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# Systematic review with meta-analysis: automated low-flow ascites pump therapy for refractory ascites

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## Summary

**Background:** Few effective treatments are available for patients with cirrhosis and refractory ascites. New treatment modalities are needed for these patients.

**Aim:** To synthesise the available evidence on the efficacy and safety of automated low-flow ascites pump therapy in patients with cirrhosis and refractory ascites.

**Methods:** Electronic databases were searched for trials evaluating automated low-flow ascites pump therapy in patients with refractory ascites.

**Results:** Nine studies were included. Eight were case series, one was a randomised controlled trial. Pooled estimate rates were 0.62 (95% CI = 0.49-0.74) for the absence of requirement of large volume paracentesis (LVP) after pump insertion, 0.30 (95% CI = 0.17-0.47) for acute kidney injury, 0.27 (95% CI = 0.13-0.49) for bacterial peritonitis and 0.20 (95% CI = 0.09-0.37) for urinary tract infection. There was high heterogeneity between studies which was often reduced or eliminated in sensitivity analyses by excluding studies of patients with a mean or median model for end-stage liver disease (MELD) score > 15. Results of sensitivity analyses were similar to those of overall analyses. Mean increase in serum creatinine level after pump insertion was 23 µmol/L (95% CI = 10-35) with no heterogeneity between studies. The pooled estimate rate for pump-related side effects was 0.77 (95% CI = 0.64-0.87) with low heterogeneity between studies.

**Conclusion:** This meta-analysis demonstrates that most patients treated with automated low-flow ascites pump therapy do not require LVP after pump insertion. Acute kidney injury occurs in 30% of patients and creatinine levels increase by a mean of 23 µmol/L after pump insertion. Bacterial peritonitis and urinary tract infection occur in 27% and 20% of patients respectively.

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr Y Yuan. The Handling Editor for this article was Professor Gideon Hirschfield, and it was accepted for publication after full peer-review.

  

## 1 | INTRODUCTION

Refractory ascites is one of the most common life-threatening complications in patients with cirrhosis. Once it has developed, median survival is about 6 months.[1] Current standard-of-care treatment combining salt restriction, diuretics and repeated large volume paracentesis (LVP) is associated with poor nutritional status and reduced quality of life. Transjugular intrahepatic portosystemic shunt (TIPS) has been proposed in highly selected patients and may increase transplant-free survival.[2] However, the use of TIPS faces several challenges. First, TIPS can be harmful in patients with severe liver failure and should be considered with caution in these patients.[3] Second, TIPS appears to be more effective in patients with recurrent rather than refractory ascites,[4] further limiting the number of candidates. Thus, repeated LVP remains the only therapeutic option for many patients. New treatment modalities are needed.

During the past 10 years, an automated low-flow ascites pump system (Alfapump system®) has been proposed as an alternative therapy in patients with refractory ascites.[5] This system uses an automated pump that allows removal of ascites from the peritoneal cavity into the urinary bladder where it can be eliminated through urination. Recently, a randomised controlled trial demonstrated that automated low-flow ascites pump therapy reduced the need for LVP and improved the quality of life and nutritional parameters in patients with untreatable ascites compared to the standard of care.[6] However, this study, similar to previous uncontrolled studies, included a limited number of patients. Since automated low-flow pump system therapy is gaining interest, a precise estimate of its effectiveness and safety is warranted before the recommendation of its use becomes widely applied.

Meta-analysis is a quantitative technique that enables pooling data from trials in order to decrease random errors. It also allows for assessment of the magnitude of impact of a particular factor.[7-10] In this study, we performed a meta-analysis of trials evaluating automated low-flow ascites pump therapy in patients with cirrhosis and refractory ascites. Our objective was to assess the effect of the automated low-flow ascites pump on the need for LVP and its safety in this patient population.

## 2 | MATERIALS AND METHODS

This systematic review is reported in accordance with the PRISMA statement.[11]

### 2.1 | Literature search

Medline (PubMed), Web of Science, Cochrane library and manual searches were combined and last performed on 30 April 2019. Key search terms were “alfapump”, “automated low flow ascites pump”, “ascites”, “pump”. Terms were combined within each database. General reviews and references from published trials were also used. The exact search term combinations can be found in Appendix S1. Duplicate publications were excluded. Only articles published in English were considered. Two observers (AL and AM) also screened all abstracts presented between 2015 and 2019 at the Liver Meeting of the American Association for the Study of Liver Diseases (AASLD) and the International Liver Congress of the European Association for the Study of the Liver (EASL).

### 2.2 | Criteria for inclusion and exclusion of studies

Randomised controlled trials and observational studies were included. In order to reduce risks of bias, strict inclusion and exclusion criteria were defined prior to the literature search. To be considered, a study had to: a) include patients with cirrhosis; b) include patients with refractory ascites despite the use of standard-of-care treatment; c) use an automated low-flow ascites pump system. When several publications existed covering the same study population, only the most recent was taken into account. Studies were excluded when the manuscript or a summary was not available and when useful data could not be obtained, despite contact with the authors.

