Roy *et al. Egyptian Liver Journal* (2024) 14:41
https://doi.org/10.1186/s43066-024-00350-7

Egyptian Liver Journal

REVIEW

Open Access

Effectiveness of albumin infusion for the management of hyponatremia in decompensated cirrhosis: a systematic review

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Abstract

Background Hyponatremia portends a poor prognosis in decompensated cirrhosis and is an independent predictor of mortality. Multiple modalities have been evaluated in the management of hyponatremia, including albumin infusion. However, the effect of albumin infusion on the resolution of hyponatremia is unclear. We conducted a systematic review to explore the available literature on the use of albumin infusion in hyponatremia.

Methods We performed a comprehensive search up to 31st December 2022 using MEDLINE, EMBASE, and Scopus for studies reporting the effectiveness of albumin infusion in the resolution of hyponatremia. The impact of albumin infusion of any dose, administration frequency, and duration of therapy was recorded. The study protocol was prospectively registered (CRD42021245914).

Results The literature search yielded 1322 references after duplicate removal. Only seven studies (three randomized trials, three cohort studies, and one case series) satisfied the predefined selection criteria after a full-text review. While hyponatremia was clearly defined as serum sodium < 130 meEq/L in all studies, two studies explicitly defined hyponatremia resolution (serum sodium > 135 mEq/L). No differentiation was made between the types of hyponatremia. The strength of the albumin infusion used was 5% and 20%. All but one study reported significant improvement in hyponatremia with albumin infusion. A subgroup analysis showed albumin infusion improved 30-day survival (odds ratio 0.43, 95% CI 0.25–0.74, $I^2 = 0$.) No studies reported adverse events or the impact of concomitant associations (diuretic withdrawal, lactulose use, sepsis).

Conclusion Despite available literature on the use of albumin infusion for the resolution of hyponatremia, the level of evidence remains low. Large prospective studies with pre-defined selection criteria and endpoints are required to generate the evidence.

Keywords Decompensated cirrhosis, Hyponatremia, Albumin, Ascites, Systematic review

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Introduction

Traditionally in non-cirrhotic individuals, hyponatremia is defined as a serum sodium level of < 135 mEq/l [1]. However, in cirrhosis, the cut-off for defining hyponatremia has arbitrarily been set at 130 mEq/l [2]. Irrespective of the cut-off levels, hyponatremia in cirrhosis portends a grave prognosis and is associated with worse outcomes both in the pre-transplant and post-transplant settings [3]. The importance of hyponatremia itself is evident in the widespread use of the MELD-Na (Model for End-Stage Liver Disease-Sodium) score, which serves as a better predictor of survival than MELD alone [3, 4]. Despite the established role of hyponatremia in cirrhosis, management options of hyponatremia have not been elucidated. Although fluid restriction, hypertonic saline, and vaptans have been advocated in the setting of hypervolaemic hyponatremia, the evidence to support the same has not been robust [3].

The use of albumin infusion in cirrhosis has been postulated to have pleiotropic effects [5]. However, the recommended use of albumin in cirrhosis is backed by strong evidence only in specifically selected settings. These include the prevention of paracentesis-induced circulatory dysfunction (PICD), prevention of acute kidney injury (AKI) in spontaneous bacterial peritonitis (SBP), volume expansion in AKI, and the diagnosis and therapy of hepatorenal syndrome (HRS) in conjunction with vasopressors [6]. Albumin infusion has been suggested to have a potential role in improving hyponatremia in current guidelines but is supported by minimal data [3]. The principal aim of this review is to refine our understanding of the role of albumin infusion in the improvement of hyponatremia in decompensated cirrhosis by reviewing the currently available evidence.

Methods

The study protocol was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols and was registered in the International Prospective Register of Systematic Reviews (PROSPERO; ID 245914) [7].

Eligibility criteria

Types of studies

All available randomized control trials (RCTs), cohort studies, case–control studies, and case series investigating the effectiveness of albumin infusion in the improvement of hyponatremia in patients with cirrhosis were included. All studies published or accepted for publication either in full or in abstract form were included. Review articles, non-English language articles, pediatric studies, animal studies, editorials, clinical practice guidelines, and studies that have been retracted from the publication were excluded.

Types of participants

Studies that included patients greater than 18 years of age with decompensated cirrhosis and hyponatremia were included.

