study protocol stated eligibility criteria, information sources, search strategy and data collection process in advance.

Eligibility criteria were defined as recommended by the SPIDER tool [17]. Only studies referring to patients with refractory ascites caused by liver cirrhosis as defined by current guidelines were included [12]. We included RCTs, prospective clinical trials, observational cohorts and case-control studies investigating the following treatment modalities: LVP with albumin substitution, TIPS, alfapump®, PIPC and PVS. We excluded OLT as it is not strictly a therapy for RA. For a study to be included, it had to report the frequency of at least one of the following: need for LVP, mortality or complications.

The search was performed on Medline and Embase. The last search was conducted on November 12, 2019. A search strategy was documented in advance. Search terms were “refractory ascites”, “liver cirrhosis” and the treatment, i.e. “LVP and albumin”, “TIPS”, “alfapump®”, “PIPC” and “PVS”. The search was conducted by VW and studies were selected for further analysis by applying the criteria mentioned above. Whenever there was incertitude about the inclusion of a study, SGR was consulted.

Case reports, patients with RA due to other causes than liver cirrhosis (e.g. malignant ascites), patients treated for other indications than RA (e.g. TIPS for variceal bleeding), studies with a follow up shorter than 3 months (except for PIPC) and studies with less than five patients were excluded. Whenever a study cohort contained several indications for treatment or different etiologies of RA, the author of the study was asked for specific data. Only English or German articles were included, articles in other languages were considered if they had an English abstract. We also included abstracts if they included enough data to fulfill the criteria. If study cohorts from the same center overlapped, only the most recent cohort was analyzed. All authors of the newer studies up to 2010 were asked for more detailed information by mail in case there was missing data.

2.2. Data collection

Data collection was carried out systematically and included year of publication, number of patients, study type, follow up period, study population characteristics such as age, distribution of gender, etiology of cirrhosis, MELD score and Child-Pugh score, need for LVP, incidence of complications and mortality. Whenever possible, information was collected for a 12-month period after the intervention.

Depending on the treatment option, different complications were brought into focus. As for TIPS, we analyzed HE. AKI and infections were analyzed for alfapump®, SBP for PIPC, DIC and infections for PVS and infections, SBP, AKI and HE for LVP respectively.

2.3. Assessment of study quality

As we expected most of the studies to be observational, all studies included for data extraction were rated by a modified Newcastle Ottawa Scale simultaneously to data extraction [18].

2.4. Statistical analysis

Statistical analysis was performed with Comprehensive Meta-Analysis Software (CMA), Version 3.3.070, Biostat, Englewood, USA. Binary data were expressed as event rate with 95% confidence interval (95% CI) and summarized by random effects model. The results were displayed in forest plots. It was only possible to summarize continuous variables, if they were reported as mean and standard deviation (SD), continuous variables reported as median and interquartile range had to be excluded. The follow up periods differed substantially. To form comparable groups, studies were divided in subgroups according to their follow up period. As there were numerous TIPS studies, we performed a subgroup analysis comparing older (1993–2006) versus newer studies (2010–2019). In addition, we calculated the median Child-Pugh score of patients included in these studies and compared patients with Child-Pugh score below and above the median (respectively Child-Pugh score <9.3 vs. ≥ 9.3).

Heterogeneity between studies was assessed with I^2 and τ [2]. A value of $I^2 > 50\%$ was considered as substantial heterogeneity between studies and a value $>75\%$ as considerable heterogeneity. Significance was defined as p-value < 0.05.

3. Results

3.1. Study selection

On Medline and Embase, 983 and 551 were screened for eligibility, respectively. After the exclusion of duplicates, 166 studies were considered for inclusion. Eighty-nine studies were excluded for various reasons (Supp. Fig. 1). In total, 77 studies were included.

