A META-ANALYSIS ARTICLE

Tolvaptan Improves Refractory Ascites and Overall Survival in Cirrhosis: A Meta-Analysis

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ABSTRACT

Introduction: Refractory ascites is a frequent complication associated with liver cirrhosis. Tolvaptan, a V2-receptor antagonist, has shown effectiveness in improving refractory ascites. This meta-analysis sought to assess the effectiveness of tolvaptan in patients suffering from cirrhosis and refractory ascites.

Methods: Databases including Google Scholar, Cochrane, ClinicalTrials.gov, PubMed, and PubMed Central were systematically queried to search for papers from January 1, 2020, to August 10, 2023. Eligible publications for this study included all research evaluating body weight reduction and overall survival rates in patients with refractory ascites according to their response to tolvaptan. The meta-analysis included five studies, encompassing 530 patients with cirrhosis and refractory ascites who were treated with tolvaptan. Research characteristics were documented for all included studies, and outcomes were recorded for tolvaptan responders compared to non-responders.

Results: The statistical analysis revealed a significant weight reduction in tolvaptan responders in comparison to non-responders, with a risk ratio (RR) of 1.92 and a confidence interval (CI) of 1.12 to 3.31. The results of the heterogeneity analysis performed on the two outcomes, weight reduction and overall survival in tolvaptan responders, were I^2=84%, τ^2=0.1328, $p<0.01$, and I^2=86%, τ^2=0.6006, respectively.

Conclusion: The clinical application of tolvaptan improves symptoms in cirrhotic patients with refractory ascites, resulting in increased survival rates. Nonetheless, additional randomized controlled trials of a larger scale are necessary to validate the findings of this study, accurately predict the benefits of tolvaptan, and identify the patients who would derive the most benefit from its use.

Keywords: Cirrhosis; overall survival; refractory ascites; tolvaptan; human & health

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Highlights:

1. Our meta-analysis covers the most recent studies and confirms that tolvaptan improves survival rates in cirrhotic patients with refractory ascites, hence reducing morbidity and mortality.
2. Notable weight reduction is seen in patients with refractory ascites who respond to tolvaptan.

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INTRODUCTION

Ascites is among the most prevalent and significant complications of decompensated liver cirrhosis. As the disease advances, patients often develop refractory ascites, characterized by a lack of response to conventional diuretics or the emergence of severe side effects that prevent their continued use. Every year, ascites in approximately 5–10% of hospitalized patients eventually progress to refractory ascites (Singh et al., 2023). According to the guidelines of the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL), refractory ascites is defined as ascites that persists despite adherence to a sodium-restricted diet and treatment with high doses of diuretics, specifically daily doses of 160 mg of furosemide and 400 mg of spironolactone. Patients are also considered to have refractory ascites if they experience a rapid recurrence of ascites following therapeutic paracentesis. Diuretic therapy failure is characterized by the inability to maintain sufficient urinary sodium excretion (<78 mmol per day) or the onset of complications associated with diuretic use, such as hepatic encephalopathy, renal failure, or hyponatremia (Fortune & Cardenas, 2017). The initial assessment of patients with ascites includes a thorough review of their medical history and a comprehensive physical examination. Diagnostic tests involve abdominal Doppler ultrasonography, liver function tests (total bilirubin, international normalized ratio, and albumin), complete blood count, renal function tests (creatinine and blood urea nitrogen), serum and urine electrolytes (sodium, potassium, and magnesium), ascitic fluid analysis (serum-ascites albumin gradient (SAAG), total protein concentration, and polymorphonuclear

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leukocytes count and culture), and urine analysis with spot urine protein (Biggins et al., 2021).

The treatments of refractory ascites typically include limiting sodium intake and performing large-volume paracentesis (5 liters or more), accompanied by albumin infusions to mitigate the risk of paracentesis-induced circulatory dysfunction (Macken et al., 2022). Non-selective beta-blockers (Téllez & Albillos, 2022), transjugular intrahepatic portosystemic stent shunt (TIPSS) (Tripathi et al., 2020), and automated low-flow ascites pump (Wong et al., 2020) are among other medical interventions used for refractory ascites. Furthermore, tolvaptan is commonly used for the treatment of refractory ascites in cirrhotic patients. Tolvaptan belongs to the class of vasopressin V2-receptor antagonists. It exerts its pharmacological action by inhibiting vasopressin and causing downregulation of aquaporin, leading to aquaresis. It is a diuretic that inhibits water reabsorption without disturbing electrolyte excretion. Tolvaptan is frequently used to treat hyponatremia in patients with syndrome of inappropriate antidiuretic hormone secretion, heart failure, or other medical conditions (Bellos, 2021).