### 2.3 | Endpoints and criteria for combinability

Endpoints were defined prior to the beginning of the meta-analysis. Primary endpoints were the number of patients who did not require LVP after automated low-flow ascites pump insertion, reduction in the number of LVPs per month after pump insertion and occurrence of the following adverse events: development of acute kidney injury, change in serum creatinine levels, development of bacterial peritonitis and development of urinary tract infection. When specified, acute kidney injury was defined as an increase in serum creatinine ≥0.3 mg/dL within 48 hours after implant or an increase in serum creatinine of ≥50% from baseline within 7 days after implant.[6,12] Bacterial peritonitis and urinary tract infection were defined according to the Baveno VI Consensus workshop.[13] Secondary endpoints were complications related to the automated low-flow ascites pump system (overall number of patients with at least one complication directly related to the pump system and, in more detail, the number of patients with peritoneal catheter dysfunction, bladder catheter dysfunction, pump dysfunction or who had explantation of the pump due to adverse events, pump replacement or pump pocket infection or wound dehiscence), the feasibility of the placement of the pump system, access to liver transplantation and occurrence of hepatic encephalopathy.

### 2.4 | Data extraction

Data extraction was performed independently by two investigators (AL and AM) using standardised data collection forms. Discrepancies in data interpretation were resolved by discussion, re-review of the studies and consultation with one other author (PD) when necessary.

### 2.5 | Quality score

The methodological quality of the studies was assessed using the NHLBI quality assessment tool for case series studies.[14]

### 2.6 | Statistical analysis

We used a random effects model to obtain a summary estimate of primary outcomes (using the inverse variance method) among patients treated with the automated low-flow ascites pump system.[15] The random model was chosen because it takes into account the possibility of heterogeneity between studies.[16] Data on all patients were extracted to allow intention-to-treat analyses. The overall treatment effect was expressed as event rate, a measure of how often a particular statistical event occurs within a group of experiments, with 95% confidence intervals (95% CI) or as mean difference with 95% CI.

The methodological section of each study was reviewed to determine whether any discrepancies could be identified. When a discrepant study was identified, sensitivity analyses excluding this study were performed. Heterogeneity was assessed using Cochran's Q test [17] and the $I^2$ statistic. More specifically, the $I^2$ statistic was used to estimate inconsistency in meta-analyses, representing the percentage of the between-study variability due to heterogeneity rather than chance.[18] A significant Cochran's Q statistic (below 0.10) was chosen as a threshold for significant heterogeneity across studies. The following cut-offs were used to quantify heterogeneity with the $I^2$ statistic: 0%-25%, low; 25%-50%, moderate; >50%, high heterogeneity.[18] To assess the extent of publication bias, the Egger test and the Begg and Mazumdar test were used.[17,19] A $P < .05$ was considered statistically significant. All statistical analyses were performed using Comprehensive Meta-Analysis (Biostat, Englewood, NJ).

## 3 | RESULTS

### 3.1 | Study population

Figure 1 summarises the flow chart of the selection of studies for inclusion in the meta-analysis. We screened 309 references; 40 were selected for full-text retrieval. Of these, nine were included in the analysis.[5,6,12,20-25]

Seven studies were published as full-text articles[5,6,12,20-23] and two in abstract form.[24,25] With the exception of one randomised controlled trial,[6] all other studies were case series; only patients treated with automated low-flow ascites pump were considered in the meta-analysis (Table 1).

A total of 206 patients with refractory ascites were treated with automated low-flow ascites pump. Follow-up of each study ranged between 6 and 24 months. Sixty-two per cent of the patients had alcoholic cirrhosis. Mean model for end-stage liver disease (MELD) score ranged between 11 and 16 (Table 1).

### 3.2 | Study quality

With the exception of one randomised controlled trial,[6] all other studies were observational. Table S1 details the quality of these included studies.

