

The Effect of Long-Term Human Albumin Administration on the Mortality of Adult Patients with De Compensated Liver Cirrhosis: A Meta-Analysis and Systematic Review

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1. Abstract

1.1. Introduction: Liver disease accounts for approximately 2 million deaths per year worldwide, 1 million due to complications of cirrhosis. Mortality trends in cirrhosis have been increasing in the Philippines; data from 1990 to 2010 showed that there has been an overall increase of mortality by 53.7%. One of the promising treatment options for patients with cirrhosis is the use of human albumin. One postulated mechanism states that the common hallmark in the pathophysiology of complications of advanced cirrhosis is circulatory dysfunction. Based on this pathophysiological basis, targeting circulatory dysfunction appears to be a promising therapeutic approach to decrease the development of complications, which would then lead to a decrease in mortality. Besides its oncotic properties, albumin may exert other biological properties such as antioxidant, improvement of endothelial function and immuno modulatory effects that may be also useful for the prevention of complications of cirrhosis.

1.2. Objective: To determine the effect of long-term human albumin administration on the mortality rate of adult patients with decompensated liver cirrhosis.

1.3. Methods: We conducted a systematic literature search using PUBMED, MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Google Scholar, and Research Gate. Studies fulfilling the inclusion and exclusion criteria were quality assessed based on the criteria provided in the Cochrane Handbook for Systematic Reviews of Interventions. The number of mortalities reported on follow-up in the included studies was combined and analyzed using the Review Manager (Rev Man) Version 5.3 with 95% confidence interval.

1.4. Results: Five studies were included with a total of 830 patients. Results showed that there is a 32% decrease in mortality rate [RR 0.68 (0.48 to 0.96, 95% CI, Z = 2.22, p 0.03)] after long term human albumin administration with standard medical therapy as compared to those who received standard medical therapy alone. When a subgroup analysis was done to exclude the study which gave Midodrine on top of human albumin, it showed that there was a 36% decrease [RR 0.64 (0.44 to 0.91, 95% CI, Z = 2.48, p = 0.01)] in patients given long term human albumin which was less heterogenous.

1.5. Conclusion: The study suggests that long term human albumin administration might have a beneficial effect in reducing mortality and the incidence of cirrhosis-related complications among adult patients with decompensated liver cirrhosis; although investigators suggest that larger, multi-centered, and double-blinded randomized controlled trials with longer follow-up periods should be done to generate more robust data to validate these claims.

2. Introduction

Liver disease accounts for approximately 2 million deaths per year worldwide, 1 million due to complications of cirrhosis. Cirrhosis is currently the 11th most common cause of death globally and liver cancer is the 16th leading cause of death; combined, they account for 3.5% of all deaths worldwide [1]. Mortality trends in cirrhosis have been increasing in the Philippines; data from 1990 to 2010 showed that there has been an overall increase of mortality by 53.7% [2]. Global and regional-level estimates of chronic liver disease-related disability-adjusted life years (DALYs) and years of life lost consistently show cirrhosis within the top 20 causes. The largest burden is seen in South-East Asia. The main causes of cirrhosis in Western and industrialized countries are alcohol and NAFLD, while viral hepatitis B is the primary cause in China and other Asian countries [1].

Complications, such as ascites, gastrointestinal bleeding, hepatic encephalopathy, and jaundice, herald the decompensation of cirrhosis—the final stage of the disease. Decompensated cirrhosis carries a poor prognosis because the median survival time is about 2 years, and it imposes a heavy burden on health-care costs, mainly due to the need for repeated hospital admissions. The current approach to patients with decompensated cirrhosis relies on the individual management of each complication. Therefore, there is an unmet need for an overall therapeutic strategy able to prevent the development of complications, thus reducing hospital readmissions and costs, and improving quality of life and survival [6].

One of the promising treatment options for patients with cirrhosis in decompensation is the use of human albumin. There are a few mechanisms as to the role of human albumin in decompensated cirrhosis that have been postulated by several studies: First, the common hallmark in the pathophysiology of complications of advanced cirrhosis is circulatory dysfunction, characterized by effective arterial hypovolemia. The reduction in effective arterial blood volume leads to the activation of endogenous vasoconstrictor systems (renin-angiotensin-aldosterone system, sympathetic nervous system, and vasopressin) that are responsible for some of the major complications of cirrhosis. Based on this pathophysiological basis, targeting circulatory dysfunction appears to be a promising therapeutic approach to decrease the development of complications. Vasoconstrictors and albumin have been shown to be useful to improve circulatory function in patients with advanced cirrhosis and, the combination of both drugs is currently the standard of care for the management of hepatorenal syndrome (HRS). There is large amount of evidence showing that albumin is effective in preventing circulatory dysfunction following large-volume paracentesis, HRS in the setting of SBP

and for the management of type 1 HRS. Besides its oncotic properties, albumin may exert other biological properties such as antioxidant, improvement of endothelial function and immuno modulatory effects, that may be also useful for the prevention of complications of cirrhosis [3].