Recent studies suggest that tolvaptan may help treat refractory ascites in liver disease patients. Tolvaptan potentially can increase urine output, decrease body weight, and reduce fluid retention, leading to an overall waistline reduction. Various randomized and controlled trials have been conducted to determine the efficacy of tolvaptan in improving the symptoms of refractory ascites and enhancing overall patient survival (Arase et al., 2019; Tang et al., 2020; Tsuzuki et al., 2023).

A 2019 meta-analysis reported by Bellos et al. (2020) evaluated the effectiveness of tolvaptan in improving overall survival in patients with liver cirrhosis and refractory ascites. The study confirmed that the response to tolvaptan in patients with refractory ascites has a prognostic significance and is associated with improved overall survival. Additionally, the study also highlighted the need for large-scale future trials that consider patient comorbidities and concomitant medicines to study the effectiveness of tolvaptan. The current study aimed to gather additional evidence, specifically on whether tolvaptan use correlates with weight loss and overall survival improvement in cirrhotic patients with refractory ascites. While the 2019 study focused on survival as the primary outcome, this study expanded the scope by investigating the potential impact of tolvaptan on weight loss, an area previously under-researched.

METHODS

Systematic review and meta-analysis study design

The current study adhered to the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Muka et al., 2020). The selection criteria were established beforehand, with studies considered eligible if they directly assessed the impact of tolvaptan on the outcomes of patients with refractory ascites, categorized as responders and non-responders. The selection of studies occurred in three distinct stages. First, all titles and/or abstracts of electronic articles were screened for eligibility. The titles/abstracts that presumably met the selection criteria were retrieved in full text for a thorough review. Ultimately, the analysis included all observational studies, both prospective and retrospective, that documented the relevant outcomes. Small case series involving fewer than ten patients, case reports, meta-analyses, animal studies, conference abstracts, and review articles were excluded from the scope of this analysis. Any discrepancies related to article retrieval and/or statistical analyses were resolved through consensus among all authors involved in this study.

Literature search and data collection

A literature search was carried out using Google Scholar, PubMed, Cochrane Central Register, PubMed Central, and ClinicalTrials.gov. The search keywords “tolvaptan/vaptan in refractory” were utilized in Google Scholar, whereas “tolvaptan OR vaptan” AND “Refractory Ascites” were used for an advanced search in the remaining four databases (Tawfik et al., 2019). The literature search was performed to obtain papers from January 1, 2020, to August 10, 2023. Articles published from the year 2020 to the last search date were shortlisted for the study. A preliminary review was performed on each of the titles, and inclusions were subsequently determined, as exhibited in the PRISMA flow diagram (Figure 1).

Inclusion and exclusion criteria for this study

Studies testing the effect of tolvaptan against refractory ascites in comparison to conventional diuretics were included in this study. In addition, the meta-analysis included studies involving patients with liver cirrhosis and refractory ascites. This study covered clinical trials, prospective trials, and retrospective trials that had a population of no fewer than ten patients and utilized tolvaptan as the interventional drug of choice. Such studies were selected in which tolvaptan was active in improving patient survival, facilitating weight loss, and increasing urine output. In addition, studies comparing tolvaptan activity between responders and non-responders were selected. Excluded from the analysis were case reports, small case series with fewer than ten patients, conference abstracts, review articles, meta-analyses, and animal studies. Studies involving patients with heart failure were also excluded from the meta-analysis. Lastly, studies that did not fit the eligibility criteria and those lacking comparative data between responders and non-responders were excluded (Tawfik et al., 2019).

Indices investigated in this study

The data extracted from each study included the following aspects: the proportion of patients with hepatitis C or hepatocellular carcinoma, the name of the first author, serum sodium levels, mean age, study design, sample size, Child-Pugh score, blood urea nitrogen levels, year of publication, inclusion and exclusion criteria, concomitant medications, albumin levels, tolvaptan dose, and the definition of tolvaptan response (Tawfik et al., 2019). The outcomes of interest were ascites symptom improvement and overall patient survival. The discrepancies in data extraction were resolved by two independent reviewers. Titles containing "retracted" or "erratum" were omitted from consideration.