Types of interventions

Studies investigating the impact of albumin infusion of any dose, administration frequency, and duration of therapy were included.

Types of comparators

Studies with a comparator group as a placebo, an alternative intervention, or no intervention were included.

Objectives

To assess the effectiveness of albumin infusion on the resolution of hyponatremia in patients with decompensated cirrhosis. As a secondary objective, the impact of albumin administration on 30-day mortality in patients with hyponatremia was assessed.

Information sources and search strategy

MEDLINE, EMBASE, and Scopus databases were searched separately to acquire data from relevant studies, with the last search conducted on 31st December 2022. The search strategy was augmented by cross-checking of references of all primary retrieved articles. The predefined search strategy was ("Albumin" OR "Colloid") AND ("hyponatremia" OR "hyponatraemia" OR "serum sodium") AND ("Cirrhosis" OR "Chronic Liver Disease" OR "End-Stage Liver Disease" OR Ascites), and no additional filters were applied.

Study selection

Duplicate records of the same report were removed using reference management software. Articles were screened by title and abstract by two independent reviewers (AR, SG) by abstract and title. In case of uncertainty, the item was included in a full-text review carried out by two independent reviewers. In case of a lack of agreement at this stage, a third reviewer was consulted. Extraction of data was done by two reviewers independently (SS, SS) and in duplicate.

Assessment of quality of studies

The Newcastle–Ottawa Scale was used to assess the quality of studies [8]. Randomized controlled trials were assessed using the Risk of Bias 2 (RoB 2) tool. The final

decision on the overall quality was reached through discussion and consensus.

Synthesis methods

The following data were extracted:

- Study design: type of study, author, country, year/s, and duration of the study.
- Study participants: selection method and criteria, baseline characteristics,
- Interventions: dosage and frequency, size of intervention and comparison groups, length of follow-up.
- Outcomes: definition, time points, number of events, unadjusted and adjusted effect estimates, covariates used for adjustment, the quantity of missing data and reasons for missingness, and statistical methods

The proportion (%), mean (± standard deviation), or median (range) were described as appropriate. Random effects meta-analysis was conducted if uniform endpoints were reported in at least three studies. The heterogeneity in estimates was assessed by Tau^2, I^2, and the chi-square test (Q-statistic). All analyses were done with Medcalc and Comprehensive Meta-analysis version 2. Publication bias assessment was not done due to a limited number of studies.

Results

Search results

The initial search identified 1749 results. A total of 1322 results (after excluding duplicates) were screened based on title and abstract. After exclusion, we had 22 publications that were eligible for full-text review, of which 7 studies finally satisfied our selection criteria [three randomized trials (one available only as an abstract), three cohort studies, and one case series [9–15]. The study selection process is presented in a detailed flow diagram in Fig. 1. The characteristics of the studies are shown in Table 1. The quality of the non-randomized studies as per the Newcastle–Ottawa Scale is shown in Supplementary Table S1. Supplementary Figure S1 shows the risk of bias for randomized studies.

Definition of hyponatremia and criteria for resolution

Five studies [9–13] defined hyponatremia as serum sodium ≤ 130 mEq/L, with Jalan et al. [12] classifying patients < 130 mEq/L as severe hyponatremia. Two other studies defined hyponatremia as serum sodium ≤ 135 mEq/L [14, 15]. Only two studies clearly defined the resolution of hyponatremia as serum sodium of > 135 mEq/L [9, 15]. The study by China et al. utilized data from a larger trial where patients were stratified as per sodium levels (≤ or ≥ 130) and looked at the interactions between albumin administration and changes in sodium levels and MELD scores [13, 14]. However, the study did not analyze a definitive endpoint of hyponatremia resolution.

Type of population

All the studies included patients with decompensated cirrhosis (DC) as a broad group. While Bajaj et al. [9] included admitted patients with or without acute or chronic liver failure belonging to the North American Consortium for the Study of End-Stage Liver Disease (NACSELD) cohort, Jalan et al. specifically looked at a population of refractory ascites [12].