Second, the occurrence of renal failure is one of the main complications of Spontaneous Bacterial Peritonitis (SBP) and a major prognostic factor. Renal failure is also common in patients with infections other than SBP and its occurrence is associated with an increased risk of death. The beneficial effects of albumin are likely related to its capacity to increase intravascular volume, improve endothelial dysfunction, and/or other biological properties [4]. It has been demonstrated that elevated circulating prostaglandin E₂ (PGE₂) levels contribute to immune suppression in acutely decompensated patients. The plasma protein albumin binds and catalyzes inactivation of PGE₂. Albumin is synthesized in the liver and levels fall as the synthetic function of the liver declines in advanced cirrhosis, making PGE₂ more bio available. In addition, the binding capacity of endogenous albumin is known to be defective in cirrhosis [5].

Third, sustained systemic inflammation and pro-oxidant state have been shown to contribute to circulatory and extra hepatic organ dysfunctions in advanced cirrhosis. Albumin exerts non-oncotic properties, such as antioxidant and scavenging activities, binding and transport of exogenous and endogenous substances, and regulation of endothelial function and inflammatory or immune responses. Such properties would make albumin potentially able to target several pathophysiological mechanisms underlying decompensated cirrhosis, providing another reason for the use of albumin with the broader target of preventing complications, besides improving the management of ascites [6].

There has been no meta-analysis done yet on the effect of human albumin in the mortality of patients with decompensated liver cirrhosis. Our study aims to determine whether such a treatment could improve survivability or decrease mortality that it may serve as another treatment option for this patient population.

2.1. Research Question

Among patients with Decompensated Liver Cirrhosis, what is the effectiveness of long-term human albumin administration in terms of mortality?

2.2. Objectives

221. General Objectives: To determine the effect of long-term human albumin administration on the mortality rate of adult patients with decompensated liver cirrhosis.

222 Specific Objectives

- To determine the incidence of other cirrhosis-related complications arising in patients taking long term human albumin compared to those without.
- To determine the incidence of adverse drug reactions following the administration of human albumin.

3. Methodology

3.1. Types of Participants

Adult patients (more than or equal to 18 years of age) with decompensated liver cirrhosis.

3.2. Types of Interventions

Human Albumin at doses: 20 grams twice per week [8], human albumin 25 grams per week for one year and then 25 grams every 2 weeks thereafter [7], human albumin 40 grams twice weekly for 2 weeks then 40 grams weekly thereafter [6], human albumin 40 grams every 15 days with Midodrine 15 to 20 mg/day [3], human albumin 20% was administered intravenously; drug dosing was adjusted by at approximate doses of 1.5 g/kg/d at inclusion (day 1) and 1.0 g/kg/d after 48 h (day 3) [9].

3.3. Types of Outcome Measures

- The mortality rate between patients with liver cirrhosis treated with human albumin.
- The incidence of cirrhosis-related complications.
- The incidence of adverse events from the treatment with human albumin.

3.4. Types of Studies

Randomized-Controlled Trials

3.5. Search Methods for Identification of Studies

351. Electronic searches: A highly sensitive search strategy was used for identifying randomized controlled trials. Both electronic and manual means of retrieving relevant studies were performed. Electronic searches (search strategy not limited by language and publication status) were completed of PUBMED, MEDLINE (1966 to February 8, 2020; National Library of Medicine, Bethesda, USA), EMBASE (1974 to February 8, 2020; Elsevier Science, New York, USA), Cochrane Central Register of Controlled Trials, Google Scholar, and Research Gate. The reference lists of all identified papers were searched for further information.

The search strategy combined the search terms ((“serum albumin, human”[MeSH Terms] OR (“serum”[All Fields] AND “albumin”[All Fields] AND “human”[All Fields]) OR “human serum albumin”[All Fields] OR (“human”[All Fields] AND “albumin”[All Fields]) OR “human albumin”[All Fields]) AND (“liver cirrhosis”[MeSH Terms] OR (“liver”[All Fields] AND “cirrhosis”[All Fields]) OR “liver cirrhosis”[All Fields] OR “cirrhosis”[All Fields] OR “fibrosis”[MeSH Terms] OR “fibrosis”[All Fields])) AND (“mortality”[Subheading] OR “mortality”[All Fields] OR “mortality”[MeSH Terms]) were used in the PubMed search engine.

