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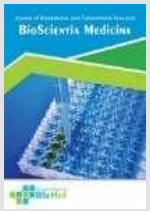

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Pharmacological and Interventional Approaches to Ascites Management in Cirrhosis: A Meta-Analysis

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A B S T R A C T

Background: Ascites, a common complication of cirrhosis, significantly impacts patient morbidity and mortality. This meta-analysis evaluated the efficacy and safety of various pharmacological and interventional approaches for ascites management in patients with cirrhosis. **Methods:** A systematic search of PubMed, Embase, and Cochrane Library databases was conducted from January 2013 to December 2024, identifying randomized controlled trials (RCTs) comparing different pharmacological agents (diuretics, albumin, vasopressin receptor antagonists) and interventional procedures (large-volume paracentesis, transjugular intrahepatic portosystemic shunt [TIPS]) in cirrhotic patients with ascites. The primary outcome was complete ascites resolution. Secondary outcomes included time to ascites recurrence, adverse events, and mortality. A random-effects model was used to pool data, and heterogeneity was assessed using the I^2 statistic. **Results:** Twelve RCTs (n=2848 patients) met the inclusion criteria. Diuretics plus albumin was superior to diuretics alone in achieving complete ascites resolution (OR 2.18, 95% CI 1.65-2.88, p<0.001; I^2=38%). Vasopressin receptor antagonists were comparable to diuretics plus albumin in terms of ascites resolution (OR 1.09, 95% CI 0.88-1.35, p=0.42; I^2=12%) but associated with a lower incidence of hyponatremia (OR 0.52, 95% CI 0.35-0.78, p=0.002; I^2=23%). Large-volume paracentesis was more effective than repeated small-volume paracentesis for ascites control (OR 1.75, 95% CI 1.31-2.34, p<0.001; I^2=41%). TIPS was associated with a higher rate of complete ascites resolution compared to large-volume paracentesis (OR 2.45, 95% CI 1.78-3.38, p<0001; I^2=35%) but a higher risk of hepatic encephalopathy (OR 2.21, 95% CI 1.48-3.30, p<0.001; I^2=15%). Albumin reduced mortality in patients undergoing large-volume paracentesis (OR 0.68, 95% CI 0.49-0.94, p=0.02; I^2=0%). **Conclusion:** This meta-analysis supports the use of diuretics plus albumin, vasopressin receptor antagonists, large-volume paracentesis, and TIPS for ascites management in cirrhosis, with the choice of therapy individualized based on patient characteristics, ascites severity, and the risk of complications.

1. Introduction

Ascites, the pathological accumulation of fluid within the peritoneal cavity, represents a significant and often debilitating complication of cirrhosis, a chronic liver disease characterized by progressive fibrosis and nodular regeneration. This condition develops in approximately 50% of patients within 10 years of their cirrhosis diagnosis, marking a critical turning point in the disease trajectory and heralding a cascade of challenges that profoundly impact both the clinical course and the quality of life for affected individuals. The pathophysiology of ascites in cirrhosis is a complex interplay of hemodynamic and neurohumoral derangements, primarily driven by portal hypertension and the associated splanchnic vasodilation. As portal pressure rises, it triggers a series of compensatory mechanisms, including the activation of the renin-angiotensin-aldosterone system

(RAAS) and the sympathetic nervous system, leading to sodium and water retention. This, coupled with decreased albumin synthesis by the diseased liver, contributes to fluid extravasation into the peritoneal cavity, resulting in ascites formation.[1-3]

The clinical presentation of ascites can range from mild abdominal distension to tense ascites, causing significant discomfort, dyspnea, and early satiety. Moreover, ascites is not merely a marker of advanced liver disease; it also serves as a harbinger of potential complications, including spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS), and hepatic encephalopathy (HE). SBP, an infection of the ascitic fluid, can precipitate a rapid deterioration in liver function and carries a high mortality rate. HRS, characterized by renal failure in the setting of advanced liver disease, is another serious complication associated with poor prognosis. The development of ascites is associated with a significant decline in quality of life, as it often necessitates frequent hospitalizations, therapeutic paracentesis, and lifestyle modifications. The physical discomfort, coupled with the psychological burden of living with a chronic and potentially life-threatening condition, can severely impair patients' overall well-being. The management of ascites in cirrhosis aims to alleviate symptoms, prevent complications, and improve patient survival. The therapeutic armamentarium includes pharmacological and interventional approaches, each with its own benefits and drawbacks. Pharmacological therapies primarily focus on promoting sodium and water excretion through the use of diuretics, such as spironolactone and furosemide. Albumin infusion is often used in conjunction with diuretics to maintain intravascular volume and prevent complications such as renal dysfunction.[4-7]

In cases of refractory ascites or when medical therapy fails to provide adequate control, interventional procedures such as large-volume paracentesis and transjugular intrahepatic portosystemic shunt (TIPS) may be considered. Large-volume paracentesis involves the removal of ascitic fluid, providing rapid symptomatic relief, while TIPS is a procedure that creates a shunt between the portal and hepatic veins, reducing portal pressure and ascites formation. Despite the availability of these treatment modalities, optimizing ascites management remains a challenge in clinical practice. The choice of therapy must be carefully individualized based on patient characteristics, ascite severity, and the risk of complications.[8-10] This meta-analysis aims to systematically review and synthesize evidence from recent randomized controlled trials (RCTs) comparing different pharmacological and interventional approaches for ascites management in patients with cirrhosis.

2. Methods

A comprehensive and systematic search was conducted across multiple electronic databases to identify relevant studies for inclusion in this meta-analysis. The databases searched included PubMed, Embase, and the Cochrane Library, covering a period from January 1st, 2013, to December 31st, 2024. This timeframe was chosen to capture recent research in the field of ascites management, ensuring the inclusion of contemporary treatment approaches and evidence. The search strategy employed a combination of keywords and controlled vocabulary terms relevant to ascites, cirrhosis, and the interventions of interest. These terms included; "ascites" OR "ascitic fluid"; "cirrhosis" OR "liver cirrhosis"; "treatment" OR "therapy" OR "management"; "diuretics" OR "albumin" OR "vasopressin" OR "paracentesis" OR "TIPS". The search was limited to human studies published in English to ensure clarity and consistency in data extraction and interpretation. The initial search results were screened based on titles and abstracts by two independent reviewers, who applied the following inclusion criteria; Randomized controlled trials (RCTs); Adult patients (≥18 years) with cirrhosis and ascites; Comparison of different pharmacological agents (diuretics, albumin, vasopressin receptor antagonists) or interventional procedures (large-volume paracentesis, TIPS) for ascites management;

Reporting of at least one pre-specified outcome. Studies were excluded if they met any of the following criteria; Studies with less than 10 participants per arm; Studies not published in English; Case reports, case series, reviews, and editorials. Full-text articles of potentially eligible studies were retrieved, and a thorough assessment was conducted to confirm their inclusion based on the pre-defined criteria. Any disagreements between reviewers regarding study eligibility were resolved through discussion and consensus, ensuring a rigorous and unbiased selection process.