Associated complications with hyponatremia for albumin use

A major challenge in designing studies addressing hyponatremia is the presence of associated complications like AKI, SBP, and PICD, for which albumin is a guideline-recommended therapy, hence making it unethical to deny albumin usage in such a population. In the retrospective analysis of Bajaj et al., out of 1126 patients who had hyponatremia at admission, 777 received intravenous albumin infusion [9]. The indications for using albumin were diverse (AKI, 52%; SBP, 15%; post-large volume paracentesis, 33%). Only 29% of the patients received albumin for hyponatremia correction itself without an additional indication. The study from China et al. used a pragmatic approach to albumin administration to reach a targeted level of albumin of > 30 g/L. The study found a higher usage of albumin in patients with hyponatremia and additional complications (AKI, HRS, PICD) than in those with only hyponatremia [13]. Bai et al. used albumin primarily for ascites, post-paracentesis, and hypoalbuminemia [14].

Strength and dose of albumin usage

The strength of albumin used was variable in the different studies, with 20% human albumin being the most commonly used dose [8, 11, 13, 15]. The cumulative dose administered also varied with the study by Jalan et al., the cumulative doses used were 40 gm/day for seven days (280 gm) [12, while in the study by Bajaj et al., the mean dose of albumin received was 225 (IQR 100–400) g [9]. The study by Bajaj et al. also showed that for hyponatremia resolution, a total dose of 314 g (Youden Index value) yields a sensitivity of 0.45 and a specificity of 0.80 with an area under the curve (AUC) of 0.64 [9]. The study by China et al. used albumin at a strength of 20%. Patients with hyponatremia in the targeted albumin group received a mean total of 239.4 g (SD 129.1) of albumin, while the standard care group received 123.2 g (SD 138.4) [13].