We used the following search terms in the Cochrane search strategy: “Albumin” in Title, Abstract, Keywords AND “Mortality”, “Cirrhosis”, “Midodrine”, and “Randomized Controlled Trial” in Search All Text in the Trials. The summary of the search strategy is demonstrated in (Figure 1) below.

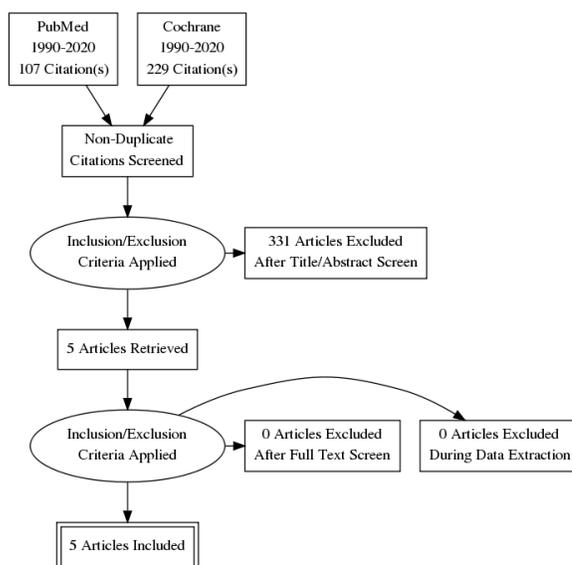


Figure 1: PRISMA flow chart showing the inclusion and exclusion of articles

3.5.2 Other Resources: Manual searches were also conducted in Google Scholar and <http://www.researchgate.net>. In addition, for articles that were either unpublished or full-text not available in the internet, the authors were contacted via their respective emails.

3.6. Selection Criteria

The investigators included randomized controlled trials that at least compared one group that used albumin with varied doses with another group that did not. Each of the coauthors independently assessed the suitability of each study for inclusion in the meta-analysis.

3.7. Data Collection and Analysis

3.7.1 Data Extraction: The two independent reviewers assessed the quality of the studies based on the criteria provided in the Cochrane Handbook for Systematic Reviews of Interventions; the results of these individual assessments were then compared by a third and independent reviewer. In cases in which the assessments varied, these differences were resolved by the third and independent reviewer. Studies were assessed as high-quality or low risk of bias if they fulfilled the following criteria:

- Treatment allocation was randomized with adequate concealment.
- The treatment and control groups were balanced in terms of known determinants of outcome.
- Outcome assessment was done in a double-blind manner.
- Outcome detection methods used were similar for both groups.
- Treatment and control groups were treated equally in terms of other therapeutic and co-interventions received frequency of follow-up and general quality of care.
- An intention-to-treat analysis was conducted and

Drop-out rates between groups were comparable. On the other hand, studies were considered fair-quality or moderate risk of bias if any subtle biases were present, such as:

- Unclear allocation concealment
- Absence of blinding; and

No intent-to-treat analysis. And lastly, studies were considered low-quality or high risk of bias if any of the frank biases was seen:

- Significant differences between the treatment and control group in terms of known predictors of outcome.
- Obvious differences in the general quality of care received by subjects in both groups.

- Marked difference in drop-out rates; and
- Outcome detection methods were different for both groups.

The outcomes of interest were the mortality rate in all study groups in each study; the researchers were also interested in obtaining data on the number of patients who developed cirrhosis-related complications and any adverse effects from albumin administration. Some of the retrieved studies, however, did not state the presence of the mentioned outcomes (cirrhosis-related complications and adverse drug reactions). The researchers have contacted the authors of the articles via e-mail regarding data on those outcomes.

3.8. Data Analysis: The mortality rates were combined and analyzed using a random-effects model in Review Manager (Rev Man) Version 5.3. A 95% confidence interval was used. These were classified as dichotomous; it is one of only two possible categorical responses. For dichotomous data, the risk ratio or the probability that an event will occur were determined for each comparison. A forest plot was constructed to show the overall effect of intervention against control in all the studies grouped together. Other outcomes included incidence of cirrhosis-related complications and adverse effects were presented as narratives.

