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Original Research

Efficacy and Safety of Steroids in Acute Heart Failure: A Systematic Review and Meta-analysis

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Abstract

Background: Persistent congestion in acute heart failure (AHF) is associated with worse clinical outcomes. The use of steroids may provide therapeutic benefits by alleviating congestion, overcoming diuretic resistance, and mitigating the harmful effects of neurohormonal activation. This approach could potentially improve hemodynamic status and support better management of AHF, ultimately leading to enhanced patient recovery and reduced complications.

Objective: To evaluate the efficacy and safety of steroids in acute heart failure (AHF) as compared to the standard of care (SOC).

Search strategy: We used PubMed, Scopus, Google Scholar, and a manual search to identify Randomized controlled trials published up to October 15, 2024.The protocol was registered in PROSPERO **(**CRD42024601261**)**

Selection Criteria: All full-text randomized control trials (RCTs) that investigated steroids in heart failure were included. Results were pooled, where appropriate, using a random-effects model.

Results: Three RCTs with 563 participants [282 Steroid, 281 (SOC)] were identified. No statistically significant difference is seen in mortality as well as NT-proBNP levels between the steroid plus SOC and control group (RR=0.59, 95% CI=0.06–6.13, p=0.66, (I^2=51%, p=0.15) and (MD=0.14, 95% CI=−0.62 to 0.90, p=0.71, I^2=91%, p<0.0006), respectively.

Conclusion: Steroids have no significant effect on all-cause mortality or NT-proBNP levels in patients with AHF.

Keywords: Acute Heart Failure; Corticosteroids; Mortality.

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Introduction

Heart failure (HF) is a clinical syndrome defined by a combination of symptoms, such as shortness of breath (dyspnea), difficulty breathing while lying flat (orthopnea), and swelling in the lower limbs. It is also marked by signs like elevated jugular venous pressure and pulmonary congestion [1]. HF is often caused by structural and/or functional abnormalities of the heart, which lead to reduced cardiac output and/or increased pressures within the heart chambers. A diagnosis of AHF is made when patients present acutely with signs and symptoms of heart failure, often with decompensation of pre-existing cardiomyopathy [2].

Effective pharmaceutical interventions are crucial as the prevalence of acute heart failure (AHF) is rising with the ageing population in the U.S., where there are over one million hospitalisations each year [3]. AHF is also associated with significant readmission rates exceeding 25% in 3 months and 50% in six months [4].

Diuretics are a vital component of symptomatic CHF management. However, they induce diuretic effects at the cost of worsening renal function [5, 6]. An increase in serum creatinine (SCr), whether linked to diuretic use or not, may be associated with poor prognosis [7]. Vasoactive agents to augment cardiac function have been evaluated in patients with AHF but have shown limited efficacy [8]. New therapeutic strategies for patients with heart failure are thus needed. Few studies have indicated that glucocorticoid therapy can be used safely in patients with AHF in the short term. A study done in China noted a remarkable SCr reduction after 7 days of treatment and the therapy did not cause heart failure deterioration [7]. Inflammatory activation was shown to be associated with heart failure (HF) and found that highly sensitive C-reactive protein (hsCRP) was associated with more signs of congestion and increased mortality and recurrent HF in patients admitted for acute HF (AHF) [9]. A randomised control trial of patients with AHF and high hsCRP levels, a 7-day burst steroid administration was associated with reduced inflammatory activation during the steroid administration, improved quality of life, and reduced 90-day risk of worsening HF or HF readmission [10]. As per our knowledge, no systematic review and meta-analysis are available to date.

With this background, we found that there was a need to undertake a systematic review to summarise the results of various studies to determine the efficacy and safety of steroids compared to the standard of care in the management of Acute Heart Failure.

Methods

Research question & selection criteria

This SRMA addresses the research question, “Does steroid (I) decrease mortality (O) in patients with acute heart failure (P) compared to standard care (C)?” following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [11]. To answer this question, we systematically searched the literature and identified eligible articles based on the selection criteria defined using a PICO format (Population, Intervention, Comparator, and Outcome).

We included all randomized controlled trials (RCTs) comparing the Efficacy and Safety of Steroids in Acute Heart Failure. The study was registered at a publicly visible registry (PROSPERO), with the record ID CRD42024601261.