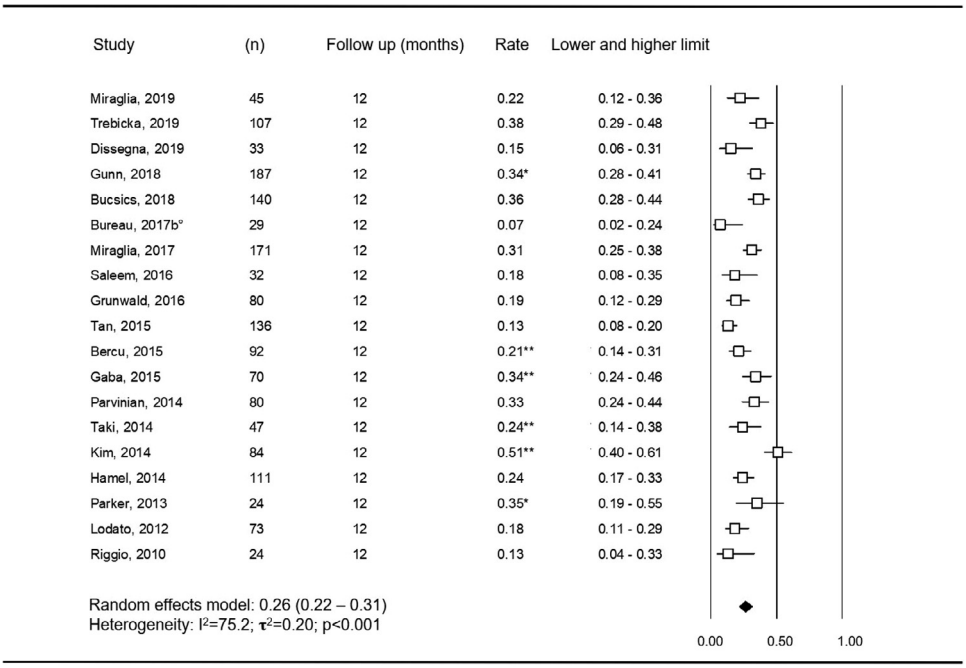
3.2. TIPS

Forty-seven studies [19–65] reported the outcome of patients with TIPS, baseline characteristics are summarized in Supp. Tables 1 and 2. MELD scores were only indicated in newer studies and ranged from 11 to 17, the summarized average MELD score was 13.4 (95% CI 12.5–14.2). Child-Pugh scores were within 8–11 and the average Child-Pugh score was 9.3 (95% CI 9.06–9.54). If only newer studies were considered, the Child-Pugh score was lower and averaged 8.8 (95% CI 8.5 – 9.2).

LVP was needed in 27% of patients during follow up at around 12 months (95% CI 21%–35%, I^2=82.2, $\tau^2 = 0.48$, p<0.001).

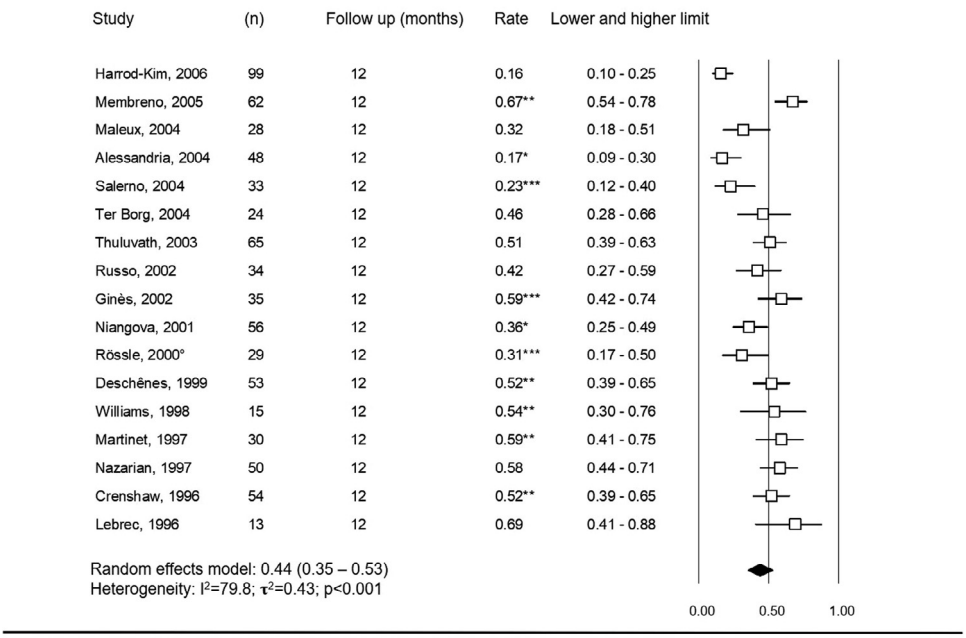
Mortality at 12 months was indicated or could be estimated in 36 out of 47 studies (Supp. Tables 3 and 4). The pooled proportion of mortality at 12 months was 33% (95% CI 29%–39%) with significant heterogeneity among studies (I^2=82.1, $\tau^2 = 0.37$, p<0.001). The mortality at 12 months was 26% in newer (95% CI 22%–31%, I^2=75.2, $\tau^2 = 0.20$, p<0.001) (Fig. 1) versus 44% in older studies (95% CI 35%–53%, I^2=79.8, $\tau^2 = 0.43$, p<0.001) (Fig. 2). Mortality rate at 12 months and Child-Pugh score were available in 19 studies, which were included in the subgroup analysis based on liver function. Average mortality rate was 20% (95% CI 14%–28%, I^2=72.0, $\tau^2 = 0.28$, $p = 0.000$) in the subgroup with less severe liver dysfunction (Child-Pugh score $<$ 9.3 points) and 41% (95% CI 30%–53%, I^2=84.6, $\tau^2 = 0.45$, $p = 0.000$) in the subgroup with worse liver function (Child-Pugh score $\geq$ 9.3 points), respectively.