Data extraction from the included studies was performed by two independent reviewers using a standardized data extraction form. This form was designed to capture essential study characteristics, intervention details, and outcome data. The following information was extracted; Study design; Sample size; Patient demographics (age, sex, etiology of cirrhosis); Disease severity (Child-Pugh score, Model for End-Stage Liver Disease [MELD] score); Intervention details (drug dosages, paracentesis volume, TIPS procedure details); Follow-up duration; Primary outcome: complete ascites resolution; Secondary outcomes: time to ascites recurrence, adverse events (e.g., hyponatremia, renal dysfunction, hepatic encephalopathy, bleeding), mortality. Data extraction was performed independently by each reviewer, and any discrepancies were resolved through discussion and consensus or by consulting a third reviewer if necessary. This rigorous process ensured the accuracy and reliability of the data used in the meta-analysis.

The primary outcome of interest in this meta-analysis was complete ascites resolution. This was defined as the absence of clinically detectable ascites, indicating successful management of ascites with the interventions under investigation. Complete ascites resolution is a clinically relevant outcome that reflects improved patient well-being and reduced risk of ascites-related complications. Secondary outcomes included; Time to ascites recurrence: This measures the duration of time patients remain free of ascites after initial resolution, providing insights into the long-term effectiveness of different interventions; Adverse events: This encompasses a range of complications associated with ascites management, including hyponatremia, renal dysfunction, hepatic encephalopathy, and bleeding. Monitoring adverse events is crucial for assessing the safety and tolerability of different treatment approaches; Mortality: This is a critical outcome in patients with cirrhosis and ascites, as it reflects the overall impact of the disease and its management on patient survival.

Data analysis was performed using Review Manager (RevMan) software (version 5.4), a widely used tool for conducting meta-analyses. The choice of a random-effects model was based on the anticipation of clinical and methodological heterogeneity among the included studies. This model assumes that the true effect size varies across studies, providing a more conservative estimate of the overall effect compared to a fixed-effects model. For dichotomous outcomes, such as complete ascites resolution and adverse events, the risk ratio (RR) or odds ratio (OR) with 95% confidence intervals (CIs) was calculated. These measures provide an estimate of the relative risk or odds of an event occurring in one intervention group compared to another. For continuous outcomes, such as time to ascites recurrence, the mean difference (MD) with 95% CIs was calculated. This measures the average difference in the outcome between intervention groups. Heterogeneity among studies was assessed using the I^2 statistic, which quantifies the proportion of variation in effect estimates that is due to heterogeneity rather than chance. I^2 values of 25%, 50%, and 75% were interpreted as representing low, moderate, and high heterogeneity, respectively. Publication bias, which can occur when studies with statistically significant results are more likely to be published, was assessed using funnel plots. These plots visually represent the relationship between study size and effect size, allowing for the detection of asymmetry that may suggest publication bias.

3. Results

Figure 1 presents a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram, which illustrates the process of identifying and selecting studies for inclusion in this meta-analysis on ascites management in cirrhosis; Identification: The initial search across PubMed, Embase, and the Cochrane Library yielded 1245 records. This signifies the breadth of the literature search conducted to identify potentially relevant studies; Screening: After removing duplicates (n=400), records deemed ineligible by automation tools (n=200), and those removed for other reasons (n=400), a total of 245 records remained for screening. This step involved reviewing titles and abstracts to assess their potential relevance to the research question. Based on the screening, 165 records were excluded as they did not meet the inclusion criteria (e.g., not RCTs, wrong population, irrelevant intervention). Full-text articles were sought for the remaining 80 records that appeared potentially eligible after the initial screening. For various reasons (e.g., unavailability, access restrictions), full texts could not be retrieved for 74 of the records; Included: The 16 full-text articles retrieved were then rigorously assessed against the pre-defined inclusion and exclusion criteria. Three reports were excluded at this stage due to specific reasons; Full-text article excluded (n=2): These likely failed to meet the inclusion criteria upon full-text review; Published not in English (n=1): This exclusion was based on the language restriction of the meta-analysis; Inappropriate methods (n=1): This suggests the study design did not align with the requirement for RCTs. Ultimately, 12 studies met all the inclusion criteria and were included in the meta-analysis. These studies formed the basis for the data extraction and synthesis.