Search Strategy and Selection Criteria

For retrieving the studies for the review, we undertook a preliminary search on PubMed, Scopus and Google Scholar, using keywords related to Heart Failure”, Steroids, and “Randomised control trial. In addition to this, we manually searched through clinical trial registries relevant websites for thesis and

dissertations or additional articles. A bibliographic search was also undertaken to retrieve relevant articles. Only full-text articles were included. We did not limit our search to a time and included all studies from inception till the time of the search. The reference list of included studies was reviewed to identify any articles which could be included. The two independent co-authors (NS & NK) further checked all the citing references. In cases where conflicts arise, resolution will be achieved through the intervention of a third reviewer (SC), whose decision will serve as the final determination. To achieve reproducibility, we have reported the search strategy across all the databases in Table S1 [Supplementary File].

Inclusion criteria

Participant criteria: We included randomized controlled trials (RCTs) that investigated the use of steroids in the treatment of people with Acute heart failure.

Exclusion criteria

Participant criteria: Patient refusal**;** Any signs of infection**;** Any condition that would contraindicate glucocorticoid use**;** Poorly controlled hypertension; clear history of type I or II diabetes mellitus**;** active myocarditis**;** malignancy or other terminal illness with an expected life expectancy,3 months and cardiogenic shock.

Other criteria specific to meta-analysis: Study protocols were prepared; Ongoing trials or trials with unpublished results; Pre-print data which was not peer-reviewed; Abstracts and/or Conference proceedings; Articles published in a non-English language; Editorials and letters and Observational studies, including case reports and case series

Outcomes

The primary and secondary outcomes were decided based on the preliminary search undertaken. All-cause mortality was selected as the primary outcome for this review. The secondary outcomes selected were: i) Time of the first event of worsening heart failure, ii) Number and type of Adverse events, iii) N-terminal pro-B-type natriuretic peptide (NT pro-BNP levels), iv) Hospital readmission, v) Quality of life, vi) High-sensitivity C-reactive protein (Hs CRP levels).

Study selection and data extraction

Study Selection

Using the pre-defined search strategy bearing the MeSH (medical sub-heading) terminologies, the articles were screened for their titles and abstracts by two independent co-authors (M.G and H.S.), eliminating duplicates and/or irrelevant articles using the Rayyan software. Articles not meeting the inclusion criteria were removed, and the remaining ones were assessed for full-text screening to include in the present review. For any disagreement regarding selecting articles, co-authors P.G. and N.P. were approached.

Data Extraction and Outcome Measures

Relevant data from each article about the reported outcomes of interest were extracted and entered by co-authors M.G and H.S which were reverified by co-author S.C according to a pre-designed data extraction sheet. For any conflict of interest, a consensus was achieved by discussing or consulting with co-authors N.S. and N.K. The information was extracted into an Excel spreadsheet for the required variables. From the data extracted, a table was generated consisting of the following variables: General characteristics, study characteristics, participants, intervention, and outcomes.

Risk of Bias Assessment

The risk of bias for the included studies was studied using the Risk of Bias 2 tool for randomised controlled trials by SS and MG, and any discrepancy was discussed and resolved with SC. Seven risk-of-bias domains were assessed for primary outcome in each study, namely random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias were covered for quality assessment and each domain was given a rating of low risk (green), high risk (red) or unclear (yellow) risk of bias. The traffic plot graph was prepared using RoB 2 software [12].

Data synthesis and summary measures

Continuous data were summarised as mean difference (MD) with 95% confidence interval (CI), while dichotomous data were reported as risk ratio (RR). When median values were provided, the median was treated as the mean, and the standard deviation (SD) was calculated from the interquartile range as SD = IQR/1.35. We employed the Mantel-Haenszel (MH) method using Review Manager 5 (RevMan) Version 5.4 for quantitative data synthesis. Heterogeneity was assessed with the I2 statistic and chi-square test. We considered I2 > 50% as indicating statistically significant heterogeneity [13,14]. If substantial heterogeneity was present, a random effects model was applied to those clinical outcomes in the meta-analysis.