3.9. Test for Heterogeneity: Heterogeneity was quantified using the chi square test for heterogeneity with $p < 0.10$ as the cut-off for significant heterogeneity. Heterogeneity can be interpreted as a percentage of total variation between studies that is attributable to heterogeneity rather than to chance. The I^2 test will be used to assess the degree of heterogeneity, i.e. $I^2 > 50\%$ suggests significant degree of heterogeneity or a value of 0% indicates no observed heterogeneity.

4. Results

4.1. Description of Studies

After thoroughly searching PUBMED, the Cochrane Central Register of Controlled Trials (CENTRAL), in addition to manual searches in www.researchgate.net and Google Scholar, a total of 4 studies were identified to be potentially eligible for inclusion in the meta-analysis. After thorough scrutiny, no articles were excluded (Figure 1). All four studies were left for more detailed review; reference lists of articles were reviewed and no additional trials were identified.

4.2. Quality Assessment of Included Studies

Based on the criteria set by Cochrane Group, the quality of the retrieved studies was assessed independently by the two authors (Figure 2). The assessment done was then checked by a third party (senior co-author) to amend the differences.

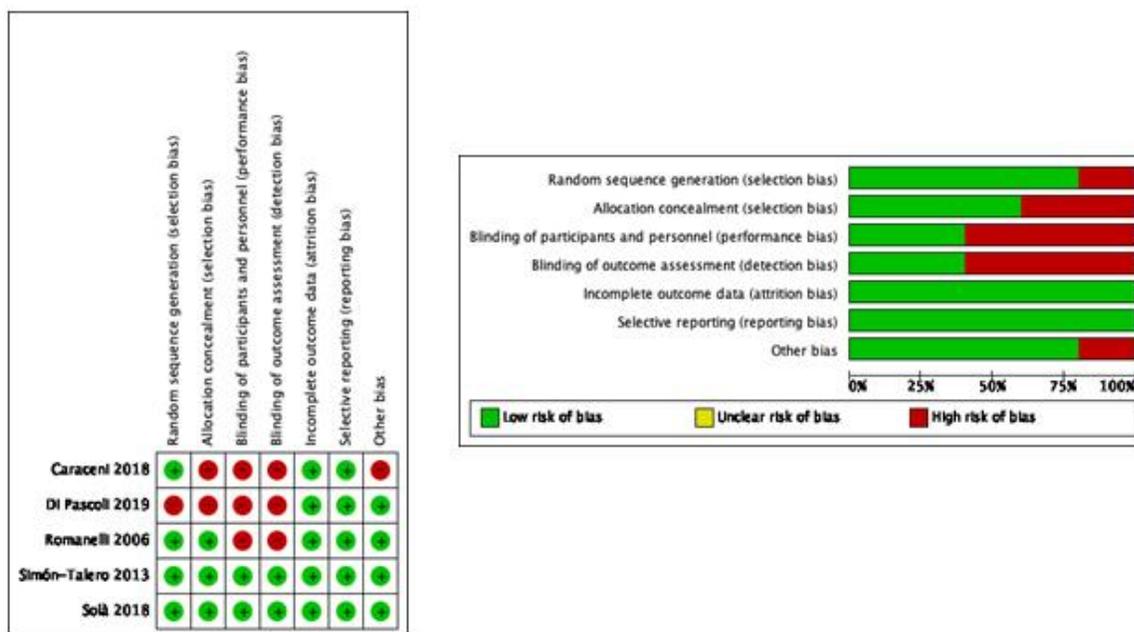


Figure 2: Quality Assessment of the studies included in the Meta-Analysis

All studies (excluding that of [3, 9] had performance and detection bias since the patients were aware that they were being given human albumin versus those who had standard medical therapy alone. This, however, does not affect the mortality rate of the patients.

The investigators also expected the data to be heterogenous since the doses of human albumin used between studies were different. In the study of [3], they gave Midodrine on top of the human albumin. It is because of this difference in intervention that the investigators will made a subgroup analysis excluding this particular study so that the results may be, more or less, solely attributed to the administration of human albumin. The endpoint in the study was also 24 week or 6 month mortality; this is much less than the 18 month and 24 month recorded mortalities in the other studies.

The outcome was also measured via number of deaths per group on

follow-up which is an objective measurement and is not affected by the subjects knowing if they received the intervention or not. Only the studies of [3] and [9]. had low risk for detection and performance bias since that study used a double-blinded approach, unlike the others.