Thirty-four studies reported the rate of HE and on average, 40% of patients with TIPS developed HE during follow up (95% CI 35%–46%, I^2=81.6, $\tau^2 = 0.37$, p<0.001), but the follow up period and the assessment of HE differed throughout the studies. Sometimes only overt HE was assessed, whereas other studies investigated HE with specific tests. If only studies with a follow up



°also recurrent ascites. *estimated by 1-year overall survival. **estimated by cumulative 1-year survival.

Fig. 1. Mortality at 12 months in patients with transjugular intrahepatic shunt (TIPS) from 2010 to 2019.



°also recurrent ascites. *estimated by 1-year overall survival. **estimated by cumulative 1-year survival. *** estimated by 1-year transplant-free survival.

Fig. 2. Mortality at 12 months in patients with transjugular intrahepatic shunt (TIPS) from 1993 to 2006.

around 12 months were considered, the occurrence of HE was 36% (95% CI 28%–45%, I^2=84.3, τ^2 = 0.46, p<0.001) (Supp. Fig. 2). If only newer studies were considered, the rate of HE was lower (30%, 95%CI 21%–42%, I^2=88.4, τ^2 = 0.51, p<0.001) than in older studies (45%, 95% CI 31%–60%, I^2=76.8, τ^2 = 0.50, p<0.001). Subgroup analysis of HE by liver function was not possible, as there was not enough data available. In studies with a follow up period up to 60 months, 47% of patients were affected by HE (95% CI 37%–58%, I^2=86.7, τ^2 = 0.44, p<0.001).

3.3. Alfapump®

In a period from 2013 to 2018, 6 studies [66–71] were published on alfapump®. Baseline characteristics are displayed in supp. Table 5. MELD scores were between 11 and 16 and Child-Pugh scores between 8 and 10. The average MELD score was 13.4 (95% CI 12.1–14.7) and the average Child-Pugh score 8.8 (95% CI 8.3–9.3), respectively. Data was predominantly available up to six months, thereby the meta-analysis was performed for this time point.

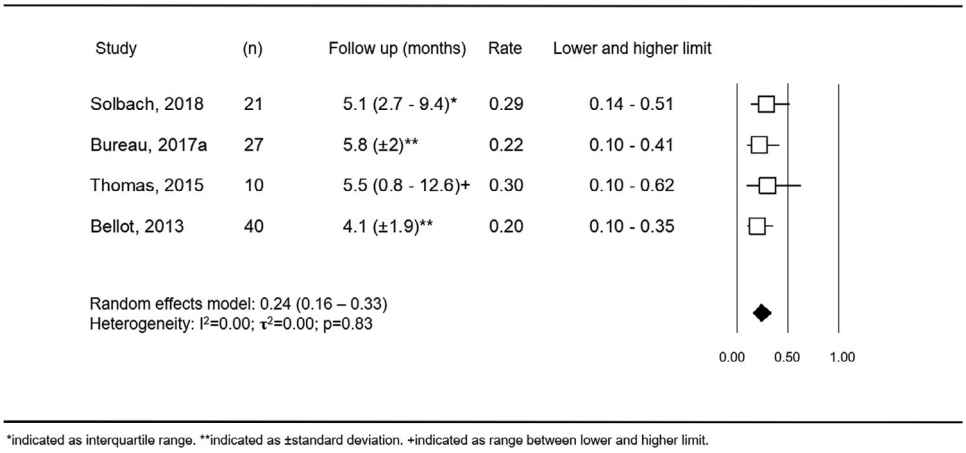


Fig. 3. Mortality at 6 months in patients with alfapump®.