Assessment of Quality of Evidence - GRADE pro analysis

The overall quality of evidence for each outcome was evaluated using the GRADE pro-GDT (Guideline Development Tool) software, based on the principles of the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system [15]. The assessment considered several factors, including the risk of bias, directness of evidence, consistency and precision of results, risk of publication bias, the magnitude of the effect, dose-response gradient, and the influence of residual plausible confounding. Each of these factors contributed to the final grading of the evidence for each outcome. The quality of the evidence was categorised as high, moderate, low, or very low based on the collective consideration of these domains. The GRADE pro-GDT software was accessed online for analysis from the site https://gradepro.org/ [16].

Results

Study selection and characteristics

The initial search using the specified databases identified 1465 studies. After removing duplicates and excluding non-relevant studies, 983 studies remained. Further application of the inclusion and exclusion criteria reduced this number to 4 studies. Finally, after excluding non-randomized studies, conference proceedings, and studies with unavailable data, three randomized controlled trials (RCTs) were included in the review. The study selection process is outlined in the PRISMA 2009 Flow Diagram (Figure 1).

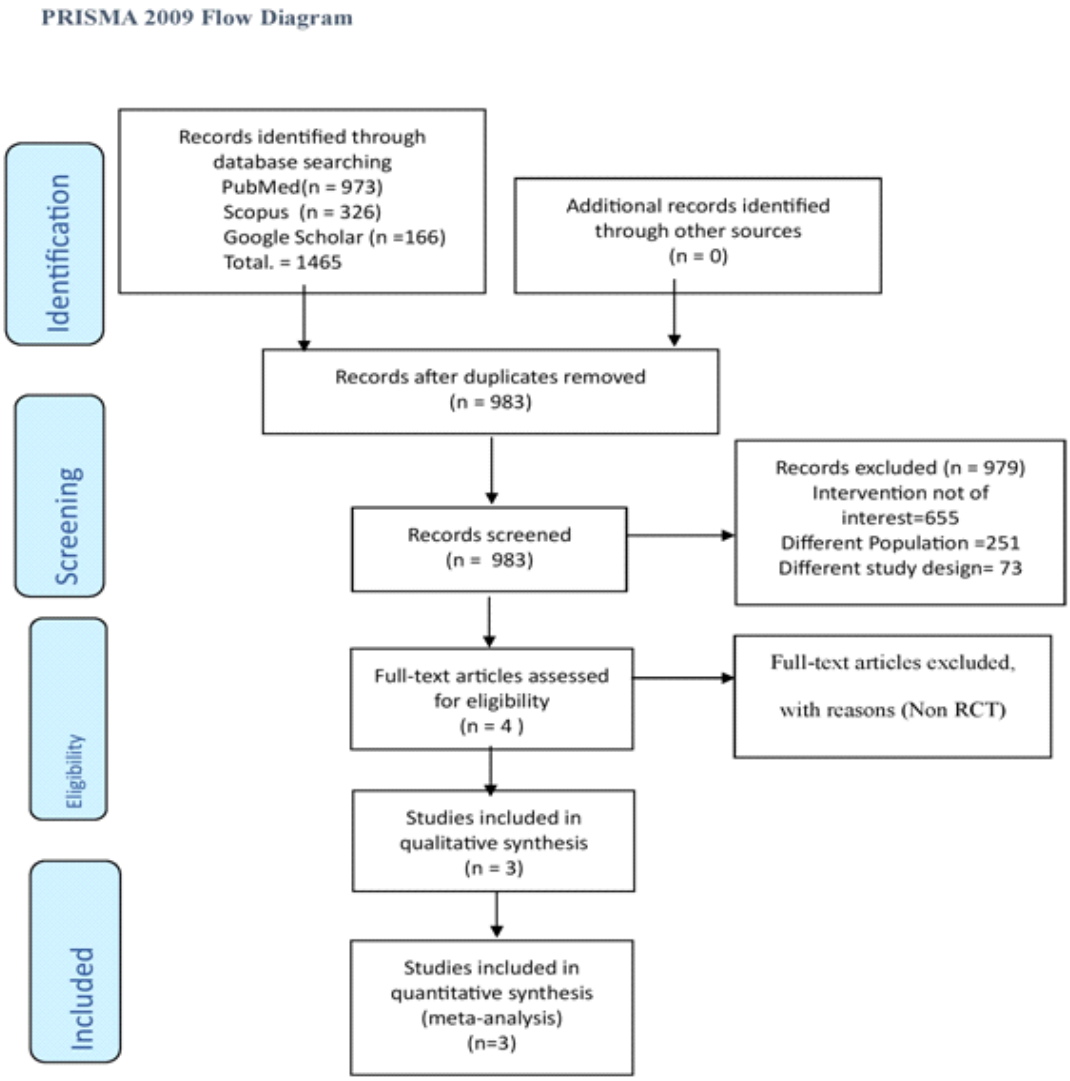

Figure 1: Prisma Flow diagram for studies selected for systematic review and meta-analysis