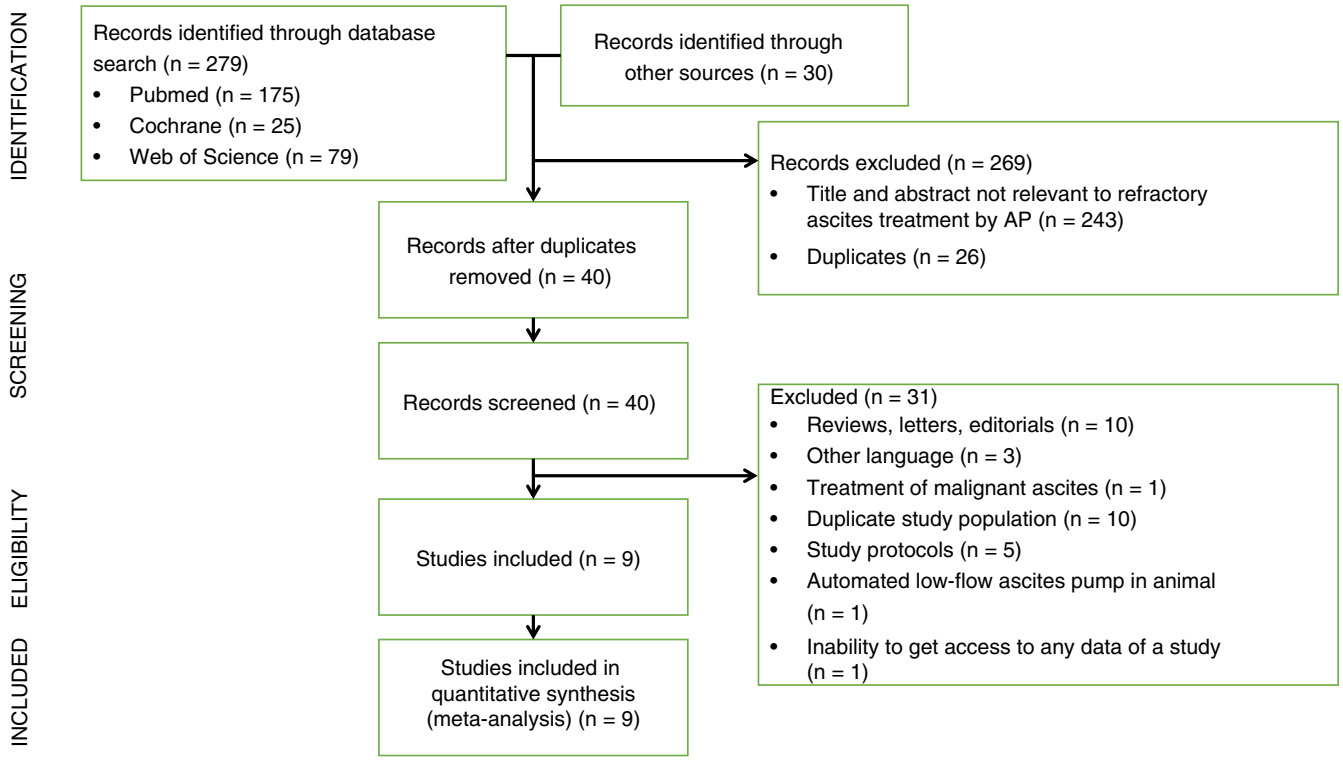


**FIGURE 1** Flow chart of the selection of studies for inclusion in the meta-analysis

**TABLE 1** Characteristics of the nine included studies

| Authors | Study design | N | Age (y, mean) | Alcoholic cirrhosis n (%) | Male n (%) | Child-Pugh score (mean/ % of Child-Pugh class C) | MELD score (mean) | Participating countries | Long-term antibiotic use after insertion of automated low-flow ascites pump | Albumin infusion after automated low-flow ascites pump insertion |
|---|---|---|---|---|---|---|---|---|---|---|
| Solbach 2018[21] | Case series retrospective | 21 | 56 | 13 (62%) | 12 (57%) | 9.6/ NA | 15.3 | Germany | Yes (norfloxacin 400 mg twice daily) | No |
| Stirnimann 2017[22] | Case series prospective | 56 | 62 | 39 (70%) | 43 (77%) | 8.9/ 29% | 13.6 | Switzerland, Germany, United Kingdom, Spain | Yes (norfloxacin 400 mg daily in most cases) | Yes for 24 patients (decision on a case by case basis) |
| Bureau 2017[6] | Randomised controlled trial | 27 | 61 | 20 (74%) | 21 (78%) | 8.2/ 12% | 12.2 | United Kingdom, France, Austria, Spain, Italy | Yes for 26 patients (norfloxacin 400 mg daily or ciprofloxacin 750 mg per week) | Only in case of acute kidney injury or bacterial peritonitis |
| Sola 2017[12] | Case series prospective | 10 | 59[a] | 6 (60%) | 6 (60%) | 8[a]/ 22% | 11[a] | Spain | Yes (norfloxacin 400 mg daily) | Only in case of acute kidney injury or bacterial peritonitis |
| Thomas 2015[23] | Case series | 10 | NA | 10 (100%) | 4 (40%) | NA/ 60% | 16[a] | Germany | No (norfloxacin only 14 days postoperatively) | Only in case of acute kidney injury |
| Bellot 2013[5] | Case series prospective | 40 | 59[a] | 17 (43%) | 28 (70%) | 8.5/ 25% | 12.6 | Spain, Germany, Bulgaria, Belgium | No for the first 21 patients, yes for the 19 next patients | No for the first 21 patients, yes for the 19 next patients |
| Karkhanis 2017[20] | Case series | 3 | 57 | 3 (100%) | 0 (0%) | NA/ 33% | 11.3 | United Kingdom | No | Yes for 1 patient<br>No for 2 patients |
| Wong 2018[24] | Case series | 30 | 60 | 14 (47%) | 17 (57%) | NA/ NA | 15.1 | North America | Yes (type and dose of antibiotic not provided) | Yes |
| Nair 2015[25] | Case series retrospective | 9[b] | 74[a] | NA | 6 (67%) | NA/ 43% | NA | United Kingdom | NA | NA |

Abbreviation: NA, not available.
[a]Expressed as median.
[b]Two of these patients did not have cirrhosis.