At six months, 41% of alfapump® patients required at least once LVP (95% CI 29%–54%, I^2=53.7, $\tau^2 = 0.18$, $p = 0.07$).

All studies indicated mortality, four of which with a follow up around six months (Supp. Table 6). Mortality around six months was 24% (95% CI 16%–33%) with low heterogeneity (I^2=0.00, $\tau^2 = 0.00$, $p = 0.83$) (Fig. 3).

Overall AKI rate was 36% (95% CI 21%–56%, I^2=59.0, $\tau^2 = 0.42$, $p = 0.045$) and 31% (95% CI 18%–48%, I^2=44.0, $\tau^2 = 0.22$, $p = 0.15$) (Supp. Fig. 3) in a time-averaged analysis around six months, respectively.

Referring to all studies, the infection rate was 41% (95% CI 27%–57%, I^2=69.1; $\tau^2 = 0.41$; $p = 0.01$). If the analysis was limited to studies reporting infection rate at 6 months, the frequency was 44% (95% CI 28%–61%, I^2=59.9, $\tau^2 = 0.29$, $p = 0.06$) (Supp. Fig. 4). The most common infections were urinary tract infection (UTI), bacterial peritonitis, wound site infection and sepsis. The frequency reported for spontaneous bacterial peritonitis or device-related peritonitis ranged from 30% to 52% [66,68,70], for urinary tract infection (UTI) 7.5%–50% [68,70], for wound site infection 10%–20% [69,70] and 10%–17.5% for sepsis [68,70], respectively.

3.4. PVS

Fourteen studies [72–85] reported the outcome of patients with PVS. Baseline characteristics are found in Supp. Table 7. The studies differed in terms of which shunt system they used: LeVeen shunts [74–77], saphenoperitoneal shunts [82–84], Denver shunts [78–81], unclear [73,85] or more than one option [72]. MELD score was only reported in one study [81] and Child-Pugh scores in three studies [74,76,82].

Four studies indicated a requirement for LVP at around 12 months of 27% (95% CI 20%–44%, I^2=82.3, $\tau^2 = 0.65$, $p<0.001$). In studies with a follow up period between 15 and 60 months, the need for paracentesis was distributed heterogeneously (I^2=89.0; $\tau^2 = 0.87$; $p<0.001$) and ranged from 12% to 59%.

Nine studies indicated mortality around 12 months after insertion (Supp. Table 8). The pooled proportion was 44% (95% CI 32%–58%, I^2=76.7, $\tau^2 = 0.44$, $p<0.001$) (Fig. 4). In studies with a follow up period up to 48 months, mortality was 55% (95% CI 46%–64%, I^2=31.4, $\tau^2 = 0.05$, $p = 0.21$).

As for complications, 6% of all patients with PVS developed DIC during hospitalization (95% CI 4%–11%, I^2=0.00, $\tau^2 = 0.00$, $p = 0.73$) (Supp. Fig. 5). Overall, 16% had at least one infection (95% CI 10%–26%, I^2=74.4; $\tau^2 = 0.57$; $p<0.001$) (Supp. Fig. 6). At around 12 months, 15% of patients with PVS were affected by an infection (95% CI 7%–30%, I^2=71.1, $\tau^2 = 0.70$, $p = 0.004$).

3.5. PIPC

Five studies [86–90] published results concerning PIPC. Baseline characteristics are shown in supp. Table 9. Three studies reported MELD scores, these were high and ranged from 16 to 17 [86–88].

There was no need for LVP reported. Follow up periods ranged from 1 to 4 months and overall mortality in four studies in this period was 66% (95% CI 33%–89%, I^2=82.5, $\tau^2 = 1.57$, $p = 0.001$) (Supp. Table 10 and supp. Fig. 7). Reinglas et al. [88] exhibited a very low mortality (27%) compared to the other studies. If Reinglas et al. [88] was excluded from analysis, the mortality rate was 76% (95% CI 61%–87%, I^2=0.00; $\tau^2 = 0.00$; $p = 0.60$).