Terminological definitions for the analysis of the chosen studies

The analysis of refractory ascites was conducted according to its criteria outlined by the AASLD and EASL guidelines, which characterize it as unresponsive to a sodium-

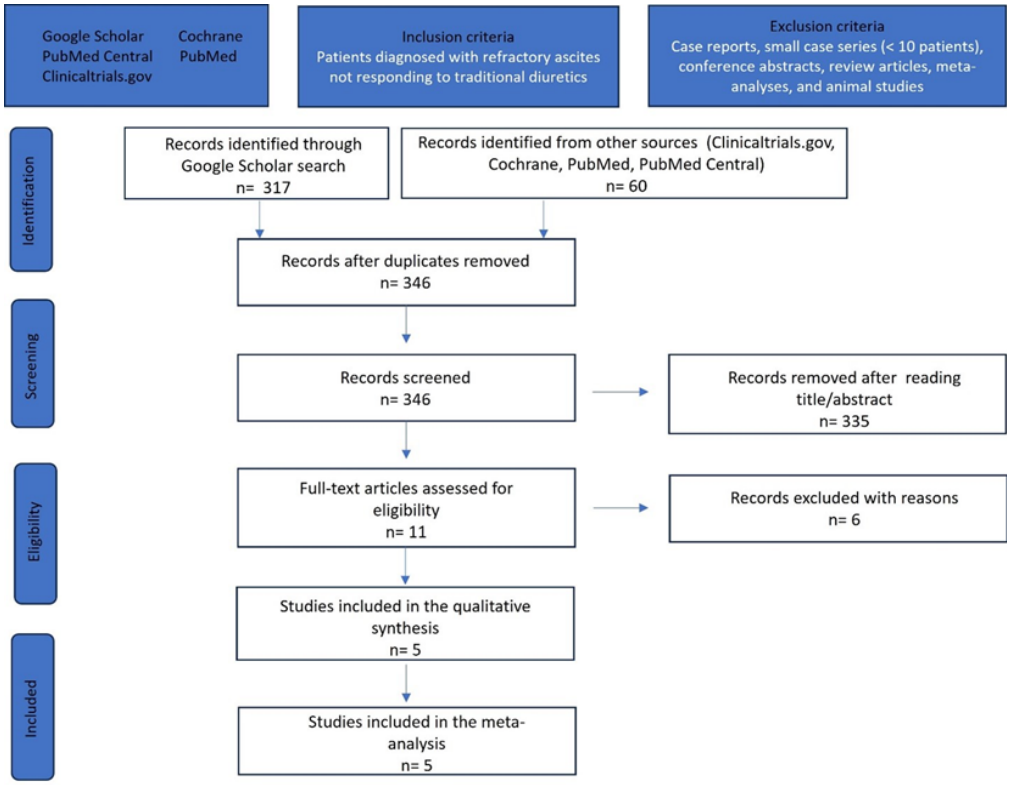

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the search strategy

restricted diet and high doses of diuretics, specifically 160 mg of furosemide and 400 mg of spironolactone daily. Furthermore, the patients were classified as having refractory ascites if they experienced a rapid recurrence of ascites following therapeutic paracentesis. Diuretic therapy failure was identified by the inability to sustain sufficient urinary sodium excretion (<78 mmol per day) or the onset of complications associated with diuretic use, such as hepatic encephalopathy, renal failure, or hyponatremia (Fortune & Cardenas, 2017).

A serum sodium level of <130 mmol/L indicated the occurrence of hyponatremia (Fortune & Cardenas, 2017). A large-volume paracentesis (LVP) was defined as the extraction of ascites above 5 L (Macken et al., 2022). A post-paracentesis rise in plasma renin activity, or paracentesis-induced circulatory dysfunction (PICD), manifested with an increase in plasma renin activity (PRA) occurring on the sixth day following paracentesis. This increase was considered significant when it exceeded 50% of the PRA value measured before the paracentesis and reached a level greater than 4 ng/mL/h (Kulkarni et al., 2020). This study categorized the research subjects as tolvaptan responders and non-responders. Tolvaptan responders were patients with a good response to tolvaptan, defined as a body weight reduction of more than 1.5 kg after seven days of starting tolvaptan therapy. On the other hand, tolvaptan non-responders were patients who did not show a body reduction above 1.5 kg following seven days of tolvaptan treatment.

Assessment of the quality of the selected studies

The quality of the included observational studies was evaluated using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) assessment tool (Sterne et al., 2016). Each study was assessed for risk of bias across the following seven domains: participant selection, outcome measurement, intervention classification, confounding, reported result selection, deviations from intended intervention, and missing data. A risk of bias assessment table was constructed, and a corresponding traffic light plot was also created. The tool was implemented by two independent reviewers, and any discrepancies were resolved through consensus among the authors.