#### 3.2.1 | Assessment of potential differences in baseline study characteristics that may influence outcomes

The methodological analysis of each study identified discrepancies in three studies in which median or mean MELD score was >15[21,23,24] (Table 1). As MELD score might influence the rate of adverse events related to the procedure, sensitivity analyses excluding the Thomas,[23] the Solbach[21] and the Wong [24] studies were performed.

### 3.3 | Outcomes

#### 3.3.1 | Primary endpoints—Treatment effectiveness

Data on treatment effectiveness were available for 196 patients. The pooled estimate rate for the absence of requirement for LVP after automated low-flow ascites pump insertion was 0.62 (95% CI = 0.49-0.74, Figure 2 and Table 2). There was high heterogeneity between studies ($P$ = .02, $I^2$ = 68%). The mean difference in the

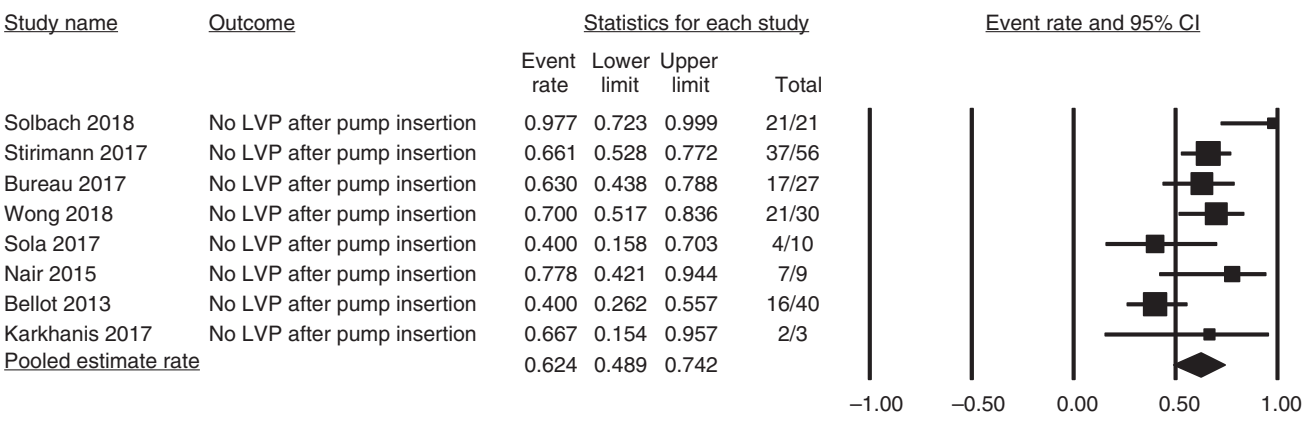


**FIGURE 2** Pooled estimate rate for the absence of requirement of LVP in patients with cirrhosis and refractory ascites treated with automated low-flow ascites pump therapy. Abbreviations: LVP, large volume paracentesis

number of LVPs before and after insertion of the automated low-flow pump system was 2.1 per month (95% CI = 0.6-3.5, Table 2, Figure S1). There was high heterogeneity between studies ($P < .001$, $I^2 = 97\%$). The results of sensitivity analyses excluding studies that included patients with MELD score >15 are provided in Table S2. These analyses reduced but did not eliminate heterogeneity between studies.

No publication bias was detected by the Egger test ($P = .3$) or by the Begg and Mazumdar test ($P = .3$).

### 3.3.2 | Primary endpoints—Occurrence of acute kidney injury, bacterial peritonitis or urinary tract infection

Data on occurrence of acute kidney injury were available for 141 patients. The pooled estimate rate for acute kidney injury was 0.30 (95% CI = 0.17-0.47, Figure 3 and Table 2). There was high heterogeneity between studies ($P = .02$, $I^2 = 61\%$). The results of sensitivity analyses excluding studies in which median or mean MELD score was > 15 are provided in Table S2. These analyses reduced but did not eliminate heterogeneity between studies. The mean difference in serum creatinine before and after insertion of the automated low-flow pump system was 23 μmol/L (95% CI = 10-35, Table 2). There was no heterogeneity between studies ($P = .7$, $I^2 = 0\%$).

Data on occurrence of bacterial peritonitis were available for 104 patients. The pooled estimate rate for bacterial peritonitis was 0.27 (95% CI = 0.13-0.49, Figure 4 and Table 2). There was high heterogeneity between studies ($P = .03$, $I^2 = 63\%$). The results of sensitivity analyses excluding studies in which median or mean MELD score was >15 are provided in Table S2. These analyses eliminated heterogeneity between studies.

Data on occurrence of urinary tract infection were available for 104 patients. The pooled estimate rate for urinary tract infection was 0.20 (95% CI = 0.09-0.37, Figure 5 and Table 2). There was high heterogeneity between studies ($P = .05$, $I^2 = 57\%$). The results of sensitivity analyses excluding studies in which median or mean MELD score was >15 are provided in Table S2. These analyses did not eliminate heterogeneity between studies.