SBP developed in 15% of patients with PIPC in the follow up period (95% CI 6%–32%, I^2=76.8, $\tau^2 = 0.80$, $p = 0.002$) (Fig. 5). Contrary to mortality, the rate of SBP was proportionally high in Reinglas et al. [88]. In a separate analysis without Reinglas et al. [88], the rate of SBP was lower (10%, 95% CI 7%–15%, I^2=0.00, $\tau^2 = 0.00$, $p = 0.84$).

3.6. LVP

LVP studies were mainly RCTs comparing new treatment options to standard of care procedure. In total, we included 15 studies [27,41,46,48,50,58,64,65,71,74,76,91–94]. Baseline characteristics are found in supp. Table 11. MELD scores ranged from 11 to 20 and Child-Pugh scores from 8 to 11. Eight studies indicated MELD scores with SD, the summarized score averaged 14.3 (95% CI 11.5–17). Child-Pugh score and SD were reported in 12 studies. The estimated Child-Pugh score average was 9.2 (95% CI 8.9–9.4).

Mortality around 12 months was estimated by summarizing 12 studies (Supp. Table 12) and was 45% (95% CI 38%–53%, I^2=61.4, $\tau^2 = 0.18$, $p = 0.003$) (Supp. Fig. 8). Overall, 33% developed HE (95% CI 25%–42%, I^2=73.9; $\tau^2 = 0.36$; $p<0.001$). If only studies with a follow up period around 12 months were considered, the rate of HE was 40% (95% CI 30%–52%, I^2=71.2, $\tau^2 = 0.29$, $p = 0.002$).

As for other complications, only a few studies indicated the frequency and the follow up period was widely distributed. Infections developed in 22% of patients in a follow period between 6 and 24 months (95% CI 17%–28%, I^2=0.00, $\tau^2 = 0.00$, $p = 0.57$). SBP was diagnosed in 10% in a follow up period between 11 and 50 months (95% CI 5%–17%, I^2=37.9, $\tau^2 = 0.18$, $p = 0.19$).

4. Discussion

The aim of this study was to provide a synopsis of current data about the treatment of RA. There is an increasing amount of ob-

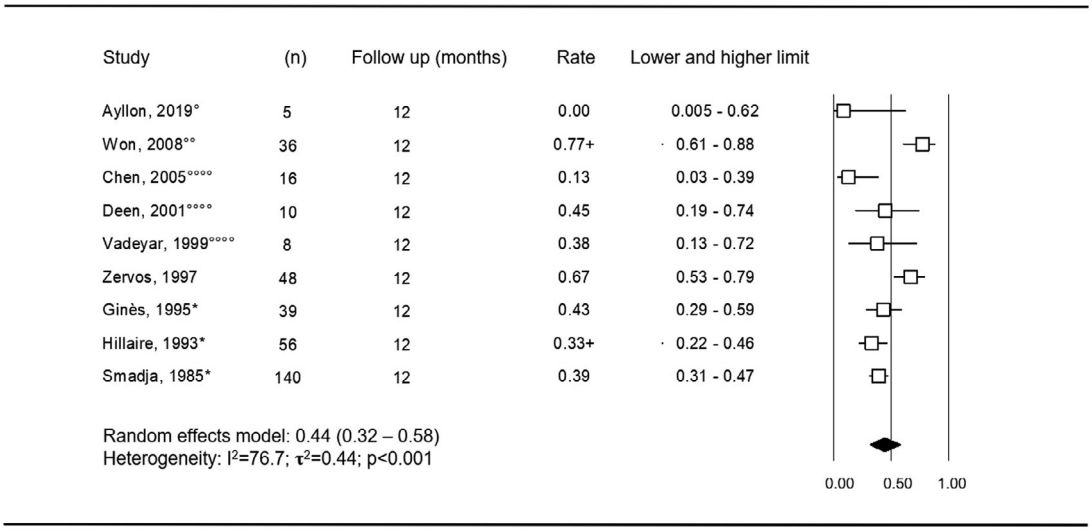


Fig. 4. Mortality at 12 months in patients with peritoneovenous shunts.