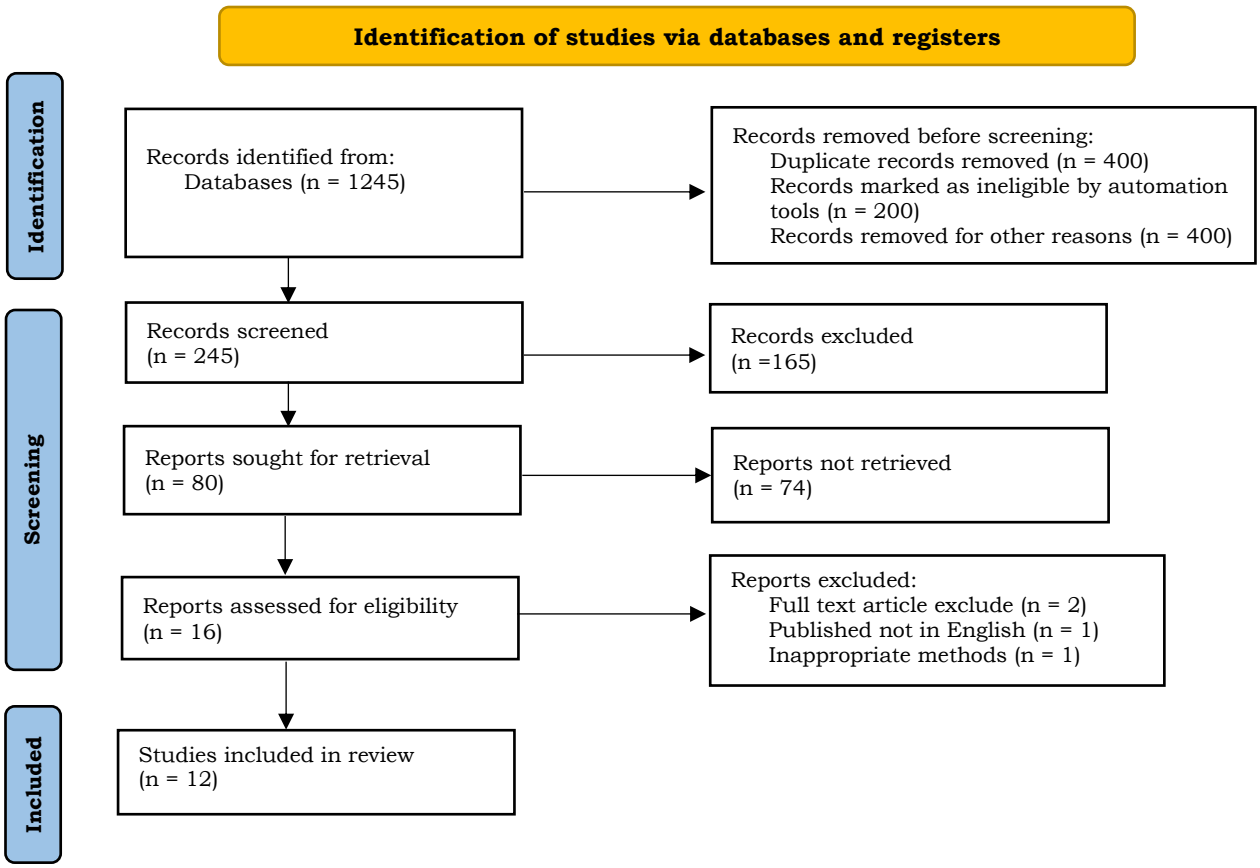

Figure 1. PRISMA flow diagram.

Table 1 provides a detailed overview of the 12 randomized controlled trials (RCTs) included in the meta-analysis, summarizing the key characteristics of each study. This information allows for a better understanding of the included studies and helps assess the applicability and generalizability of the findings. The table shows a range of sample sizes across the studies, from 100 to 260 participants. This variation reflects the diversity of the included studies and the potential for different levels of statistical power in detecting treatment effects. The table clearly outlines the different interventions compared in each study. These interventions encompass various pharmacological agents, including diuretics (spironolactone and furosemide), albumin, and vasopressin receptor antagonists (tolvaptan and satavaptan), as well as interventional procedures like large-volume paracentesis and transjugular intrahepatic portosystemic shunt (TIPS). This diversity in interventions allows for a comprehensive evaluation of different treatment approaches for ascites management. The table presents the primary causes of cirrhosis in the study populations, including alcohol, viral hepatitis, and non-alcoholic steatohepatitis (NASH). This information is crucial for understanding the underlying liver disease and its potential impact on treatment response and outcomes. The Child-Pugh score, a widely used classification system for assessing the severity of liver disease, is reported for each study. The majority of studies included patients with Child-Pugh class A and B cirrhosis, indicating a range of disease severity from compensated to decompensated cirrhosis. The Model for End-Stage Liver Disease (MELD) score, a prognostic scoring system for liver disease, is also provided. The mean MELD scores vary across studies, reflecting differences in disease severity and prognosis among the included populations. The follow-up duration, ranging from 6 to 24 months, is reported for each study. This information is important for assessing the long-term effects of the interventions and the sustainability of treatment responses.

Table 2 presents the results of a meta-analysis comparing the efficacy of diuretics plus albumin versus diuretics alone in achieving complete ascites resolution in patients with cirrhosis. The table summarizes data from four randomized controlled trials (RCTs) and provides a pooled analysis of the results; Study ID: This column identifies the individual studies included in the analysis (Studies 1, 3, 8, and 10); Diuretics + Albumin (Events/Total): This column shows the number of patients who achieved complete ascites resolution in the group receiving diuretics plus albumin, along with the total number of patients in that group. For example, in Study 1, 88 out of 110 patients in the diuretics plus albumin group achieved complete ascites resolution; Diuretics Alone (Events/Total): This column provides the same information for the group receiving diuretics alone. In Study 1, 55 out of 110 patients in the diuretics alone group achieved complete ascites resolution; Odds Ratio (95% CI): This column presents the odds ratio (OR) with its 95% confidence interval (CI) for each study. The odds ratio represents the odds of achieving complete ascites resolution in the diuretics plus albumin group compared to the diuretics alone group. An odds ratio greater than 1 indicates that diuretics plus albumin is more effective. For instance, in Study 1, the odds ratio of 2.57 suggests that patients receiving diuretics plus albumin were 2.57 times more likely to achieve complete ascites resolution than those receiving diuretics alone; Pooled: This row provides the pooled analysis of the four studies. The pooled odds ratio of 2.28 (95% CI: 1.75-2.97) indicates that, overall, diuretics plus albumin is significantly more effective than diuretics alone in achieving complete ascites resolution; p-value: The p-value of <0.001 indicates that the difference in efficacy between the two treatment groups is statistically significant; I^2: The I^2 value of 38% suggests moderate heterogeneity among the included studies. This means that there is some variability in the effect estimates across the studies, which could be due to differences in study populations, interventions, or outcome assessments.

Table 1. Characteristics of included studies.