No publication bias was detected by the Egger test ($P > .2$ for all analyses) or by the Begg and Mazumdar test ($P > .2$ for all analyses).

### 3.3.3 | Secondary endpoints—Pump-related adverse events

Data on overall pump-related adverse events were available for 100 patients. The pooled estimate rate for overall pump-related adverse events was 0.77 (95% CI = 0.64-0.87, Table 2). There was low heterogeneity between studies ($P = .3$, $I^2 = 23\%$).

Data on peritoneal catheter dysfunction were available for 197 patients. The pooled estimate rate for peritoneal catheter dysfunction was 0.18 (95% CI = 0.11-0.29, Table 2). There was moderate heterogeneity between studies ($P = .07$, $I^2 = 47\%$). The results of sensitivity analyses excluding studies in which median or mean MELD score was > 15 are provided in Table S2. These analyses did not eliminate heterogeneity between studies.

Data on bladder catheter dysfunction were available for 176 patients. The pooled estimate rate for bladder catheter dysfunction was 0.17 (95% CI = 0.11-0.26, Table 2). There was low heterogeneity between studies ($P = .25$, $I^2 = 23\%$).

Data on pump dysfunction were available for 206 patients. The pooled estimate rate for pump dysfunction was 0.24 (95% CI = 0.16-0.35, Table 2). There was moderate heterogeneity between studies ($P = .05$, $I^2 = 48\%$). The results of sensitivity analyses excluding studies in which median or mean MELD score was > 15 are provided in Table S2. These analyses did not eliminate heterogeneity between studies.

Data on explantation of the pump due to adverse events were available for 206 patients. The pooled estimate rate for explantation of the pump due to adverse events was 0.24 (95% CI = 0.19-0.31, Table 2). There was no heterogeneity between studies ($P = .6$, $I^2 = 0\%$).

**TABLE 2** Endpoints among the nine included studies

| Authors | N | Technical success (n patients) | Follow-up (mean, mo) | Number of LVPs before pump insertion (mean) | Number of LVPs after pump insertion (mean) | No LVP after pump insertion (n patients) | Acute kidney injury (n patients) | Creatinine levels before pump insertion (mean, μmol/L) | Creatinine levels after pump insertion (mean, μmol/L) | Bacterial peritonitis (n patients) | Urinary tract infection (n patients) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Solbach 2018[21] | 21 | 21 | 6[h] | 2.3 ± 2.7/ week[b,k] | 0/ week[i,k] | 21 | 0 | 140 ± 36.1[b] | 168.7 ± 73.9[b,d,l] | 11 | 4 |
| Stirnimann 2017[22] | 56 | 56 | 24 | 2.9 ± 1.8/ month[b] | 0.3 ± 0.3/ month[b] | 37 | NA | Change: 46.6 ± 71.2[b,e,l] | | 5[j] | 1[j] |
| Bureau 2017[6] | 27 | 27 | 6 | NA | 0.2/ month[k] | 17 | 11 | Change: 18.1 ± 30.3[b,f,l] | | NA | NA |
| Sola 2017[12] | 10 | 10 | 12 | 7.5/ 3 months[k] | 1.8/ 3 months[k] | 4 | 7 | 96.8[a,k] | 96.8[a,m,k] | 3 | 5 |
| Thomas 2015[23] | 10 | 10 | 12 | 3.4 ± 0.8/ month[b] | 0.4 ± 1.0/ month[b] | NA | 3 | 167.2 (88-246.4)[c,k] | 220 (105.6-422.4)[c,n,k] | NA | NA |
| Bellot 2013[5] | 40 | 40 | 6 | 3.4/ month[k] | 0.2/ month[k] | 16 | 11 | 106 ± 33[b] | 127 ± 59[b,g,l] | 13 | 3 |
| Karkhanis 2017[20] | 3 | 3 | 7 | 1.0 ± 0/ month[b] | 0.2 ± 0.2/ month[b] | 2 | 1 | 82 ± 33.2[b] | 88.6 ± 49.2[b,o] | 0 | 1 |
| Wong 2018[24] | 30 | 30 | 12 | 24.4 ± 16.0/ year[b,k] | 2.7 ± 4.6/ year[b,k] | 21 | 4 | NA | NA | 1 | 4 |
| Nair 2015[25] | 9 | 9 | NA | 3/ month | NA | 7 | NA | NA | NA | NA | NA |