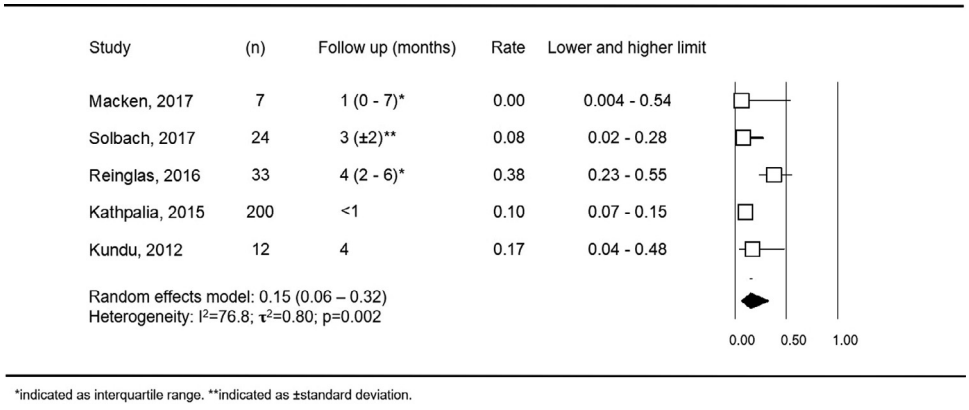


Fig. 5. Spontaneous bacterial peritonitis in patients with permanent indwelling peritoneal catheters.

servational studies assessing mortality and frequency of complications.

TIPS has been shown to be effective in the treatment of RA, but there is still uncertainty regarding its impact on survival. Some meta-analyses showed a trend towards better survival [6], others significantly better survival [3,7] or no impact on survival [4,5] as compared to LVP. However, these meta-analyses included older RCTs with bare stents. More recent studies reported a survival benefit in patients with TIPS compared to patients with LVP [25,27,64,65]. In our study, patients with TIPS had a lower 12-month mortality rate compared to patients with LVP (33% versus 45%); however, the MELD score was slightly higher in patients with LVP than in patients with TIPS.

Mortality seemed to be lower in patients with TIPS in newer studies (44% versus 26% in older studies). We assumed that several factors contributed to the lower mortality in recent studies. As previously highlighted by Tan et al. [25], the improvement in survival may not result from covered stents alone, but merely reflects a new era in the management of patients with TIPS due to a better patient selection. Several factors associated negatively with post-TIPS survival were identified such as age >65 years [50,64], low albumin [64], functional disability or sarcopenia [24,95], low GFR or high creatinine [20,29,32,38,47,56], high bilirubin [32,50,56], low platelet count [32], low sodium [50] and high MELD score [35]. The effect of patient selection was also reflected in our subgroup analysis, in which the mortality was lower in patients with lower Child-Pugh score (20% in Child-Pugh $<$ 9.3 versus 41% in patients with Child-Pugh score $\geq$ 9.3 points). Improvements in patient selection might also have led to lower rates of HE in patients with TIPS as the rate of HE in newer studies was lower than in older studies (30% versus 45% at 12 months) and was similar when compared to patients with LVP (40%).

Compared to TIPS, alfapump® is a relatively new method and a first systematic review has recently been published [8]. Our estimate of the rate of AKI was similar (31%) compared to Lepida et al. [8] (30%) and is probably higher than in patients with LVP as shown in Bureau et al. [71] Interestingly, the most recent and solely real-life study [66] did not report any occurrence of AKI, even though the amount of ascites mobilized per day was similar to other studies [69,70]. Additionally, Solbach et al. [66] reported no decrease of albumin contrary to other studies [67,70], even though albumin infusions were not administered. One would expect that the prevention of low intravascular volume by lowering the daily mobilization of ascites or the substitution of albumin might be necessary to impede the occurrence of AKI, as it has been proposed that alfapump® might mimic the PICD. [68] Besides renal complications, infections were frequent (44% at six months). However, the only published RCT [71] did not report a higher risk for infection in patients with alfapump® versus LVP. The most frequent types of infection were bacterial peritonitis, UTI, sepsis and