The three included studies comprised a total of 563 participants. Among the total participants, 281 (49.91%) were assigned to the control group (standard of care), while 282 (50.09%) were assigned to the intervention group (Steroid). The study characteristics, including study design, population, number of participants in both the intervention and control groups, as well as the primary and secondary outcomes, are summarized in **Table 1.**

Table 1: Study Characteristics of participants

Study ID	Study design	Population	Baseline characteristics I/C	Intervention comparator	Primary Outcome	Secondary Outcome
Cotter et al 2024 (10)	RCT Parallel group randomized open label study	Patients with acute heart failure N = 101 I-49, C-52	N-terminal pro B-type natriuretic peptide, pg/mL Baseline median (IQR) 4275.5 [2161.0 – 8987.0] / 4528.0 [2829.5– 7725.0]	Prednisolone (40mg- 7days OD) + Usual care	Mortality: 1/49 vs. 0/52	Nt pro-BNP (pg/ml) 1872.2 (3031.27)/ 3021.3 (5306.48) P =0.5821
Buttler et al 2017 (17)	Double-blind and placebo (or low-dose)-controlled randomized clinical trial	Patients with acute heart failure N = 360 I-182, C-178	Age, median 65 (57-76) / (65 (54-74), Women 65 (36)/ 64 (36) N-terminal pro B-type natriuretic peptide, pg/mL Baseline median (IQR) NT-proBNP levels 4601 pg/mL (IQR, 2697-9596 pg/mL) /3753 pg/mL (IQR, 1968–7633 pg/ml)	Spironolactone (100 mg) + Usual care	Not reported	NT-proBNPpg/ml 2998(3124.6) /1787.33 (1085.2) (P=0.76
Liu et al 2014 (7)	RCT, non-blinded, parallel study	Patients with Acute heart failure N = 102 I-51, C-51	Age, mean 58.49 (14.9) /56.2(16.32) Women 19 (37.25)/ 14(27.45)	Dexamethasone (20mg iv stat) + Prednisolone (1mg /kg/day-7days OD) +Usual care	I = 3/51 C = 10/51	Not Reported

Risk of Bias assessment

The risk of bias for individual studies was assessed using the Cochrane Collaboration's Risk of Bias 2 (RoB 2) tool. Since only two studies shared a common primary outcome and two with one common secondary endpoint, the risk of bias assessment was conducted specifically for these studies. Overall, the studies by Cotter et al. [10], Buttler et al. [17] and Liu et al [7] were deemed to have a low risk of bias, as there were no concerns regarding participant selection, intervention classification, or deviations from the planned interventions. A visual summary of the risk of bias for each study is presented in Figure 2.