| Authors | Overall pump-related complication (n patients) | Peritoneal catheter dysfunction (n patients) | Bladder catheter dysfunction (n patients) | Pump dysfunction (n patients) | Explantation for adverse events (n patients) | Pump replacement (n patients) | Pump pocket infection or wound dehiscence (n patients) | Access to liver transplantation (n patients) | Occurrence of hepatic encephalopathy (n patients) |
|---|---|---|---|---|---|---|---|---|---|
| Solbach 2018[21] | 15 | 6 | 4 | 4 | 4 | 2 | 2 | 4 | NA |
| Stirnimann 2017[22] | NA | 18 | 2 | 11 | 17 | 11 | 4 | 9 | NA |
| Bureau 2017[6] | 26 | 2 | 4 | 12 | 3 | 4 | 3 | 3 | 2 |
| Sola 2017[12] | 7 | 3 | 2 | 4 | 2 | 1 | 1 | NA | 6 |
| Thomas 2015[23] | NA | 0 | 1 | 1 | 1 | 0 | 3 | 1 | NA |
| Bellot 2013[5] | NA | 5 | 9 | 2 | 11 | NA | 4 | 5 | 13 |
| Karkhanis 2017[20] | 2 | 0 | 1 | 1 | 0 | 0 | 2 | 1 | NA |
| Wong 2018[24] | 22 | 3 | NA | 8 | 8 | 8 | NA | 1 | NA |
| Nair 2015[25] | 9 | NA | 3 | 3 | 1 | 2 | NA | NA | NA |

Abbreviations: LVP, large volume paracentesis; NA, not available.
[a]Expressed as median.
[b]Expressed as mean ± standard deviation.
[c]Expressed as median (min-max).
[d]Available in 11 patients.
[e]Available in 33 patients.
[f]Available in 23 patients.
[g]Available in 29 patients.
[h]Overall pump in situ time for 18 patients.
[i]As long as the pump was working properly.
[j]These patients had bacterial peritonitis or urinary tract infection leading to pump explantation; as the total number of patients presenting these adverse events were not specified, these numbers were not used in statistical analysis.
[k]These data were not included in statistical analyses, due to the unit used for this data or the absence of data for standard deviation, based on the requirements of meta-analysis.
[l]At 3 mo.
[m]At 1 mo.
[n]At 2 mo.
[o]At 15 d.

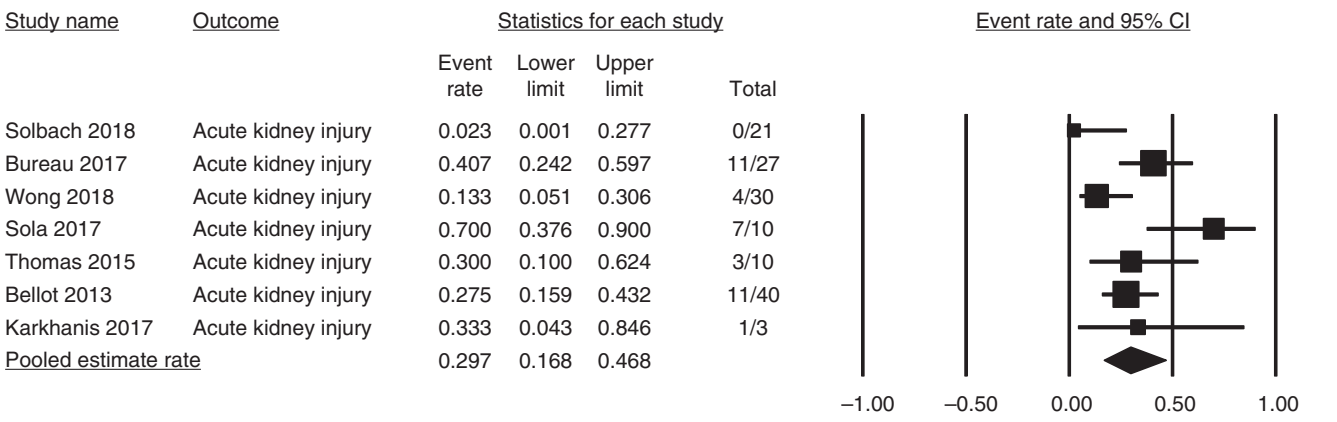


**FIGURE 3** Pooled estimate rate for acute kidney injury in patients with cirrhosis and refractory ascites treated with automated low-flow ascites pump therapy

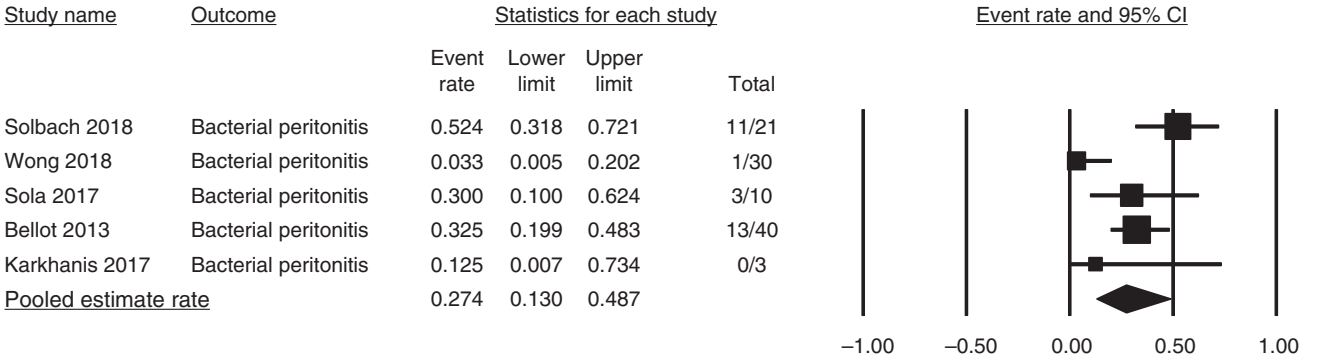


**FIGURE 4** Pooled estimate rate for bacterial peritonitis in patients with cirrhosis and refractory ascites treated with automated low-flow ascites pump therapy