Statistical analysis conducted on the selected studies

The R Statistical Software for Windows version 4.3.0 (R Core Team, 2023) was utilized for the statistical meta-analysis. The dependent variable of interest for the meta-analysis was the difference in weight loss between the tolvaptan responders and non-responders, regarded as a normally distributed variable. The studies provided enough information for weight reduction at a minimum of one timepoint and were thus included in the meta-analysis. A meta-analysis employing the random-effects model was performed, and forest plots were utilized to present the prediction interval for assessing certainty (Dettori et al., 2021).

The effect sizes were calculated using odds ratio/risk ratio models, along with a 95% confidence interval (CI). Anticipating significant heterogeneity due to the inclusion of studies employing different lines of therapy for ascites (i.e., diuretics, domiciliary albumin, midodrine, TIPSS), patient characteristics (e.g., Child-Pugh classification), and clinical settings, the overall statistical heterogeneity was quantified by the degree of inconsistency (I^2). If substantial heterogeneity was observed (I^2<25%), the fixed-effects model was typically favored. In instances of variability across the retrieved studies, the random-effects model was preferred to adjust for potential differences (Bell et al., 2019). Lastly, publication bias was assessed quantitatively

using Egger's regression intercept test and qualitatively by visually inspecting the symmetry of the funnel plot.

Registration of protocol for this study

This meta-analysis was recorded in the International Prospective Register of Systematic Reviews (PROSPERO), under a registration number CRD42023455316. This registration was implemented to prevent duplication as well as mitigate reporting bias (Schiavo, 2019).

RESULTS

Studies included for analysis in this study

This meta-analysis included five studies, comprising retrospective trials and prospective trials, conducted by Imai et al. (2021), Hosui et al. (2021), Osawa et al. (2022), Kawaratani et al. (2020), and Kanayama et al. (2020). The presence of refractory ascites was a prerequisite for all five included studies. The study reported by Imai et al. (2021) involved 32 patients with spontaneous bacterial peritonitis, cirrhosis, refractory ascites, and untreated hepatocellular carcinoma. In the remaining four studies, there were 555 patients with refractory ascites resulting from decompensated liver cirrhosis. Therefore, this meta-analysis included a total of 587 patients. Out of the 587 patients, 530 were given tolvaptan as an intervention, while 57 received placebo. Some of the patients also continued the prior treatment with conventional diuretics, spironolactone, and furosemide. A favorable response to tolvaptan was defined as a body weight reduction exceeding 1.5 kg after seven days of tolvaptan therapy. The most preferred dose of tolvaptan was found to be 7.5 mg, with a range of 3.75 to 7.5 mg. The detailed characteristics of the selected studies are shown in Table 1. The baseline characteristics of the patients, including albumin levels, serum sodium levels, Child-Pugh score, and the presence of hepatitis C or hepatocellular carcinoma, are presented in Table 2.

Studies excluded from this meta-analysis

Six studies conducted by Tang et al. (2020), Tsuzuki et al. (2023), Hirooka et al. (2022), Adachi et al. (2020), Suzuki et al. (2021), and Kudo et al. (2021) were excluded upon reviewing the full text. The study by Hirooka et al. (2022) analyzed cisterna chyli as an indicator of tolvaptan response, without measuring the improvement in ascites symptoms. Adachi et al. (2020) conducted the study to estimate the predictiveness of vascular stricture-related markers with regard to the early response of tolvaptan. The study by Tang et al. (2020)could not establish a definitive response regarding the efficacy of tolvaptan. Two studies, carried out by Tsuzuki et al. (2023) and Suzuki et al. (2021), were excluded as they did not directly compare tolvaptan responders to non-responders. The study by Kudo et al. (2021) was omitted due to its focus on the dose escalation of tolvaptan rather than the comparison between responders and non-responders.

Quality of the included studies according to the risk of bias

The quality assessment of the studies included in this meta-analysis was determined using the ROBINS-I tool, as exhibited in Table 3. A low to moderate risk of bias was observed for all included studies. Two studies, conducted by Osawa et al. (2022) and Kanayama et al. (2020), indicated a moderate risk of overall bias. The three remaining studies demonstrated a low risk of overall bias (Kawaratani et al., 2020; Hosui et al., 2021; Imai et al., 2021). Figure 2 displays the traffic light plot representing the results of the bias risk assessment across seven domains. The primary source of bias stemmed from outcome measurement, as assessors were aware of the intervention administered to the study group. In addition, missing data might have contributed to the risk of bias, mainly due to the lack of data from all the patients enrolled in the studies.