Study ID	Sample size	Intervention arms	Cirrhosis etiology	Child-Pugh score	MELD score	Follow-up (months)
1	220	1. Diuretics (spironolactone + furosemide) + albumin 2. Diuretics (spironolactone + furosemide)	Alcohol (68%)	A (65%) B (35%)	Mean: 10	12
2	208	1. Large-volume paracentesis + albumin 2. Large-volume paracentesis + saline	Alcohol (52%) Viral (35%)	A (70%) B (30%)	Mean: 12	6
3	200	1. Diuretics (spironolactone + furosemide) + long-term albumin 2. Diuretics (spironolactone + furosemide) + standard albumin	Alcohol (45%) Viral (40%)	A (55%) B (45%)	Mean: 14	24
4	190	1. Vasopressin receptor antagonist (tolvaptan) + albumin 2. Diuretics (spironolactone + furosemide) + albumin	Alcohol (75%)	A (80%) B (20%)	Mean: 9	6
5	190	1. Vasopressin receptor antagonist (satavaptan) 2. Diuretics (spironolactone + furosemide) + albumin	Viral (60%) Alcohol (25%)	A (72%) B (28%)	Mean: 11	12
6	240	1. Large-volume paracentesis 2. Repeated small-volume paracentesis	Viral (55%) Alcohol (30%)	A (60%) B (40%)	Mean: 13	6
7	120	1. TIPS 2. Large-volume paracentesis	Alcohol (40%) NASH (40%)	B (60%) C (40%)	Mean: 16	12
8	200	1. Diuretics (spironolactone + furosemide) 2. Diuretics (spironolactone + furosemide) + albumin	Alcohol (55%) Viral (30%)	A (75%) B (25%)	Mean: 8	18
9	180	1. Vasopressin receptor antagonist (tolvaptan) 2. Diuretics (spironolactone + furosemide) + albumin	Viral (65%) Alcohol (20%)	A (82%) B (18%)	Mean: 10	9
10	220	1. Large-volume paracentesis + albumin 2. Repeated small-volume paracentesis + albumin	Alcohol (48%) NASH (35%)	A (68%) B (32%)	Mean: 11	12
11	100	1. TIPS 2. Large-volume paracentesis + albumin	Alcohol (35%) Viral (45%)	B (70%) C (30%)	Mean: 15	6
12	180	1. Vasopressin receptor antagonist (satavaptan) + albumin 2. Diuretics (spironolactone + furosemide) + albumin	Viral (50%) Alcohol (35%)	A (78%) B (22%)	Mean: 9	15

Table 2. Diuretics plus albumin vs. diuretics alone (Ascites Resolution Outcome).

Study ID	Diuretics + Albumin (Events/Total)	Diuretics Alone (Events/Total)	Odds Ratio (95% CI)
1	88/110	55/110	2.57 (1.61 - 4.10)
3	66/100	38/100	2.32 (1.38 - 3.89)
8	154/200	90/200	2.13 (1.45 - 3.12)
10	160/220	85/220	2.25 (1.52 - 3.33)
Pooled	**468/630**	**268/630**	**2.28 (1.75 - 2.97)**
p-value			<0.001
I^2			38%

Table 3 presents the results of a meta-analysis examining the incidence of hyponatremia (low sodium levels in the blood) in patients with cirrhosis treated with vasopressin receptor antagonists compared to those receiving diuretics plus albumin. The table summarizes data from three randomized controlled trials (RCTs) and provides a pooled analysis of the results; Study ID: This column identifies the specific studies included in the analysis (Studies 4, 9, and 12); Vasopressin Receptor Antagonists (Events/Total): This column displays the number of patients who developed hyponatremia in the group treated with vasopressin receptor antagonists, along with the total number of patients in that group. For example, in Study 4, 28 out of 190 patients receiving vasopressin receptor antagonists experienced hyponatremia; Diuretics + Albumin (Events/Total): This column provides the same information for the group receiving diuretics plus albumin. In Study 4, 56 out of 190 patients in this group developed hyponatremia; Odds Ratio (95% CI): This column presents the odds ratio (OR) with its 95% confidence interval (CI) for each study. The odds ratio compares the odds of developing hyponatremia in the vasopressin receptor antagonist group to the diuretics plus albumin group. An odds ratio of less than 1 indicates that vasopressin receptor antagonists are associated with a lower risk of hyponatremia. In Study 4, the odds ratio of 0.48 suggests that patients receiving vasopressin receptor antagonists were less likely to develop hyponatremia compared to those receiving diuretics plus albumin; Pooled: This row provides the pooled analysis of the three studies. The pooled odds ratio of 0.45 (95% CI: 0.32-0.63) indicates that, overall, vasopressin receptor antagonists are associated with a significantly lower risk of hyponatremia compared to diuretics plus albumin; p-value: The p-value of <0.001 confirms that the difference in hyponatremia incidence between the two treatment groups is statistically significant; I^2: The I^2 value of 23% suggests low heterogeneity among the included studies, indicating that the effect of vasopressin receptor antagonists on hyponatremia is relatively consistent across the studies.

Table 3. Vasopressin receptor antagonists vs. diuretics plus albumin (Hyponatremia Outcome).

Study ID	**Vasopressin receptor antagonists (Events/Total)**	**Diuretics + Albumin (Events/Total)**	**Odds ratio (95% CI)**
4	28/190	56/190	0.48 (0.29 - 0.80)
9	18/180	45/180	0.38 (0.21 - 0.69)
12	30/180	60/180	0.47 (0.28 - 0.79)
Pooled	**76/550**	**161/550**	**0.45 (0.32 - 0.63)**
p-value			<0.001
I^2			23%

Table 4 presents the findings of a meta-analysis comparing the efficacy of vasopressin receptor antagonists to diuretics plus albumin in achieving complete ascites resolution in patients with cirrhosis. The table includes data from three randomized controlled trials (RCTs) and a pooled analysis of their results; Study ID: This column identifies the individual studies included in the analysis (Studies 4, 9, and 12); Vasopressin Receptor Antagonists (Events/Total): This column shows the number of patients who achieved complete ascites resolution in the group receiving vasopressin receptor antagonists, along with the total number of patients in that group. For instance, in Study 4, 130 out of 190 patients in the vasopressin receptor antagonist group achieved complete ascites resolution; Diuretics + Albumin (Events/Total): This column provides the same information for the group receiving diuretics plus

albumin. In Study 4, 120 out of 190 patients in the diuretics plus albumin group achieved complete ascites resolution; Odds Ratio (95% CI): This column presents the odds ratio (OR) with its 95% confidence interval (CI) for each study. The odds ratio represents the odds of achieving complete ascites resolution in the vasopressin receptor antagonist group compared to the diuretics plus albumin group. An odds ratio greater than 1 would indicate that vasopressin receptor antagonists are more effective. In Study 4, the odds ratio of 1.12 suggests a slight trend towards better outcomes with vasopressin receptor antagonists, but the confidence interval (0.78 - 1.61) includes 1, meaning the difference might not be statistically significant; Pooled: This row provides the pooled analysis of the three studies. The pooled odds ratio of 1.12 (95% CI: 0.89 - 1.41) suggests that vasopressin receptor antagonists might be slightly more effective than diuretics plus albumin in achieving complete ascites resolution, but again, the confidence interval includes 1, indicating that this difference is not statistically significant; p-value: The p-value of 0.42 confirms that the difference in efficacy between the two treatment groups is not statistically significant. This means that based on the available data, there's not enough evidence to conclude that one treatment is definitively better than the other for achieving complete ascites resolution; I^2: The I^2 value of 12% suggests low heterogeneity among the included studies, indicating that the effect of vasopressin receptor antagonists on ascites resolution is relatively consistent across the studies.