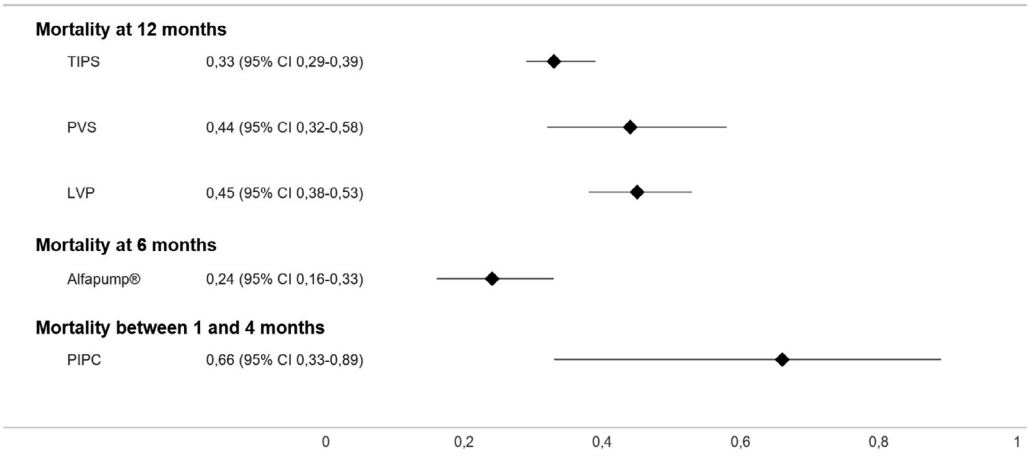


Fig. 6. Overview of mortality in all treatment options.

surgical site infections. However, we could not estimate the frequency of each infection due to differences in reporting. The mortality rate was 24% at 6 months in our study and is probably within a similar range as in patients treated with LVP, which had already been shown by Bureau et al. [71].

PVS has become less important over the last years, mainly due to poor long-term patency and severe complications such as volume overload, DIC and heart failure [13]. Our estimated mortality rate at 12 months was around 44%. The incidence of DIC, which had led to a restriction of the use of PVS, was 6% during hospitalization in our study. It had been reported that DIC and other complications such as volume overload may be prevented by evacuating ascites before the insertion of the shunt [85]. Additionally, these complications have not been reported in the most recent studies using saphenoperitoneal shunts [82–84]. These results should be interpreted, nevertheless, cautiously because most studies did not indicate the MELD or Child Pugh scores of their study population. Moreover, there are several different treatment modalities such as Denver shunt, LeVeen shunt and saphenoperitoneal shunt and diverse settings in which these shunts were used.

End of life care has gained importance in all fields of medicine and treatment with PIPC in the setting of liver cirrhosis has been brought into the focus of hepatologists [10]. PIPC alleviates straining symptoms such as abdominal distension without the need for regular hospitalizations for paracentesis [10]. As expected in a palliative setting, the mortality was high and averaged 66% in a follow up between 1 and 4 months. Reinglas et al. [88] exhibited a broad range of MELD scores at baseline (17, interquartile range 8–31) and a very low mortality (27%), so we assumed that patients were not treated in a palliative setting. Contrary to the relatively low estimated SBP rate in the other studies (around 10%), a high SBP rate (38%) was observed in Reinglas et al. [88], but authors reported that the first infection did not occur until 30 days after the insertion of PIPC. As a consequence of the high mortality in a palliative setting such as in Macken, et al. [86], the follow up of these patients was rarely longer than one month and therefore the risk of SBP was tolerably low. Therefore, even if PIPC was associated with a high risk of SBP in a long-term follow-up, it might be a safe method in end of life care of patients with a probable duration of life of a few months.

An issue marginally addressed in all treatment options was the quality of life. Three studies [46,71,72] performed a systematical assessment, others used surrogate markers such as hospitalization rate. Beneath mortality and complication rate, quality of life is an important endpoint that should be investigated in future studies.

There are several limitations of this review. First, due to the observational nature of the studies, we estimated frequencies in all treatment options and aimed to compare them. This approach allowed for a rough estimate, but is certainly not as valid as a direct comparison. Second, we did not estimate time-dependent variables such as hazard-ratio, which would be a more suitable approach, but was not possible with most of the observational studies. We tried to approximate to a time-dependent analysis by forming subgroups according to their follow up period. Third, there was considerable heterogeneity in almost all analyses. There were differences in baseline characteristics such as liver function, medical care in the follow-up and discrepancies in the assessment of complications.

In conclusion, our results suggest that TIPS, particularly in more recent studies, revealed lower mortality and HE rates as compared to other treatment modalities for RA, probably due to a matured patient selection (see Fig. 6). AKI and infections were still frequent problems after the implantation of alfapump®. Although PVS played only a minor role in the last few years, recent studies indicated lower rates of major perioperative complications such as DIC. As for PIPC, the SBP rate was low when used in an end of life setting and it might be a safe method to alleviate symptoms due to RA. Our results highlight the importance of treatment allocation depending on the patient's individual characteristics and the overall situation, but also that RA still has a poor prognosis and the only curative option is liver transplantation.

Declaration of Competing Interest

None declared.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2021.12.007.

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