Table 1. Characteristics of the selected studies

Studies (author, year)	Study designs	Inclusion criteria	Exclusion criteria	Response definition	Tolvaptan dose (mg/day)	Co-interventions
Imai et al. (2021)	Single-center retrospective study	Cirrhosis, refractory ascites, and untreated HCC	Lack of follow-up data within a week	A weight loss of ≥1.5 kg within the first week	3.75–7.50	Furosemide and spironolactone
Hosui et al. (2021)	Retrospective observational clinical study	Refractory ascites	NR	A weight loss of ≥1.5 kg within the first week	3.75–7.5	Furosemide
Osawa et al. (2022)	Retrospective observational study	Liver cirrhosis and refractory ascites	Gastrointestinal bleeding, spontaneous bacterial peritonitis, and heart failure	A weight loss of ≥1.5 kg within the first week	3.75–7.5	Furosemide and spironolactone
Kawaratani et al. (2020)	Prospective single-arm multicenter study	Liver cirrhosis and refractory ascites	Hepatic encephalopathy (West Haven grade II or higher) (16); vascular invasive in HCC, esophageal or gastric varices necessitating treatment, repeated hemorrhoidal bleeding due to rectal varices, CHF, and anuria or impaired urination (10); a history of cerebrovascular disorders; hemoglobin levels of <8.0 g/dl, total serum sodium levels of <120 or >147 mEq/L, or serum potassium levels of >5.5 mEq/L; inability to take oral medication; and patients adjudged by the investigator to be inappropriate for inclusion in the study	A weight loss of ≥1.5 kg within the first week	3.75–7.5	Furosemide and spironolactone
Kanayama et al. (2020)	Retrospective study	Refractory ascites	Peritoneovenous shunt placement, intermittent abdominal drainage, discontinued tolvaptan treatment, and patients without appropriate follow-up	A weight loss of ≥1.5 kg within the first week	3.75–7.5	NR

Notes: HCC=hepatocellular carcinoma; CHF=congestive heart failure; NR=not reported.

Table 2. Baseline characteristics of patients with refractory ascites

Studies	Research subjects	n	Mean age (age range)	Child-Pugh scores	Child-Pugh class (B/C)	HCC	HCV	BUN (mg/dL)	Serum sodium (mEq/L)	Serum albumin (g/dL)
Imai et al. (2021)	Tolvaptan responders vs. non-responders	15 vs. 17	74 (47–86)	10 (8–12) vs. 10 (8–13)	6/9 vs. 5/12	NR	6	26.3 (13.6–68.8) vs. 27.0 (11.9–80.2)	135 (126–143) vs. 132 (125–143)	2.5 (1.9–3.3) vs. 2.5 (1.8–3.6)
Hosui et al. (2021)	Tolvaptan group vs. conventional treatment group	98 vs. 51	72.6±10.4	8.7±1.3 vs. 8.8±1.3	83/66 vs. 31/26	41 vs. 19 (previous history), 8 vs. 3 (first six months), 89/60 vs. 33/24 (presence or absence)	NR	26.0±18.9 vs. 20.1±11.9	134.3±3.9 vs. 137.1±2.4	2.69±0.45 vs. 2.79±0.42
Osawa et al. (2022)	Tolvaptan responders	101	72 (36–93)		111/85	114	89 (45.4)	23.12±13.82	136.06±4.97	NR
Kawaratani et al. (2020)	Tolvaptan responders	49	68.8±11.5 (34–85)	10.1±1.7	33/36	29 (42.0%)	NR	NR	NR	NR
Kanayama et al. (2020)	Tolvaptan responders vs. non-responders	55 vs. 29	73 (29–93) vs. 71 (35–90)		A: 2, B: 26, and C: 27 vs. A: 0, B: 18, and C: 11	27 (49.1%) vs. 18 (62.1%)	NR	NR	136 (127–143) vs. 136 (120–145)	2.6 (1.7–3.8) vs. 2.8 (1.8–3.5)

Notes: HCC=hepatocellular carcinoma; HCV=hepatitis C virus; BUN=blood urea nitrogen; NR=not reported.