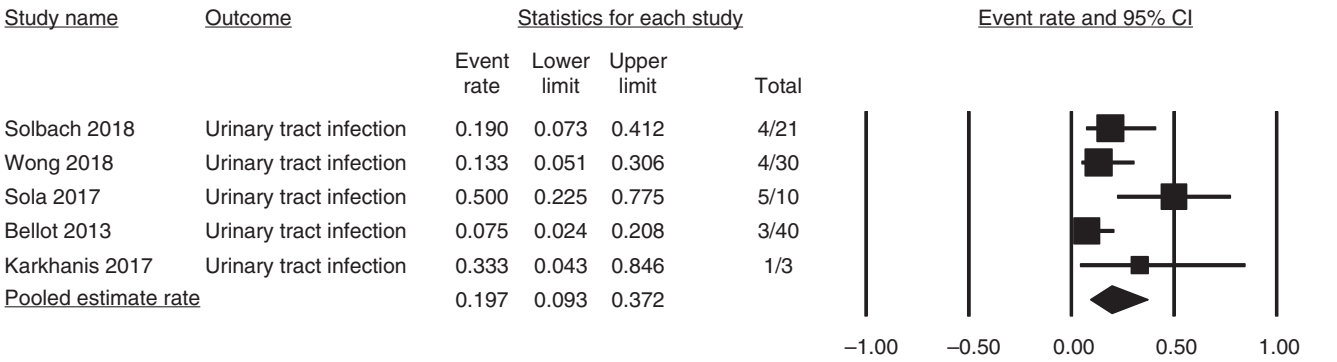


**FIGURE 5** Pooled estimate rate for urinary tract infection in patients with cirrhosis and refractory ascites treated with automated low-flow ascites pump therapy

Data on pump replacement were available for 166 patients. The pooled estimate rate for pump replacement was 0.18 (95% CI = 0.13-0.25, Table 2). There was no heterogeneity between studies ($P$ = .7, $I^2$ = 0%).

Data on pump pocket infection or wound dehiscence were available for 167 patients. The pooled estimate rate for pump pocket infection or wound dehiscence was 0.13 (95% CI = 0.07-0.22, Table 2). There was high-moderate heterogeneity between studies ($P$ = .17, $I^2$ = 34%). The results of sensitivity analyses excluding studies in which median or mean MELD score was >15 are provided in Table S2. These analyses did not eliminate heterogeneity between studies.

### 3.3.4 | Secondary endpoints—Pump placement feasibility, access to liver transplantation and occurrence of hepatic encephalopathy

Data on pump placement feasibility were available for 206 patients. The pooled estimate rate for pump placement feasibility was 0.97 (95% CI = 0.93-0.99, Table 2). There was no heterogeneity between studies ($P = .9$, $I^2 = 0\%$).

Data on access to liver transplantation were available for 187 patients. The pooled estimate rate for access to liver transplantation was 0.14 (95% CI: 0.10-0.20, Table 2). There was no heterogeneity between studies ($P = .6$, $I^2 = 0\%$).

Data on occurrence of hepatic encephalopathy were available for 77 patients. The pooled estimate rate for occurrence of hepatic encephalopathy was 0.29 (95% CI = 0.09-0.61). There was high heterogeneity between studies ($P = .01$, $I^2 = 78\%$). The results of sensitivity analyses excluding studies that included patients with MELD score> 15 are provided in Table S2. These analyses did not eliminate heterogeneity between studies.

## 4 | DISCUSSION

Despite the recent advances in patient care, many patients with cirrhosis still suffer from refractory ascites.[26,27] As only a limited number of patients with refractory ascites are eligible for TIPS, alternative therapies are needed. A number of reports have provided encouraging results for patients treated with automated low-flow ascites pump therapy. These individual publications address only a restricted number of patients. Hence, a meta-analysis was required to synthesise available data on the efficacy and safety of the automated low-flow ascites pump in this setting.