4.3. Effect of Intervention on Outcomes of Interest

4.3.1. The effect of Long-Term Human Albumin administration on the mortality rate of patients with liver cirrhosis: The five studies showed that the relative risk of mortality in patients given long term human albumin versus standard medical therapy alone is 0.68 (0.48 to 0.96, 95% CI, Z = 2.22, p 0.03) and was statistically significant. There was also low heterogeneity noted (P = 0.28, I² = 20%) (Figure 3).

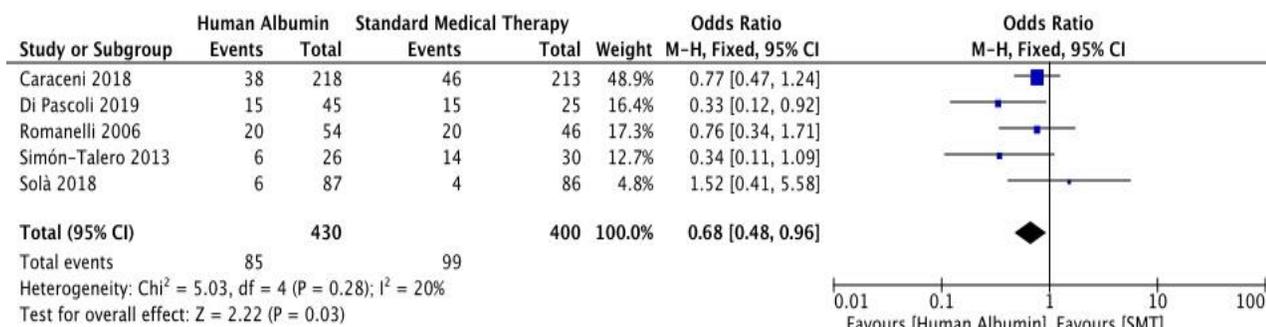


Figure 3: Forrest plot showing the effect of long-term human albumin administration on mortality rate

432 The Sub-group analysis excluding the study which had a different intervention: The investigators decided to exclude the study by [3] due to its significant heterogeneity in its study method, having exposed the subjects to Midodrine on top of human albumin and the measured mortality was only 24 weeks or 6 months on follow-up, which was not done in the other three studies. Our analysis showed a relative risk of 0.64 (0.44 to 0.91, 95% CI, $Z = 2.48$, $p = 0.01$). Heterogeneity was lower ($p = 0.33$, $I^2 = 13\%$) (Figure 4).

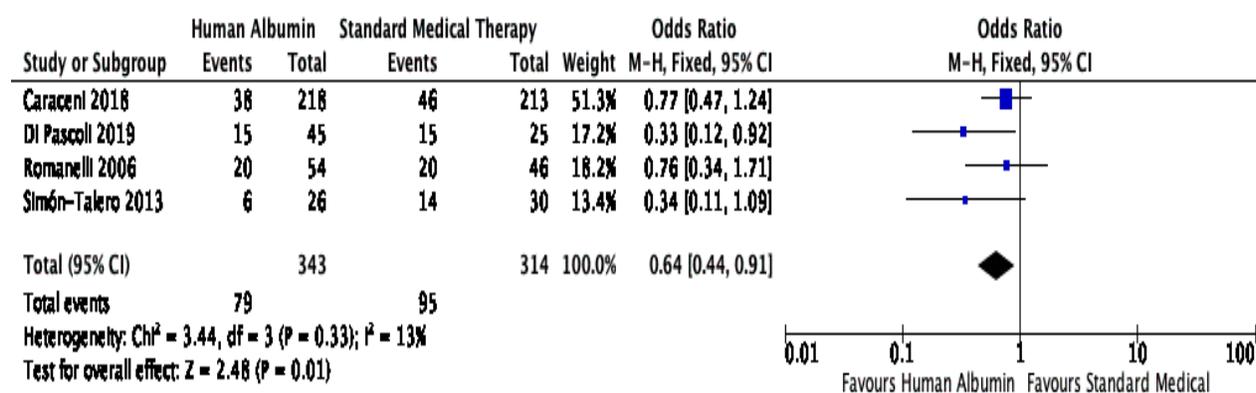


Figure 4: Forrest plot showing the relative risk of long-term human albumin administration with standard medical therapy compared with standard medical therapy alone