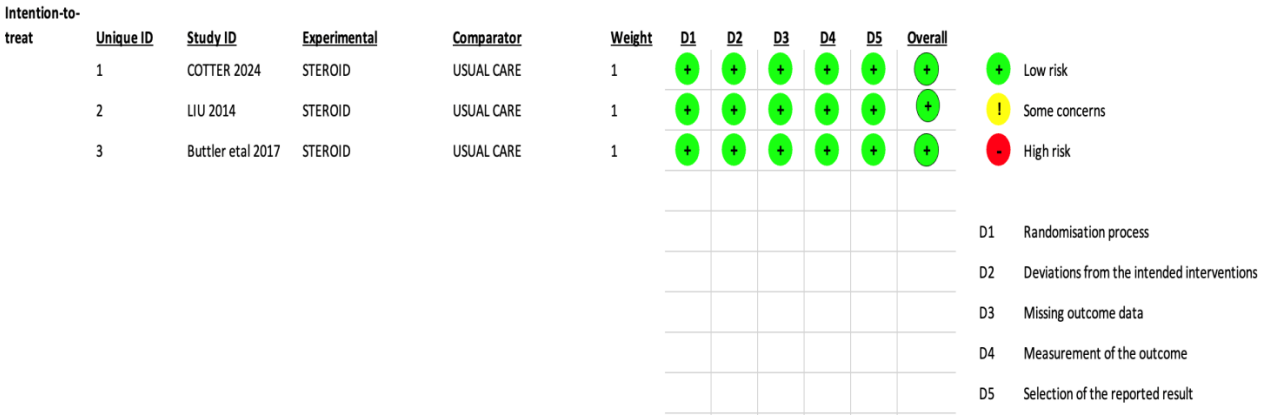

Figure 2: Risk of Bias assessment of Randomized control studies (ROB2 Scale)

Meta-analysis of primary and secondary endpoints

Primary Outcome: All-Cause Mortality

The primary outcome, all-cause mortality, was reported in two studies (Cotter et al. and Liu et al.). The meta-analysis showed no statistically significant difference in mortality between the intervention (steroid therapy plus standard care) and the control (standard care alone) groups (RR=0.59, 95% CI=0.06–6.13, p=0.66). The pooled studies demonstrated moderate heterogeneity (I^2=51%, p=0.15). The GRADE assessment classified the evidence as low quality due to imprecision, inconsistency, and limited sample size **(Figure 3).**

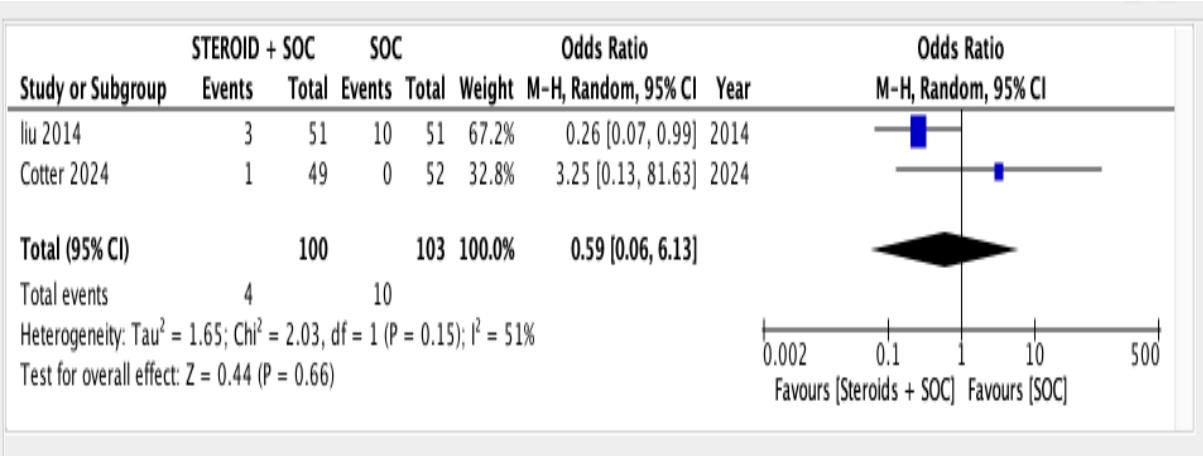

Figure 3: Forest plot of Risk ratio (RR) of Mortality with 95% confidence interval.

Secondary Outcome: Change in NT-proBNP Levels

The mean change in NT-proBNP levels was reported in two studies (Cotter et al. and Buttler et al). The intervention group showed a standardised mean difference (SMD) of 0.14 compared to the control group, which was not statistically significant (SMD=0.14, 95% CI=−0.62 to 0.90, p=0.71). The studies exhibited high heterogeneity (I^2=91%, p<0.0006), necessitating a random-effects model as shown in Figure 4. This difference was deemed clinically insignificant, and the GRADE assessment rated the evidence as moderate quality.