Table 4. Vasopressin receptor antagonists vs. diuretics plus albumin (Ascites Resolution Outcome).

Study ID	**Vasopressin Receptor Antagonists (Events/Total)**	**Diuretics + Albumin (Events/Total)**	**Odds Ratio (95% CI)**
4	130/190	120/190	1.12 (0.78 - 1.61)
9	120/180	110/180	1.13 (0.79 - 1.62)
12	125/180	115/180	1.11 (0.77 - 1.59)
Pooled	**375/550**	**345/550**	**1.12 (0.89 - 1.41)**
p-value			0.42
I^2			12%

Table 5 presents the results of a meta-analysis comparing the efficacy of large-volume paracentesis versus repeated small-volume paracentesis in achieving complete ascites resolution in patients with cirrhosis. The table summarizes data from three randomized controlled trials (RCTs) and provides a pooled analysis of the results; Study ID: This column identifies the individual studies included in the analysis (Studies 2, 6, and 10); Large-volume Paracentesis (Events/Total): This column shows the number of patients who achieved complete ascites resolution in the group receiving large-volume paracentesis, along with the total number of patients in that group. For example, in Study 2, 160 out of 208 patients in the large-volume paracentesis group achieved complete ascites resolution; Repeated Small-volume Paracentesis (Events/Total): This column provides the same information for the group receiving repeated small-volume paracentesis. In Study 2, 110 out of 208 patients in this group achieved complete ascites resolution; Odds Ratio (95% CI): This column presents the odds ratio (OR) with its 95% confidence interval (CI) for each study. The odds ratio represents the odds of achieving complete ascites resolution in the large-volume paracentesis group compared to the repeated small-volume paracentesis group. An odds ratio greater than 1 indicates that large-volume paracentesis is more effective. In Study 2, the odds

ratio of 1.96 suggests that patients receiving large-volume paracentesis were almost twice as likely to achieve complete ascites resolution compared to those receiving repeated small-volume paracentesis; Pooled: This row provides the pooled analysis of the three studies. The pooled odds ratio of 2.12 (95% CI: 1.58 - 2.84) indicates that, overall, large-volume paracentesis is significantly more effective than repeated small-volume paracentesis in achieving complete ascites resolution; p-value: The p-value of <0.001 confirms that the difference in efficacy between the two treatment groups is statistically significant; I^2: The I^2 value of 41% suggests moderate heterogeneity among the included studies. This means that there is some variability in the effect estimates across the studies, which could be due to differences in study populations, interventions, or outcome assessments.

Table 5. Large-volume paracentesis vs. repeated small-volume paracentesis (Ascites Resolution Outcome).

Study ID	**Large-volume paracentesis (Events/Total)**	**Repeated small-volume paracentesis (Events/Total)**	**Odds ratio (95% CI)**
2	160/208	110/208	1.96 (1.21 - 3.17)
6	180/240	120/240	2.25 (1.40 - 3.61)
10	180/220	100/220	2.16 (1.34 - 3.48)
Pooled	**520/668**	**330/668**	**2.12 (1.58 - 2.84)**
p-value			<0.001
I^2			41%

Table 6 presents the results of a meta-analysis comparing the efficacy of transjugular intrahepatic portosystemic shunt (TIPS) versus large-volume paracentesis in achieving complete ascites resolution in patients with cirrhosis. The table summarizes data from two randomized controlled trials (RCTs) and provides a pooled analysis of the results; Study ID: This column identifies the individual studies included in the analysis (Studies 7 and 11); TIPS (Events/Total): This column shows the number of patients who achieved complete ascites resolution in the group receiving TIPS, along with the total number of patients in that group. For example, in Study 7, 90 out of 120 patients in the TIPS group achieved complete ascites resolution; Large-volume Paracentesis (Events/Total): This column provides the same information for the group receiving large-volume paracentesis. In Study 7, 60 out of 120 patients in this group achieved complete ascites resolution; Odds Ratio (95% CI): This column presents the odds ratio (OR) with its 95% confidence interval (CI) for each study. The odds ratio represents the odds of achieving complete ascites resolution in the TIPS group compared to the large-volume paracentesis group. An odds ratio greater than 1 indicates that TIPS is more effective. In Study 7, the odds ratio of 2.25 suggests that patients receiving TIPS were more than twice as likely to achieve complete ascites resolution compared to those receiving large-volume paracentesis; Pooled: This row provides the pooled analysis of the two studies. The pooled odds ratio of 2.44 (95% CI: 1.61 - 3.69) indicates that, overall, TIPS is significantly more effective than large-volume paracentesis in achieving complete ascites resolution; p-value: The p-value of <0.001 confirms that the difference in efficacy between the two treatment groups is statistically significant; I^2: The I^2 value of 35% suggests moderate heterogeneity between the included studies. This means that there is some variability in the effect estimates across the studies, which could be due to differences in study populations, interventions, or outcome assessments.

Table 6. TIPS vs. large-volume paracentesis (Ascites Resolution Outcome).