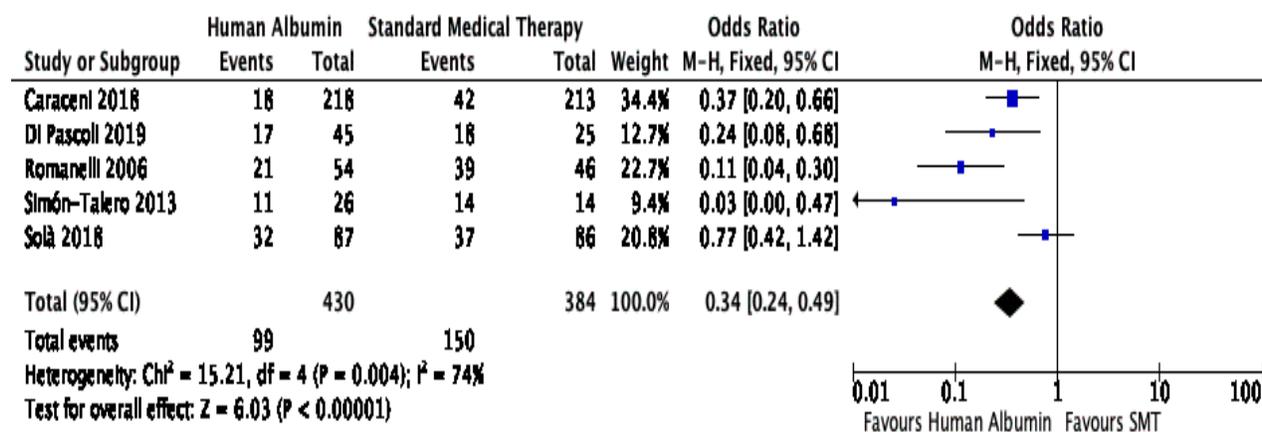


Figure 5: Forrest plot showing the effect of long-term human albumin administration on the occurrence of cirrhosis-related complications

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(Figure 6) shows that the incidence adverse events reported are highly heterogenous ($P = 0.06$, $I^2 = 72\%$), and statistically not significant with RR 1.68 (0.51 to 5.48, 95% CI, $Z = 0.86$, $p = 0.39$).

433 Cirrhosis-related Complications: The five studies showed that the relative risk of cirrhosis-related complications occurring in patients given long term human albumin versus standard medical therapy alone is 0.34 (0.24 to 0.49, 95% CI, $Z = 6.03$, $p < 0.00001$). However, there was high heterogeneity noted ($P = 0.004$, $I^2 = 74\%$), but this was expected due to the study by [3]. which used Midodrine on top of human albumin in their treatment group, this was not done in the other three studies. Furthermore, the heterogeneity could be explained by the investigators grouping all complications resulting from liver cirrhosis into one group (i.e. ascites, retractable ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, etc.).

In the study by [6], they reported five adverse events which was temporally related to human albumin infusion and consisted of: two mild allergic reactions, one episode of dizziness, and two severe sepsis cases. With regards to the two severe sepsis cases, a bacteriological analysis of the human albumin vials was done and did not show any contamination; concomitant pneumonia was diagnosed in one case also.

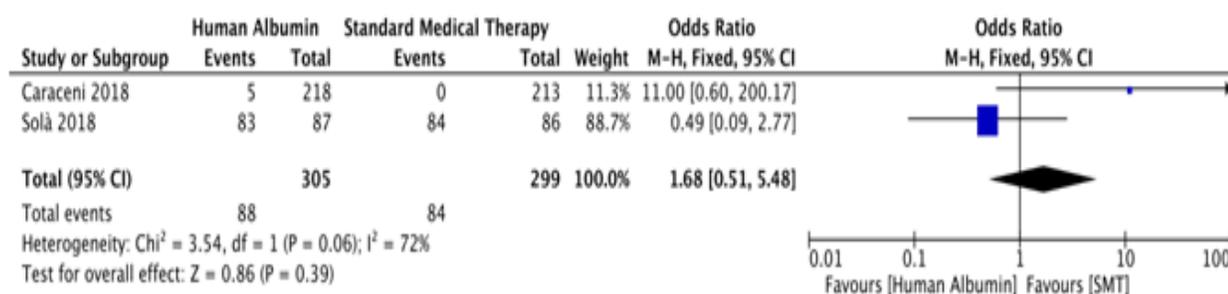


Figure 6: Forrest plot showing the incidence of reported adverse events in the two studies