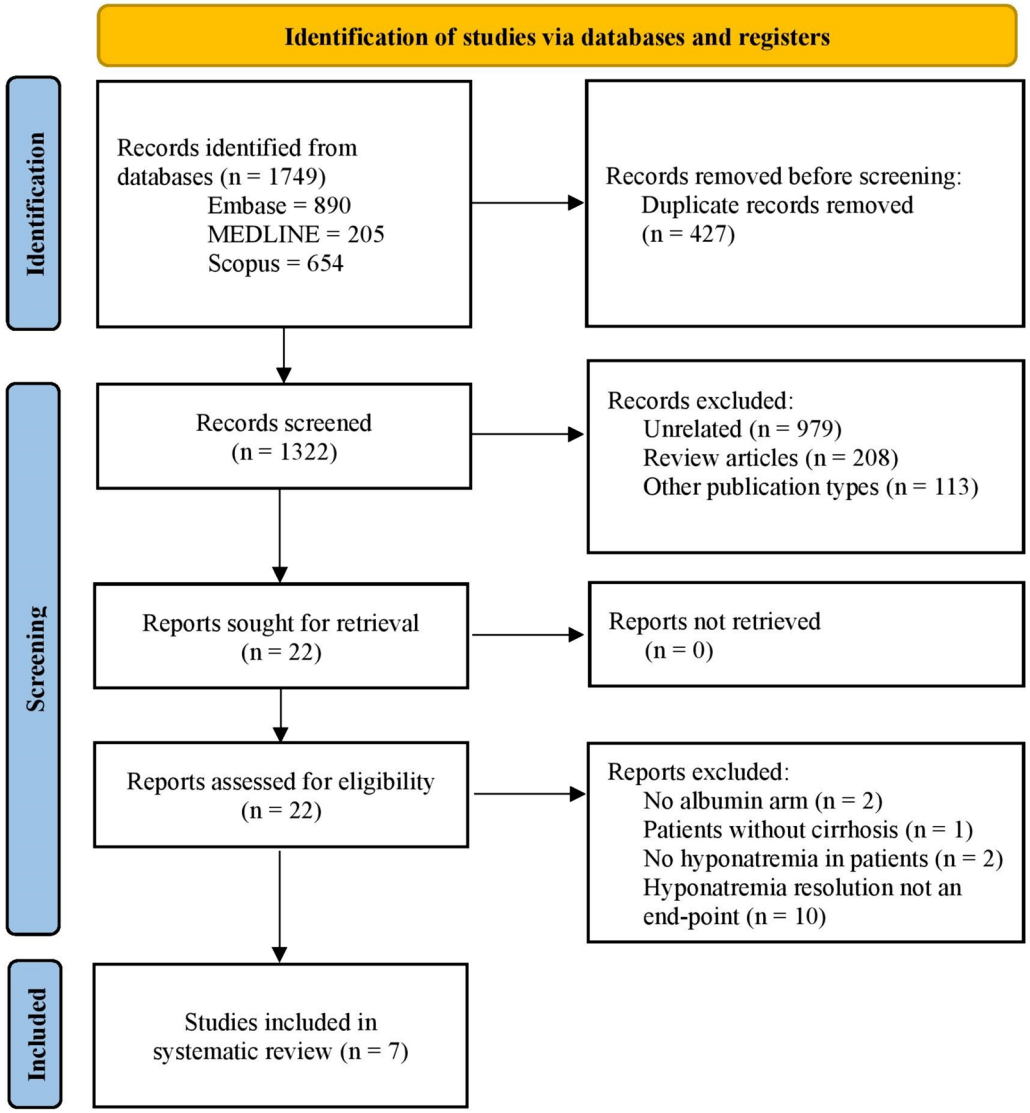

Fig. 1 PRISMA flowchart for study selection and inclusion process

Resolution of hyponatremia

In the study by Bajaj et al. [9], the resolution of hyponatremia occurred in a significantly greater number of patients who received albumin therapy (69.4% vs. 61.4% respectively, $P=0.0085$, odds ratio (OR) 1.43, 95% confidence interval (CI) 1.09–1.86) and the difference persisted even after adjustment for a difference of admission sodium levels and estimated glomerular filtration rates. However, Shen et al. [10] did not find any difference between the changes in sodium levels with or without albumin administration [10]. Jalan et al. [12] also report significant improvement in hyponatremia with albumin, although the exact resolution data was not available. In the case series, all three patients who had hyponatremia with decompensated cirrhosis had a resolution of hyponatremia with albumin [11]. In the study by China et al. [13], targeted albumin infusions increased serum sodium by 3 mmol/L compared with standard care at day 5 of the trial in patients with hyponatremia, although the resolution of hyponatremia was not specifically addressed. In the study by Bai et al. [14], in hospitalized patients with cirrhosis, the improvement in hyponatremia was significantly higher in the albumin group (82.7% versus 54.8%, $p<0.001$) [14]. On long-term administration of 40 g albumin twice a week for 2 weeks and then 40 g weekly, the resolution rate of hyponatremia at 1 month (45% vs. 28%;

Table 1 Showing characteristics of studies using albumin in the treatment of hyponatremia in cirrhosis

Authors, year	Setting, type of study	Type of publication	Population	Comparator arm	Number of patients receiving albumin	Strength and dose of albumin	Adverse events
Bajaj et al. 2018 [9]	USA, Multicentric study at 14 centers	Full article	Hospitalized cirrhosis ± ACLF*	Standard of care	Total = 1127 Albumin = 777 Control = 349	20%	Not reported
Shen et al. 2017 [10]	USA, Single-center, Retrospective	Full article	Hospitalized decompensated cirrhosis (DC**)	Crystalloid	Total = 146 Albumin = 91 Crystalloid = 55	Not reported	Not reported
Mc Cormick et al. 1990 [11]	UK, Single-center, case series	Case series	DC ($n=3$) and fulminant hepatic failure ($n=1$)	–	$N=4$	5% and 20%	Not reported
Jalan et al. 2007 [12]	UK, Single-center, randomized trial	Abstract only	DC with refractory ascites	Standard of care	Total = 24 Albumin = 12 Control = 12	Not reported	Not reported
China et al. 2021 [13]	UK, Multicentric, open-label parallel-group trial (data analysis from main trial data)	Full article	DC with ascites and serum albumin < 30 g/L who received targeted albumin to raise albumin > 30 g/L	Standard of care	Patients with Na < 130 Targeted albumin group:$n=103$ SOC group:$n=103$	Targeted albumin group:239.4 ± 129 gm Standard of care group 123 ± 138.4 gm	Not reported
Bai et al. 2023 [14]	China, Single-center, Retrospective, PSM***	Full article	Hospitalized DC	Standard of care	Total = 394 Albumin = 197 Control = 197	Median dose: 40 g (10–380)	Not reported
Zaccherini et al. 2023 [15]	Italy, Multicentric, open-label randomized trial	Full article	DC with uncomplicated ascites	Standard of care	Total = 149 Albumin = 75 Control = 74	20%, 40 g twice a week for 2 weeks, and then, 40 g weekly	Not reported

* Acute on chronic liver failure

** Decompensated cirrhosis

*** Propensity score matching

$p=0.042$) and 3 months (71% vs. 44%; $p=0.006$) were significantly higher in the albumin group [15].