Table 3. Results of the bias risk assessment using the ROBINS-I tool

Studies	Bias due to confounding	Bias in participant selection	Bias in intervention classification	Bias due to deviations from intended interventions	Bias due to missing data	Bias in outcome measurement	Bias in reported result selection	Overall
Imai et al. (2021)	Low	Low	Low	Low	Moderate	Low	Low	Low
Hosui et al. (2021)	Low	Low	Low	Low	Low	Moderate	Low	Low
Osawa et al. (2022)	Low	Moderate	Low	Low	Low	Moderate	Low	Moderate
Kawaratani et al. (2020)	Low	Low	Low	Low	Low	Moderate	Low	Low
Kanayama et al. (2020)	Low	Moderate	Low	Low	Moderate	Moderate	Low	Moderate

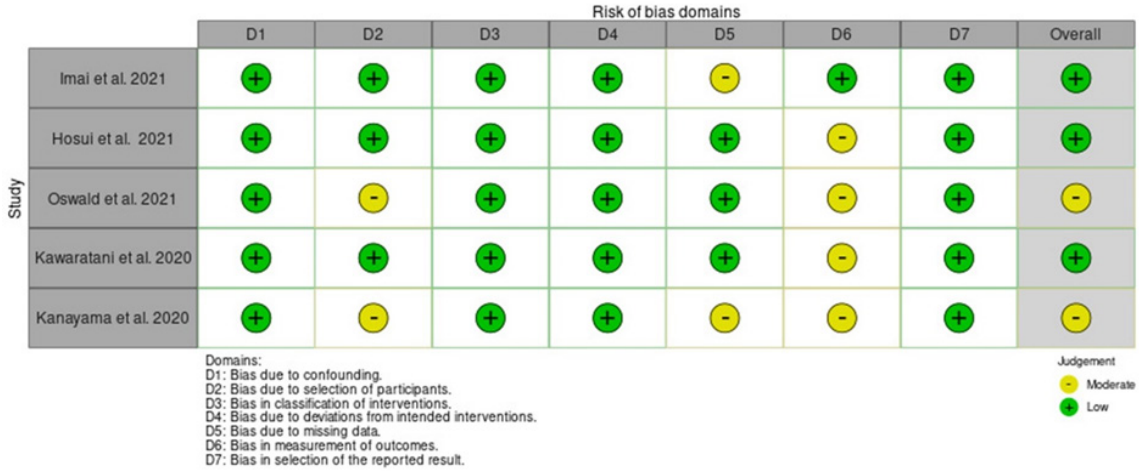

Figure 2. Traffic light plot showing the results of the ROBINS-I assessment

Results of the statistical analysis

The reduction in body weight among the tolvaptan responders was found to be statistically significant as compared to the non-responders (RR=1.47, CI=1.29–1.67). Furthermore, the studies exhibited significant heterogeneity (I^2=84%, τ^2=0.1328, p<0.01). The statistical analysis of overall survival rates indicated that the tolvaptan responders had a statistically significant survival advantage over non-responders (p<0.01). The heterogeneity for this aspect was also found to be significant (I^2=86%, τ^2=0.6006).

DISCUSSION

Currently, large-volume paracentesis with albumin substitution is the primary treatment for refractory ascites. Albumin substitution is crucial to prevent paracentesis-induced circulatory dysfunction, the main complication of large volume paracentesis. However, recent studies point out the necessity of assessing individual patient risk and characteristics, advocating for a personalized treatment strategy (Vidal-González et al., 2022; Will et al., 2022).

The pathogenesis of refractory ascites is multifactorial, involving substantial hemodynamic alterations induced by portal hypertension, leading to sodium retention and renal hypoperfusion. Due to portal hypertension, there is increased resistance to blood flow in the liver, which causes elevated hepatic sinusoidal pressure and contributes to the development of ascites. Despite the available treatment options at the present time, liver transplantation remains the ultimate choice to improve patient survival (Macken et al., 2022; Will et al., 2022). Although guidelines recommend the use of nonspecific beta blockers for the treatment of

liver cirrhosis with refractory ascites, the safety of these agents in the patients is still under debate. A prospective controlled trial identified the mechanism by which beta-blockers may hinder survival in patients with refractory ascites (Kasztelan-Szczerbinska & Cichoz-Lach, 2019; Téllez et al., 2020). There is significant debate about the effects of beta-blockers on the outcomes of patients with decompensated cirrhosis and ascites (Li et al., 2017).

Tolvaptan has been found to be effective for treating refractory ascites, owing to its capacity to induce diuresis without causing electrolyte imbalance. Prior research suggests that tolvaptan can cause weight reduction, in addition to increasing urine output and sodium concentration, without posing serious adverse effects in patients (Li et al., 2017). Tolvaptan has demonstrated a significant prognostic impact on improving overall survival in cirrhotic patients with refractory ascites. However, this finding requires validation through additional investigations on a larger scale. The identification of biomarkers to accurately predict the extent of tolvaptan response in patients will help determine the patients that may benefit from its treatment (Bellos et al., 2020). A thorough evaluation of recent data from tolvaptan trials is required to ascertain the qualitative evidence regarding the efficacy and safety of the medication for patients with end-stage liver cirrhosis and refractory ascites. The development of refractory ascites in cirrhotic patients significantly affects their survival and quality of life. There is growing evidence showing the efficacy of tolvaptan in managing ascites resistant to conventional diuretics (Adebayo et al., 2019; Larrue et al., 2021). In this meta-analysis, a favorable response was observed in all tolvaptan groups irrespective of the presence of other comorbidities, such as cancer. Tolvaptan may improve symptoms even in patients with refractory ascites complicated by hepatocellular carcinoma (Imai et al., 2021).