Table 1: Description of the Individual Studies

#	Author, Year	Study Design	Sample size (n)	Population (Baseline Characteristics)	Intervention/s	Control	Outcome
1	Caraceni et al. (2018)	Multicentre, randomised, parallel, open-label, pragmatic trial	431	Adult Patients at least 18 years-old ;Diagnosed with liver cirrhosis With uncomplicated ascites ;Ongoing diuretic treatment; Stable for at least 4 days prior to enrollment	Intravenous infusion of 20% HA in 50 mL vials in approximately 30–60 min at a dose of 40 g twice weekly for the initial 2 weeks, and 40 g weekly thereafter. The first dose was administered within 24 h after randomisation	Standard Medical Therapy was aligned with the indications from the available clinical practice guidelines.	In this trial, long-term HA administration prolongs overall survival and might act as a disease modifying treatment in patients with decompensated cirrhosis.
2	Romanelli et al. (2006)	Randomized Control Trial	100	Adult patients aged 35 to 70 years-old; Diagnosed with cirrhosis	Low-sodium diet and diuretics in increasing dosage; received low (80 mEq/d) sodium diet, spironolactone (100 - 400 mg), frusemide (25-150 mg), as appropriate; intravenously received 25 g albumin per week in the first year and 25 g every two weeks thereafter	Low-sodium diet and diuretics in increasing dosage; received low (80 mEq/d) sodium diet, spironolactone (100 - 400 mg), frusemide (25-150 mg), as appropriate	Long-term albumin administration after first-onset ascites significantly improves patients' survival and decreases the risk of ascites recurrence.
3	Di Pascoli et al. (2019)	Non-Randomized Prospective Study	70	Cirrhosis as diagnosed by liver biopsy or clinical, biochemical, ultrasound, and/or endoscopic findings; Age > 18 years; Diagnosis of refractory ascites as defined by the criteria of the International Club of Ascites	Treatment with human albumin at the doses of 20 grams twice per week; When large-volume paracentesis was needed, all patients received also albumin at the dose of 6-8 grams per liter of ascites removed	Standard Medical Therapy; When large-volume paracentesis was needed, all patients received also albumin at the dose of 6-8 grams per liter of ascites removed	The cumulative incidence of 24-month mortality was significantly lower in patients treated with albumin than in the group of patients treated with SOC. The period free of emergent hospitalization was significantly longer in patients treated with long-term administration of albumin.
4	Solà et al. (2018)	Multicenter, randomized, double-blind, placebo-controlled trial	173	Age older than 18 yr; Cirrhosis defined by standard clinical, analytical and/or histological criteria; Patients in the waiting list for liver transplantation; Patients also with ascites	Oral midodrine (and i.v. 20% human albumin. Midodrine was started at a dose of 15mg/day (1 tablet of 5mg every 8 hours). If in the next control visit (15 days) the increase in mean arterial pressure was <10mmHg, midodrine dose was increased to the maximum dose of 30mg/day (2 tablets of 5mg every 8 hours). Albumin was administered i.v. at a dose of 40g (2 flasks of 100mL of 20% albumin) every 15 days	Patients on the placebo group received 1 or 2 tablets/8 hours of placebo of midodrine. The increase in the number of tablets was performed in an identical way to that of midodrine because the study was double blind. Placebo of albumin was as 100mL flasks of 0.9% saline solution (2 flasks every 15 days)	In patients with cirrhosis awaiting liver transplantation, treatment with midodrine and albumin, at the doses used in this study, slightly suppressed the activity of vasoconstrictor systems, but did not prevent complications of cirrhosis or improved 6 months survival.
5	Simón-Talero et al. -2013	Randomized, double-blind, controlled study	56	Patients were considered to be included in the study if fulfilled the following criteria: (1) liver cirrhosis (diagnosed by clinical data or liver biopsy); (2) development of an episode of HE that was initiated within 72 h of inclusion into the study and persisted on grade P2 (West-Haven scale); (3) age between 18 and 85 years.	Albumin 20% (Grifols, SA) was administered intravenously; drug dosing was adjusted by at approximate doses of 1.5 g/kg/d at inclusion (day 1) and 1.0 g/kg/d after 48 h (day 3).	Saline (NaCl 0.9%, Grifols, SA) was contained in similar flasks and administered at equivalent volume. Treatment was infused at a rate of 5 ml/min.	The primary end point was the proportion of patients in which encephalopathy was resolved on day 4. The secondary end points included survival, length of hospital stay, and bio-chemical parameters.

In the study by [3], they reported that 83 patients from the treatment group and 84 patients from the control group developed at least one adverse event during the study follow-up. This was reportedly not statistically significant ($p = 0.628$). There were no significant differences in the number of patients who developed serious adverse events between groups ($p=0.585$) and these were considered by the investigators to be treatment related. The most frequent type of adverse events was classified as gastrointestinal, followed by cutaneous and neurological adverse events.