Survival

In the study by Bajaj et al. [9], 86% of hyponatremic patients survived at 30 days, and they found that the resolution of hyponatremia but not albumin administration was a significant predictor for survival. Shen et al. [10] showed similar six-month mortality was 22% in both the albumin and crystalloid cohorts. However, they concluded that after adjustment for hepatorenal syndrome and spontaneous bacterial peritonitis and controlling for other parameters like refractory ascites, albumin administration was associated with reduced 6-month mortality (OR 0.06 95%CI 0.005–0.4; $P=0.013$). The analysis by Jalan et al. [12] also found significantly less in-hospital mortality in patients receiving albumin (1/12 in the albumin arm vs 5/12 patients control arm; $P<0.05$). In the study by Bai et al. [14] patients who had improvement of hyponatremia during hospitalizations had a significantly lower in-hospital mortality than those who did not (8.60% versus 13.50%, $p=0.013$). On comparison according to subgroups, the differences remained (6.70% versus 14.20%, $p=0.008$), but not in the albumin group (10.00% versus 12.90%, $p=0.309$).

Subgroup *meta*-analysis

Since the number of studies was small and the endpoints were not uniform, a formal meta-analysis on hyponatremia resolution with albumin administration could not be carried out. However, with the available data, we did a random-effects meta-analysis to estimate 30-day mortality in patients with hyponatremia stratified by albumin administration (Fig. 2), which shows a favorable effect with albumin administration (odds ratio 0.43, 95% CI 0.25–0.74).

Adverse events

None of the studies reported adverse events associated with albumin administration in the management of hyponatremia.

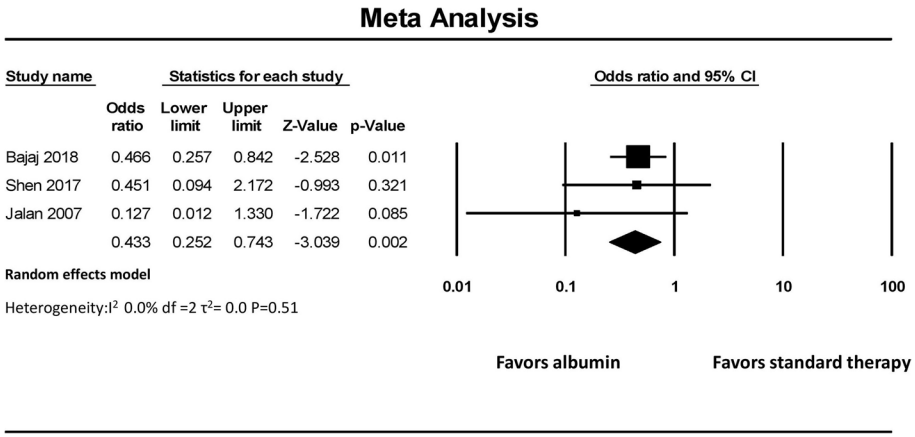

Fig. 2 Forest comparing the 30-day mortality in patients with cirrhosis and hyponatremia receiving albumin infusion vs. standard therapy

Discussion

Hyponatremia is the most common electrolyte imbalance that is encountered in patients with cirrhosis with profound clinical significance [16]. With a prevalence rate ranging from 6 to 22% depending upon the severity of hyponatremia, it is an independent predictor of complications, hospitalizations, and waitlist mortality [17–19]. However, despite its clinical significance, the management strategies for hyponatremia have been limited and plagued by a lack of evidence [3]. The crux of hyponatremia management revolves around differentiating between hypovolemic and hypervolemic states, of which the latter is more common in the context of decompensated cirrhosis [20]. While volume replacement is the primary strategy in hypovolaemic cases, the options in hypervolemic cases include fluid restriction ($\leq$1 L), hypertonic saline, vaptans, and intravenous albumin [3]. Albumin infusions have been used for multiple established conditions, but controversies exist regarding its efficacy in novel and emerging indications [5]. Along similar lines, there remains a grey zone in the evidence for the use of albumin infusion in hyponatremia which mandated this review of existing literature.