Research indicates that the two-year survival rate for patients with cirrhosis following the development of ascites is nearly 50%. In addition, the survival rate for cirrhotic patients after the development of refractory ascites is 50% after six months and 25% at one year (Lan et al., 2024). Our meta-analysis confirmed that the one-year survival rate for tolvaptan responders was significantly greater than that of non-responders ($p<0.01$), as shown in Figure 3. The use of tolvaptan was associated with substantial survival improvement.

A reduction in body weight is one of the key markers that indicate the effectiveness of tolvaptan. Our meta-analysis showed that the reduction in body weight in response to tolvaptan therapy is independent of other severe comorbidities, including hepatocellular carcinoma. Out of 530 patients treated with tolvaptan, 318 individuals demonstrated a body weight reduction of more than 1.5 kg after one week of treatment. Of the 318 tolvaptan responders, 15 individuals had untreated hepatocellular carcinoma. Moreover, hyponatremia is among the most prevalent electrolyte abnormalities observed in patients with advanced cirrhosis (John & Thuluvath, 2015). It is considered a fatal complication of conventional diuretic therapy, especially for thiazide diuretics (Sterns, 2018). Because of these complications, tolvaptan is often recommended for refractory ascites patients with hyponatremia (Wang et al., 2022). According to the findings of this meta-analysis, tolvaptan could improve the

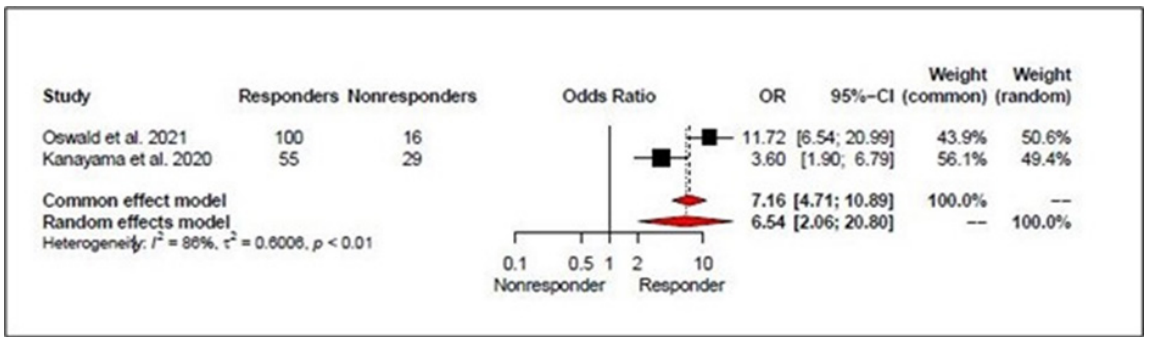

Figure 3. Forest plot illustrating the overall survival rate of tolvaptan responders compared to non-responders

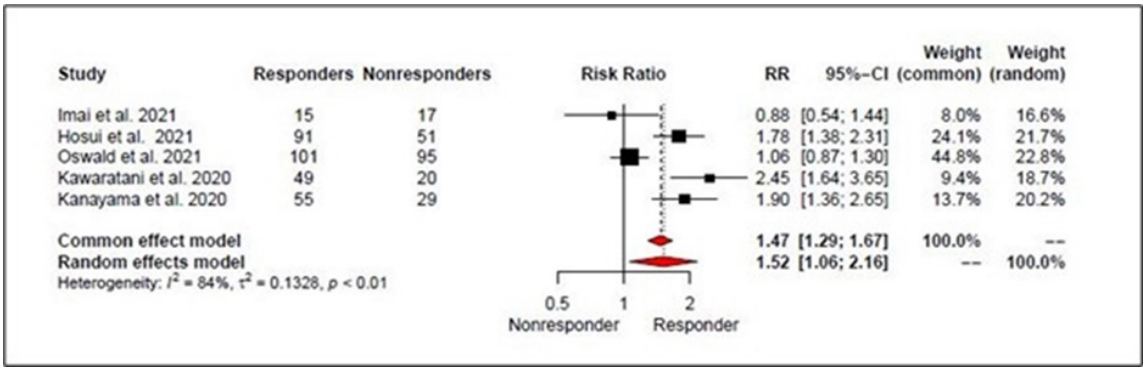

Figure 4. Forest plot showing the weight reduction in tolvaptan responders compared to non-responders

symptoms of refractory ascites without causing electrolyte imbalance in patients with hyponatremia. Tolvaptan could also help elevate sodium levels in hyponatremia patients.