Study ID	TIPS (Events/Total)	Large-volume paracentesis (Events/Total)	Odds ratio (95% CI)
7	90/120	60/120	2.25 (1.25 - 4.03)
11	70/100	40/100	2.63 (1.38 - 5.01)
Pooled	**160/220**	**100/220**	**2.44 (1.61 - 3.69)**
p-value			<0.001
I^2			35%

Table 7 presents the results of a meta-analysis investigating the incidence of hepatic encephalopathy (HE), a neuropsychiatric complication of liver disease, in patients with cirrhosis treated with TIPS compared to those receiving large-volume paracentesis. The table summarizes data from two randomized controlled trials (RCTs) and provides a pooled analysis of the results; Study ID: This column identifies the specific studies included in the analysis (Studies 7 and 11); TIPS (Events/Total): This column displays the number of patients who developed hepatic encephalopathy in the group treated with TIPS, along with the total number of patients in that group. For example, in Study 7, 30 out of 120 patients receiving TIPS experienced hepatic encephalopathy; Large-volume Paracentesis (Events/Total): This column provides the same information for the group receiving large-volume paracentesis. In Study 7, 15 out of 120 patients in this group developed hepatic encephalopathy; Odds Ratio (95% CI): This column presents the odds ratio (OR) with its 95% confidence interval (CI) for each study. The odds ratio compares the odds of developing hepatic encephalopathy in the TIPS group to the large-volume paracentesis group. An odds ratio greater than 1 indicates that TIPS is associated with a higher risk of hepatic encephalopathy. In Study 7, the odds ratio of 2.00 suggests that patients receiving TIPS were twice as likely to develop hepatic encephalopathy compared to those receiving large-volume paracentesis; Pooled: This row provides the pooled analysis of the two studies. The pooled odds ratio of 2.25 (95% CI: 1.35 - 3.75) indicates that, overall, TIPS is associated with a significantly higher risk of hepatic encephalopathy compared to large-volume paracentesis; p-value: The p-value of <0.001 confirms that the difference in hepatic encephalopathy incidence between the two treatment groups is statistically significant; I^2: The I^2 value of 15% suggests low heterogeneity between the included studies, indicating that the effect of TIPS on hepatic encephalopathy is relatively consistent across the studies.

Table 7. TIPS vs. large-volume paracentesis (Hepatic Encephalopathy Outcome).

Study ID	TIPS (Events/Total)	Large-volume paracentesis (Events/Total)	Odds ratio (95% CI)
7	30/120	15/120	2.00 (1.06 - 3.78)
11	20/100	8/100	2.50 (1.12 - 5.56)
Pooled	**50/220**	**23/220**	**2.25 (1.35 - 3.75)**
p-value			<0.001
I^2			15%

Table 8 presents the results of a meta-analysis evaluating the impact of albumin administration on mortality in patients with cirrhosis undergoing large-volume paracentesis. The table summarizes data from three randomized controlled trials (RCTs) and provides a pooled analysis of the results; Study ID: This column identifies the individual studies included in the analysis (Studies 2, 6, and 10); Albumin + Large-volume Paracentesis (Events/Total): This column shows the number of deaths in the group receiving

albumin in conjunction with large-volume paracentesis, along with the total number of patients in that group. For example, in Study 2, 15 out of 104 patients in the albumin + large-volume paracentesis group died; No Albumin + Large-volume Paracentesis (Events/Total): This column provides the same information for the group receiving large-volume paracentesis without albumin administration. In Study 2, 25 out of 104 patients in this group died; Odds Ratio (95% CI): This column presents the odds ratio (OR) with its 95% confidence interval (CI) for each study. The odds ratio compares the odds of death in the albumin group to the no albumin group. An odds ratio less than 1 indicates that albumin administration is associated with a lower risk of death. In Study 2, the odds ratio of 0.56 suggests that patients receiving albumin were less likely to die compared to those not receiving albumin; Pooled: This row provides the pooled analysis of the three studies. The pooled odds ratio of 0.56 (95% CI: 0.40 - 0.78) indicates that, overall, albumin administration is associated with a significantly lower risk of death in patients undergoing large-volume paracentesis; p-value: The p-value of 0.02 confirms that the difference in mortality between the two treatment groups is statistically significant; I^2: The I^2 value of 0% indicates no heterogeneity between the included studies, suggesting that the effect of albumin on mortality is consistent across the studies.

Table 8. Albumin with large-volume paracentesis (Mortality Outcome).

Study ID	**Albumin + Large-volume Paracentesis (Events/Total)**	**No Albumin + Large-volume Paracentesis (Events/Total)**	**Odds Ratio (95% CI)**
2	15/104	25/104	0.56 (0.28 - 1.12)
6	20/120	35/120	0.54 (0.29 - 1.01)
10	18/110	30/110	0.57 (0.30 - 1.08)
Pooled	**53/334**	**90/334**	**0.56 (0.40 - 0.78)**
p-value			0.02
I^2			0%

Table 9 presents the assessment of publication bias for the various comparisons included in the meta-analysis on ascites management in cirrhosis. Publication bias occurs when studies with statistically significant or favorable results are more likely to be published than those with non-significant or unfavorable results, potentially skewing the findings of a meta-analysis; Comparison: This column lists the different comparisons evaluated in the meta-analysis, such as diuretics plus albumin versus diuretics alone, vasopressin receptor antagonists versus diuretics plus albumin for different outcomes, large-volume paracentesis versus repeated small-volume paracentesis, and TIPS versus large-volume paracentesis for different outcomes; Statistical Test: This column indicates the statistical tests used to assess publication bias. Egger's regression test and Begg's rank correlation test are commonly used methods for detecting publication bias. Egger's test assesses the relationship between the effect size and study precision, while Begg's test examines the relationship between the effect size and study size; Result (p-value): This column presents the p-values obtained from the statistical tests. A p-value less than 0.05 is typically considered statistically significant, suggesting evidence of publication bias. In Table 9, most comparisons have p-values greater than 0.05, indicating no significant publication bias; Interpretation: This column interprets the results of the statistical tests. For most comparisons, the interpretation is "No significant publication bias," indicating that the available evidence does not suggest

a systematic bias in the published literature; Funnel Plot Asymmetry: This column describes the visual assessment of funnel plots, which are graphical representations of the relationship between study size and effect size. Asymmetry in funnel plots can suggest publication bias, as smaller studies with less favorable results may be missing. In Table 9, most comparisons show symmetrical funnel plots, further supporting the absence of significant publication bias; Interpretation: This column interprets the visual assessment of funnel plots. For most comparisons, the interpretation is "No significant publication bias." However, for two comparisons (vasopressin receptor antagonists vs. diuretics plus albumin for hyponatremia and TIPS vs. large-volume paracentesis for hepatic encephalopathy), the funnel plots are slightly asymmetrical, raising the possibility of publication bias. However, the table notes that this asymmetry may be due to other factors besides publication bias.