The rationale for the use of albumin in hyponatremia in cirrhosis

Albumin is an impermeable molecule exerting significant electronegative charge across membranes, thereby influencing the osmotic fluxes across the membrane. Therefore, in a hypoalbuminemic state like cirrhosis, a decrease in albumin leads to decreased plasma sodium concentration due to an altered Gibbs-Donnan effect which essentially describes the distribution of permeant ions across semipermeable membranes [21]. Additionally, other causes leading to hyponatremia are intravascular volume depletion (gastrointestinal losses, over diuresis) and decreased effective circulatory volume secondary [22]. Pathophysiologically, albumin infusion may improve hyponatremia either by modulating the Gibbs-Donnan effect due to hypoalbuminemia or by restoring intravascular volume. Restoring intravascular volume with a concomitant increase in free water clearance appears to be the more pertinent mechanism [22]. Additional mechanisms have also been proposed which include albumin-mediated suppression and anti-diuretic hormone suppression [23]. Importantly, the sodium content of albumin solutions also has a potential role in hyponatremia correction with the approximate sodium content in 25% albumin preparation being 145 mEq/L [23]. Hence, intravascular volume expansion along with other multifactorial effects appears to be the driving mechanism behind the role of albumin in hyponatremia management.

Current guidelines on the use of albumin in cirrhosis for correction of hyponatremia

Based upon the limited evidence, the use of albumin as a treatment option for hypoalbuminemia has not been delved in detail in most society guidelines. A summary of the major societal guidelines has been provided in Table 2 [3, 24–26].

Inferences from the review

Our systematic review yielded limited studies that directly address the question of hyponatremia resolution by administration of albumin infusion. Although few studies and a meta-analysis have looked into the decreased incidence of hyponatremia in patients already receiving albumin, the existing literature on albumin's therapeutic role is restricted to these 7 studies, of which one is a case series [27–29]. Moreover, even in limited studies, the broad classification of hyponatremia

Table 2 Recommendation on the use of human albumin in the treatment of hyponatremia in cirrhosis

Guidelines	Statement	Grade of recommendation
European Association of study of liver [3]	Albumin administration can be suggested in hypervolemic hyponatremia, but data are minimal to support its use	II-3;2
British society of gastroenterology [24]	Insufficient evidence to routinely recommend in hyponatremia	No recommendations
American Association for the Study of Liver Diseases [25]	None	No recommendations
International Ascites club [26]	None	No recommendations

(hypervolemic/hypovolemic) has not been addressed [30, 31]. Furthermore, comparator arms have been variable in the studies, and there is an evident lack of preplanned selection strategy and enrolment criteria. The key endpoints of hyponatremia resolution show conflicting results between the studies, and overall survival benefit also has divergent results. However, a key limitation of this systematic review is the overall paucity of studies which restricted the inferences to a sub-group meta-analysis.

Knowledge gaps

An analysis of the existing literature reveals significant knowledge gaps in the potential use of albumin infusions for hyponatremia in cirrhosis. Firstly, the type of hyponatremia needs to be addressed in the given study cohort. Secondly, the dosage of albumin (25% /20% /5% human albumin solution) and the duration of therapy with regard to pre-specified endpoints need to be looked at systematically. Thirdly, accounting for concomitant associations like diuretic withdrawal, lactulose administration, renal dysfunction, and sepsis, which interfere with hyponatremia resolution, needs to be done. Lastly, conceiving an adequately powered study design in a homogenous population remains a challenge and needs to be addressed in future studies.

Conclusion

Hyponatremia is the most common electrolyte imbalance in cirrhosis and has profound implications on morbidity and mortality. Despite studies reporting the beneficial role of albumin infusion in the correction of hyponatremia, the level of evidence remains low. Future, well-planned randomized trials are imperative to address the gaps in knowledge.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43066-024-00350-7.

Additional file 1: Supplementary Table S1. Newcastle-Ottawa Scale for risk of bias assessment for studies. Supplementary Figure S1. Traffic-light plot for risk of bias in randomized studies.

Acknowledgements
None.

Authors' contributions
All the authors have made substantial contributions to the conception, acquisition, analysis, interpretation of data, and drafting of the manuscript with critical appraisal. All the authors approve the final version to be published and agree to be accountable for all aspects of the work.

Funding
None.

Availability of data and materials
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable for systematic review.

Consent for publication
Not applicable for systematic review.

Competing interests
All the authors declare that they have no conflict of interest.

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Received: 29 November 2023 Accepted: 26 May 2024
Published online: 01 June 2024

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