Two of the five included studies reported adverse effects in patients following the initiation of tolvaptan treatment. In one of the studies including 147 patients treated with tolvaptan, 8.7% experienced thirst, 5.3% suffered from general fatigue, and 4.0% exhibited loss of appetite (Hosui et al., 2021). In another study, of the 196 patients treated with tolvaptan, eight stopped the treatment within one week of therapy due to adverse effects. Six patients discontinued the treatment due to renal dysfunction, one due to hypernatremia, and another one due to hepatic encephalopathy (Osawa et al., 2022).

In this meta-analysis, we incorporated data from multiple studies on weight reduction following seven days of tolvaptan treatment and survival rates after one year. Each of the included studies accounted for the presence of complications, such as spontaneous bacterial peritonitis and untreated hepatocellular carcinoma, providing a comprehensive overview of the individual research. Similar outcomes were measured across all studies, and the findings were synthesized to provide a thorough summary of available evidence regarding tolvaptan response and efficacy. Statistical analysis was also performed to determine the significance of the tolvaptan response and study outcome, thereby offering a complete interpretation of the results from the systemic search.

This study gathered recent evidence on the effectiveness of tolvaptan for refractory ascites treatment. Studies employing an identical tolvaptan response definition were included in the analysis to reduce bias. However, the inherent heterogeneity among the included trials might be a limitation of this study. The heterogeneity was found to be 84% for weight reduction and 86% for patient survival, as illustrated by forest plots in Figures 3 and 4. A heterogeneity of more than 50% is considered substantial. Furthermore, the majority of the studies included in this meta-analysis were observational and retrospective in nature. Hence, the potential bias arising from missing data could not be definitively ruled out and might impact the outcome of the analysis. Moreover, conventional diuretics were continued along with tolvaptan in most of the included studies. Analyzing tolvaptan alone might hinder the attainment of more accurate results concerning its efficacy. The reviewed studies did not include data on the Model for End-Stage Liver Disease (MELD) score or transplant-free survival in cirrhosis patients.

The findings from this meta-analysis indicated that patients with refractory ascites who responded to tolvaptan treatment had significantly improved overall survival rates. Achieving effective body weight loss, defined as a short-term clinical response, is considered a crucial prognostic factor. However, it should be noted that the present meta-analysis included observational studies. Large-scale, multicenter, randomized controlled trials are warranted to limit the possible biases due to patient selection. The current meta-analysis suggests analyzing more homogenous studies and trials to obtain stronger outcomes. In addition, studies measuring long-term response to tolvaptan in refractory ascites are required. Studies measuring long-term overall survival outcomes and improved quality of life are also necessary to consolidate the clinical application of tolvaptan in refractory ascites. Randomized controlled trials that incorporate data on the MELD score and transplant-free survival before and after tolvaptan treatment may yield a clear picture regarding tolvaptan efficacy.

CONCLUSION

The use of tolvaptan in clinical practice offers symptomatic improvement for patients with refractory ascites. Tolvaptan exhibits effectiveness in causing weight reduction as stand-alone therapy or in combination with conventional diuretics. Its administration also demonstrates improved survival time as compared to non-responders. However, trials investigating the long-term impact of tolvaptan on survival are warranted. Tolvaptan is shown to be safe and effective in patients who suffer from refractory ascites and hyponatremia, improving refractory ascites symptoms without inducing electrolyte imbalances. As most of the studies included in this meta-analysis were non-randomized trials, more large-scale randomized trials are required to support these claims, reduce the possible risk of bias due to participant selection, and provide a cohesive conclusion.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTION

All authors have contributed to all processes in this research, including preparation, data gathering and analysis, as well as drafting and approval of the article publication. CRK was involved in the conception and design of the study, the analysis and interpretation of the data, and the drafting of the article. HJ contributed to the critical revision of the article for important intellectual content, provided final approval of the article, and supplied study materials or patients. SZ offered statistical expertise, secured funding for the study, and provided administrative, technical, or logistic support. MP contributed to the collection and assembly of the data, the conception and design of the study, and the analysis and interpretation of the data.

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