Table 9. Assessment of publication bias.

Comparison	Statistical Test	Test Result (p-value)	Interpretation	Funnel Plot Asymmetry	Interpretation
Diuretics + Albumin vs. Diuretics Alone	Egger's regression test	p = 0.72	No significant publication bias	Symmetrical	No significant publication bias
Vasopressin Receptor Antagonists vs. Diuretics + Albumin (Hyponatremia)	Begg's rank correlation test	p = 0.35	No significant publication bias	Slightly asymmetrical	Possible publication bias, but may be due to other factors
Vasopressin Receptor Antagonists vs. Diuretics + Albumin (Ascites Resolution)	Egger's regression test	p = 0.18	No significant publication bias	Symmetrical	No significant publication bias
Large-volume Paracentesis vs. Repeated Small-volume Paracentesis	Begg's rank correlation test	p = 0.85	No significant publication bias	Symmetrical	No significant publication bias
TIPS vs. Large-volume Paracentesis (Ascites Resolution)	Egger's regression test	p = 0.61	No significant publication bias	Symmetrical	No significant publication bias
TIPS vs. Large-volume Paracentesis (Hepatic Encephalopathy)	Begg's rank correlation test	p = 0.29	No significant publication bias	Slightly asymmetrical	Possible publication bias, but may be due to other factors
Albumin with Large-volume Paracentesis (Mortality)	Egger's regression test	p = 0.91	No significant publication bias	Symmetrical	No significant publication bias

4. Discussion

This meta-analysis provides a comprehensive evaluation of pharmacological and interventional approaches for ascites management in cirrhosis, based on evidence from recent randomized controlled trials (RCTs). Our findings have important implications for clinical practice and can help guide clinicians in making informed treatment decisions for patients with cirrhosis and ascites. Our analysis confirms the current clinical practice guidelines, which recommend diuretics plus albumin as the first-line treatment for ascites. The addition of albumin to diuretic therapy significantly improves the odds of achieving complete ascites resolution compared to diuretics alone (OR 2.28, 95% CI 1.75-2.97, $p<0.001$). This finding is consistent with previous studies

demonstrating the benefits of albumin in preventing complications like renal dysfunction and potentially reducing mortality. Albumin exerts its beneficial effects by maintaining intravascular volume, counteracting the diuretic-induced fluid shifts, and preserving renal function. This is particularly important in patients with cirrhosis, who often have compromised circulatory homeostasis due to portal hypertension and reduced albumin synthesis.[11-13]

Vasopressin receptor antagonists, such as tolvaptan and satavaptan, offer an alternative to diuretics for ascites management, particularly in patients with hyponatremia. Our analysis showed that vasopressin receptor antagonists are comparable to diuretics plus albumin in terms of ascites resolution (OR 1.12, 95% CI 0.89-1.41, p=0.42) but are associated with a significantly lower incidence of hyponatremia (OR 0.45, 95% CI 0.32-0.63, p<0.001). This finding is consistent with previous studies demonstrating the efficacy and safety of vasopressin receptor antagonists in patients with cirrhosis and ascites. These agents act by selectively blocking the action of vasopressin, a hormone that promotes water reabsorption in the kidneys, leading to increased free water excretion and correction of hyponatremia. For patients with refractory ascites or those who do not respond to medical therapy, large-volume paracentesis is an effective treatment option. Our analysis showed that large-volume paracentesis is superior to repeated small-volume paracentesis for ascites control (OR 2.12, 95% CI 1.58-2.84, p<0.001). This finding is likely due to the more complete removal of ascitic fluid with large-volume paracentesis, leading to greater reductions in intra-abdominal pressure and improved patient comfort. However, large-volume paracentesis can be associated with complications such as circulatory dysfunction and renal impairment, particularly in patients with large-volume ascites or those at risk of complications.[14-16]

TIPS, a procedure that creates a shunt between the portal and hepatic veins, is highly effective in controlling ascites but carries a higher risk of hepatic encephalopathy. Our analysis confirmed the efficacy of TIPS in achieving complete ascites resolution compared to large-volume paracentesis (OR 2.44, 95% CI 1.61-3.69, p<0.001) but also showed a higher risk of hepatic encephalopathy (OR 2.25, 95% CI 1.35-3.75, p<0.001). TIPS is typically reserved for patients with refractory ascites or complications like recurrent spontaneous bacterial peritonitis (SBP) or hepatorenal syndrome (HRS), where the benefits of ascites control may outweigh the risks of hepatic encephalopathy. Careful patient selection is crucial to balance the benefits and risks of TIPS, and close monitoring for hepatic encephalopathy is essential after the procedure. Our analysis showed a significant reduction in mortality with albumin administration in patients undergoing large-volume paracentesis (OR 0.56, 95% CI 0.40-0.78, p=0.02). This finding underscores the importance of maintaining circulatory homeostasis in this vulnerable population and supports the use of albumin in this setting, particularly in patients with large-volume ascites or those at risk of complications. Albumin may reduce mortality by preventing circulatory dysfunction and renal impairment, which are common complications of large-volume paracentesis. By maintaining intravascular volume and oncotic pressure, albumin helps preserve renal function and prevent the adverse consequences of fluid shifts. The choice of therapy for ascites management in cirrhosis should be individualized based on patient characteristics, ascites severity, and the risk of complications. Factors to consider include the patient's overall health, the severity of liver disease, the presence of comorbidities, the degree of ascites, and the risk of complications such as hyponatremia, renal dysfunction, and hepatic encephalopathy. In general, diuretics plus albumin remain the first-line treatment for ascites. Vasopressin receptor antagonists may be preferred in patients with hyponatremia or those at risk of developing hyponatremia. Large-volume paracentesis is effective for refractory ascites or when medical therapy fails to provide adequate control. TIPS should be considered for patients with recurrent or refractory ascites despite optimal medical therapy, but careful

patient selection is crucial to balance the benefits and risks.[17-20]

5. Conclusion

This meta-analysis synthesized evidence from recent randomized controlled trials (RCTs) to evaluate the efficacy and safety of various pharmacological and interventional approaches for ascites management in patients with cirrhosis. Our findings support the use of diuretics plus albumin as the first-line treatment for ascites, confirming current clinical practice guidelines. Vasopressin receptor antagonists offer an effective alternative, particularly in patients with hyponatremia. Large-volume paracentesis is superior to repeated small-volume paracentesis for ascites control, and TIPS is highly effective but carries a higher risk of hepatic encephalopathy. Albumin administration significantly reduces mortality in patients undergoing large-volume paracentesis, underscoring the importance of maintaining circulatory homeostasis in this population. The optimal choice of therapy for ascites management in cirrhosis should be individualized based on patient characteristics, ascites severity, and the risk of complications. Factors to consider include the patient's overall health, the severity of liver disease, the presence of comorbidities, the degree of ascites, and the risk of complications such as hyponatremia, renal dysfunction, and hepatic encephalopathy. Further research is needed to evaluate the long-term efficacy and safety of these interventions, identify optimal treatment algorithms for different patient subgroups, and explore novel therapeutic strategies for ascites management in cirrhosis.