5. Discussion

Many studies have explored the use of adjunctive treatment on top of standard medical management in reducing mortality among patients with cirrhosis. While there have been a few meta-analyses on the use of human albumin in preventing or reducing certain, specific complications of cirrhosis (such as ascites, renal failure, etc.), to our knowledge, this is the first meta-analysis that looked into the mortality benefit of long-term human albumin administration. This may be due to the small number of trials done for this intervention and the varying results of each.

Our results showed that there is a 32% decrease in mortality rate [RR 0.68 (0.48 to 0.96, 95% CI, $Z = 2.22$, $p 0.03$)] among patients in the human albumin group, and 36% decrease [RR 0.64 (0.44 to 0.91, 95% CI, $Z = 2.48$, $p = 0.01$)] in the sub-group analysis which are both statistically significant. The results also showed the secondary outcome which was the incidence of cirrhosis-related complications was promising with a decrease of those complications by 66% [RR 0.34 (0.24 to 0.49, 95% CI, $Z = 6.03$, $p < 0.00001$)] although this showed high heterogeneity with ($P = 0.004$, $I^2 = 74\%$), this was expected due to the variety of the complications, the difference in the dose and duration of human albumin given, the use of Midodrine on top of human albumin, the variations of standard medical therapy used in the control group as well as the interventional group, and the primary outcome of one study [6] to be 18-month mortality rate and in the study of [9]. used 90-day mortality instead of the 24-month mortality in the other studies.

There was also a high risk for bias in the studies because of them being open-label. But just as the investigators has reiterated in the previous discussion, knowledge of having been given albumin would not affect mortality or the incidence of cirrhosis-related complications. And although the study showed a high heterogeneity (which was expected and has been explained) for the forest plot of the secondary outcomes, the investigators have still found it pertinent to report it not only because it was part of the objectives but because the weight of the benefit (66%) that human albumin gave the patients could not be disregarded.

This study cannot explain the mechanism underlying human albumin benefit. However, human albumin could have mitigated effective hypovolemia, which is a major pathogenic factor for ascites formation inducing renal sodium retention and endangering renal perfusion. This mitigation would explain a better control of ascites and related complications; which lead to lesser paracenteses. Moreover, human albumin non-oncotic properties could have antagonized mechanisms, leading to the systemic inflammation and immune dysfunction characterizing decompensated cirrhosis. This result would account for the significant reduced incidence of complications not closely linked to hemodynamic alterations, such as hepatic encephalopathy and non-SBP bacterial infections. Whether a serum albumin concentration threshold needs to be reached to achieve therapeutic effects from HA supplementation warrants further studies.

In terms of adverse effects, although the highly heterogenous study by [3]. And [6] revealed there to be so; this was considered to be statistically not significant (also not significant between the two groups) and highly heterogenous, which led the current investigators to believe that these adverse events could be brought about by complications of the cirrhosis those patients already had at baseline. Also, in one study, they used Midodrine on top of human albumin which could have been contributory. It was also reported that those who had adverse events in the [6]. study fully recovered and did not die. Thus, the investigators in the four studies, as well as this study, deemed the human albumin infusion to be well-tolerated.

6. Limitations

Until present, most of the available studies on long term human albumin administration with regards to its effect on mortality and cirrhosis-related complications are limited in terms of their small study population, high risks of bias (most are open label studies), and heterogeneity. Therefore, larger, multi-centered, and double-blinded randomized controlled trials with longer follow-up periods are needed to confirm the results and come up with more robust data to support the beneficial effects of long-term human albumin administration.

7. Conclusion

Our study showed that there is, at the very least, a trend towards benefit with regards to the mortality rate among patients with cirrhosis being given long term human albumin infusion and standard medical therapy compared to those who were only given standard medical therapy. Our study also shows a trend towards benefit in reducing cirrhosis-related complications among patients who were given the intervention.

This suggests that long term human albumin administration might have a beneficial effect in reducing mortality and the incidence of cir-

rhosis-related complications. Although human albumin is costly and is given intravenously (which could be a limiting factor in its implementation in our country) the promise of reducing mortality on follow-up which could mean more months to a patient's life outweighs the cost and is a good enough reason to do further research.

This is why the investigators suggest that larger, multi-centered, and double-blinded randomized controlled trials with longer follow-up periods should be done to generate more robust data to validate these claims.

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