In this meta-analysis, 62% of patients did not require LVP after automated low-flow ascites pump insertion. In addition, the number of LVPs decreased by a mean of 2.1 per month. Even without a control group, these results strongly suggest that automated low-flow ascites pumps are effective in controlling ascites. One of the main concerns when considering the use of an automated low-flow ascites pump for the treatment of refractory ascites is related to safety issues. Of note, acute kidney injury is particularly dreaded because, as no compensatory albumin infusion is made in this setting, poor circulatory tolerance after pump insertion can occur. This is further supported by the observation of a marked increase in plasma renin activity and norepinephrine concentration after pump insertion.[12] However, only a nonsignificant increase in renin activity was observed in the Bureau's study.[6] As the number of patients in which renin activity was assessed was limited and as other studies did not provide data on renin activity, additional data are needed to better understand how changes in renin activity influence renal function over time. In the present meta-analysis, even if the definition of acute kidney injury was not uniform between studies, acute kidney injury occurred in 30% of patients. In the same vein, serum creatinine increased by a mean of 23 μmol/L. The time at which change in serum creatinine levels was assessed was not uniform across studies. As changes in serum creatinine were usually assessed more than 1 month after pump implantation, the increase in serum creatinine levels reflects more the long-term impact than the short-term impact on renal function. Other severe side effects as urinary tract infection and bacterial peritonitis, each occured in 20% and 27% of the patients respectively. These percentages indicate that infectious complications are frequent after pump insertion, a risk that should be taken into account when considering this therapy. However, these numbers must be put into context with regard to the percentages of infectious complications that would occur in patients with refractory ascites without the use of an automated low-flow ascites pump. As there was no control group in most studies included in the present meta-analysis, the exact rate of side effects directly related to the procedure has still to be determined. Regarding technical issues, the most common pump-related adverse events were dysfunction of the peritoneal catheter, bladder catheter dysfunction and pump pocket complications. Overall, 77% of the patients experienced at least one pumprelated adverse event, a frequency that has to be taken into account when considering low-flow ascites pump implantation in cirrhotic patients with refractory ascites. Of note, the rate of pump-related adverse events was not lower in the more recent publications, leading to the conclusion that a significant proportion of patients will still present with adverse events even if the automated low-flow ascites pump becomes more widely used in the future. However, it should be noted that, despite these drawbacks, liver transplantation was performed in 14% of patients, indicating that pump insertion does not contraindicate liver transplantation later on. However, patients in whom a pump is inserted are not usually candidates for liver transplantation.

This meta-analysis mainly included case series in which a single group was examined with no within-study comparisons. Among the nine studies included in this meta-analysis, only one was randomised and controlled.[6] This randomised controlled trial, which included 27 patients treated with the automated low-flow ascites pump, provided prospective data of high quality on the effectiveness and safety profile of the automated low-flow ascites pump in patients with refractory ascites. In addition, patients treated with the automated low-flow ascites pump also showed significantly improved Chronic Liver Disease Questionnaire scores compared with patients treated with standard of care, as reported in detail in a companion article focusing on the same study population.[28] Taken together, these articles provide evidence that the automated low-flow ascites pump improves patients' health-related quality of life as early as 1 month after treatment initiation and that this improvement was maintained during follow-up. However, although randomised controlled trials are considered the best way for assessing a treatment effect, this does not fully apply to patients with cirrhosis and refractory ascites treated with automated low-flow ascites pump for a number of reasons. First, blinding the therapeutic intervention would not be possible. Second, there is no satisfactory control group to compare to patients treated

with an automated low-flow ascites pump. Third, it is likely that patients who could be enrolled in a randomised trial would differ from the average patient seen in daily practice. Hence, the results from observational studies appear to be more relevant to clinical practice[29] and the need for randomised controlled trials comparing automated low-flow ascites pump to repeated LVP in patients with refractory ascites remains a subject of debate. In our view, randomised controlled trials would be best utilised for determining the usefulness of albumin infusions as well as the role of long-term antibiotics for the prevention of kidney injury and septic complications when automated low-flow ascites pump insertion is indicated. Subgroup analyses in patients who received albumin infusion and/or long-term antibiotic therapy would have been of interest. However, this was not feasible.

A classical limitation of meta-analysis is related to the presence of heterogeneity that may prevent making robust conclusions and recommendations. This suggests that a substantial proportion of the difference in the effect between studies may be explained not only by random sampling but because of true differences between studies. In this meta-analysis, moderate to high heterogeneity was found for several analyses, suggesting that other factors than those taken into account in these analyses may have influenced the outcomes. However, heterogeneity was often reduced or even disappeared in sensitivity analyses when studies in which median or mean MELD score was >15 were excluded. Specific data according to MELD score would be of interest. However, this information was not available. Of note, pooled event rates in sensitivity analyses were similar to those observed in overall analyses, which provide additional confidence in the study results. In addition, no publication bias was identified using the Egger test and the Begg and Mazumdar test. However, these tests are usually only used when at least 10 studies are included in the meta-analysis. Thus, the absence of publication bias cannot be affirmed. On the other hand, no significant heterogeneity was observed for several endpoints, suggesting a robust and reproducible effect. Another limitation of this meta-analysis is related to the limited quality of the included studies. Finally, available data did not allow us to assess the impact of the automated low-flow ascites pump on patient prognosis, nutritional status or quality of life.

In summary, this meta-analysis found that most patients with cirrhosis and refractory ascites treated with automated low-flow ascites pump are free of LVP after pump insertion. Complications following pump insertion, such as acute kidney injury, bacterial peritonitis and urinary tract infection, each occur in 20%-30% of patients. Additional studies are required to identify potential risk factors leading to a higher incidence of side effects and to define strategies aimed at reducing the incidence of side effects when insertion of a low-flow ascites pump is considered in patients with refractory ascites.

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