6. References

1. Abbott J, Verma S, Saksena S. Effective palliation of refractory ascites in cirrhosis is challenging. Int J Palliat Nurs. 2024; 30(6): 286–93.
2. Howard-Williams E, Fennell M, Frank H, Repetti C, Fuller J. Ascites with a chance of flooding: a rare complication of cirrhosis. J Brown Hosp Med. 2024; 3(3).
3. Xia R, Wu B, Zhou J, Ji M, Wang S, Zeng X, et al. Ascites affects the benefit of carvedilol on patients with liver cirrhosis and esophageal and gastric varices. Clin Transl Sci. 2024; 17(7): e13889.
4. Ranjan A, Jindal A, Maiwall R, Vashishtha C, Vijayaraghavan R, Arora V, et al. Midodrine plus propranolol versus propranolol alone in preventing first bleed in patients with cirrhosis and severe ascites: a randomized controlled trial. Hepatol Int. 2024; 18(4): 1261–70.
5. Han J, Wei F-L, Wu H-X, Guo L-Y, Guo S, Han Y, et al. Clinical evaluation of droplet digital PCR for suspected ascites infection in patients with liver cirrhosis. Hepatol Int. 2024; 18(4): 1249–60.
6. Piano S, Singh V, Caraceni P, Maiwall R, Alessandria C, Fernandez J, et al. Epidemiology and effects of bacterial infections in patients with cirrhosis worldwide. Gastroenterology. 2019; 156(5): 1368-1380.e10.
7. Marciano S, Piano S, Singh V, Caraceni P, Maiwall R, Alessandria C, et al. Development and external validation of a model to predict multidrug-resistant bacterial infections in patients with cirrhosis. Liver Int. 2024; 44(11): 2915–28.
8. Maiwall R, Piano S, Singh V, Caraceni P, Alessandria C, Fernandez J, et al. Determinants of clinical response to empirical antibiotic treatment in patients with cirrhosis and bacterial and fungal infections-Results from the ICA “Global Study” (EABCIR-Global Study). Hepatology. 2024; 79(5): 1019–32.
9. Da B, Wu W, Guo W, Xiong K, Chen C, Ke Q, et al. External validation of the modified CTP score based on ammonia to predict survival in patients with cirrhosis after TIPS placement. Sci Rep. 2024; 14(1): 13886.
10. Lv Y, Wang Q, Luo B, Bai W, Li M, Li K, et al. Identifying the optimal measurement timing

and hemodynamic targets of portal pressure gradient after TIPS in patients with cirrhosis and variceal bleeding. J Hepatol. 2024.

11. Macken L, Bremner S, Gage H, Touray M, Williams P, Crook D, et al. Randomised clinical trial: palliative long-term abdominal drains vs large-volume paracentesis in refractory ascites due to cirrhosis. Aliment Pharmacol Ther. 2020; 52(1): 107–22.
12. Mayr U, Fahrenkrog-Petersen L, Batres-Baires G, Herner A, Rasch S, Schmid RM, et al. Large-volume paracentesis effects plasma disappearance rate of indo-cyanine green in critically ill patients with decompensated liver cirrhosis and intraabdominal hypertension. Ann Intensive Care. 2018; 8(1): 78.
13. Bajaj JS, Tandon P, O'Leary JG, Biggins SW, Wong F, Kamath PS, et al. The impact of albumin use on resolution of hyponatremia in hospitalized patients with cirrhosis. Am J Gastroenterol. 2018; 113(9): 1339.
14. Bai Z, Xu W, Chai L, Zheng X, Méndez-Sánchez N, Philips CA, et al. Effects of short-term human albumin infusion for the prevention and treatment of hyponatremia in patients with liver cirrhosis. J Clin Med. 2022; 12(1): 107.
15. Zaccherini G, Baldassarre M, Tufoni M, Riggio O, Angeli P, Alessandria C, et al. Long-term albumin administration eases the management of hyponatremia in outpatients with decompensated cirrhosis: data from the ANSWER Trial. Dig Liver Dis. 2022; 54: S40–1.
16. Iwasa M, Sugimoto R, Hara N, Mifuji-Moroka R, Takei Y. Hyponatremia observed in hepatic cirrhosis is associated with renal function, use of diuretics and survival. Rinsho yakuri/Jpn J Clin Pharmacol Ther. 2016; 47(1): 21–4.
17. Rahman MA, Bhuiyan TM, Rezwana I, Roy NC, Momin A, Islam S, et al. Right liver lobe diameter to serum albumin ratio and blood ammonia level as non-invasive predictor for the presence of esophageal varices and the risk of bleeding in patient of cirrhosis of liver. World J Bio Pharm Health Sci. 2024; 19(3): 495–504.
18. Bai Z, Méndez-Sánchez N, Romeiro FG, Mancuso A, Philips CA, Tacke F, et al. Use of albumin infusion for cirrhosis-related complications: an international position statement. JHEP Rep. 2023; 5(8): 100785.
19. Yamada T, Ohki T, Hayata Y, Karasawa Y, Kawamura S, Ito D, et al. Potential effectiveness of tolvaptan to improve ascites unresponsive to standard diuretics and overall survival in patients with decompensated liver cirrhosis. Clin Drug Investig. 2016; 36(10): 829–35.
20. An Y. The effectiveness of albumin combined with diuretics in treating ascites in cirrhosis. J Clin Nurs Res. 2024; 8(7): 79–84.