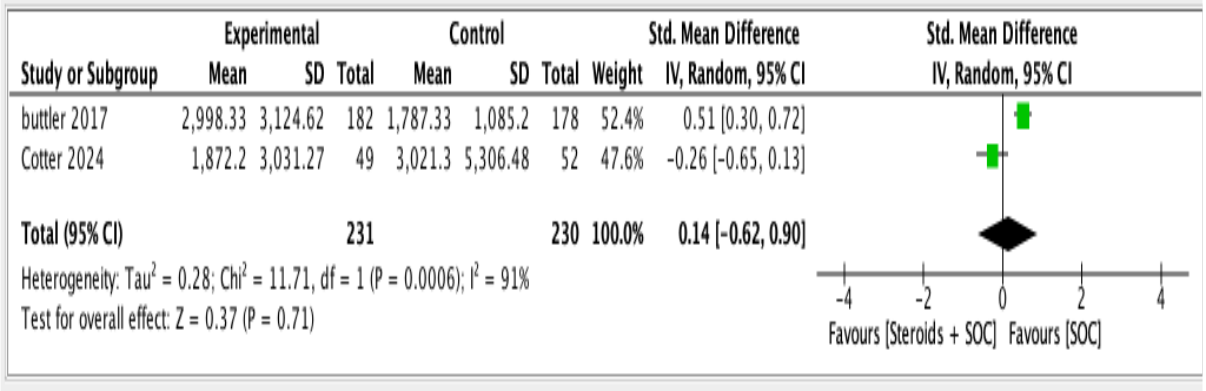

Figure 4: Forest plot of Mean difference of Nt pro-BNP with 95% confidence interval.

Publication Bias

Publication bias was not assessed due to the inclusion of only two studies, which precluded meaningful evaluation using funnel plots or statistical tests.

GRADE analysis of outcomes

The quality of evidence for primary outcomes in patients with AHF patients with steroid plus standard of care versus standard of care was assessed using the GRADE pro guideline development tool (GDT). The overall quality of evidence for all-cause mortality was graded as low. This reflects a low confidence level2 in the effect estimates, with some uncertainty due to factors such as study heterogeneity, risk of bias, and imprecision. The overall quality of evidence for Nt pro BNP was graded as Moderate. This reflects a low level of confidence in the effect estimates, with some uncertainty due to factors such as study heterogeneity. A summary of the findings, including the quality of evidence for each clinical outcome, is provided in Table 2

CI: confidence interval; MD: mean difference
Explanations
a. All studies have very low risk of bias
b. I2 > 40 %, hence serious concern with inconsistency, hence downgraded by one level
c. Mortality is patient directed outcome
d. Overall information size (OIS) of 378 in each group (OIS calculated using nMaster 2) is not met and 95% CI crosses the line of effect
e. There were not enough studies to evaluate the publication bias
f. f. I2 is >40 % hence serious concern within consistency hence downgraded by one level.

Table 2: Grade pro summary of findings among all outcomes

Certainty assessment							№ of patients		Effect			
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Steroid plus standard of care**	**Standard of care alone**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**	**Importance**
Mortality												
2	randomised trials	not serious[a]	serious[b]	not serious[c]	very serious[d]	none[e]	100	103	-	MD **0.61 higher** (0.07 higher to 5.12 higher)	⨁◯◯◯ Very low[a,b,c,d,e]	
Nt pro BNP (assessed with: mmol/L)												
2	randomised trials	not serious	serious[f]	not serious	not serious	none	231	230	-	MD **0** (0 to 0)	⨁⨁⨁◯ Moderate[f]	

Discussion

This SRMA of three RCTs involving 563 participants in total, evaluated the role of adjuvant steroid therapy along with the standard care in patients with AHF. The findings suggest that the adjuvant treatment of steroids has no beneficial impact on the primary endpoint, of all-cause mortality. However, the included studies indicate that steroid use in AHF patients may be effective in improving laboratory parameters and other secondary outcomes.

When patients with AHF and increased inflammatory markers get steroid therapy, their hsCRP levels are suppressed for the first seven days after admission. Additionally, the brief steroid treatment led to a considerably lower risk of a worsening heart attack through day 91 and a higher increase in health-related quality of life (at day 7) [17]. In contrast to worsening heart failure, glucocorticoid medication produced clinical improvement. Prednisone's short-term treatment has been associated with a notable urea rise and a less apparent decline in the estimated glomerular filtration rate during the first days of entry. Simultaneously, there were patterns of lower loop diuretic dosages, fewer rales, and a notable increase in EQ-VAS-measured quality of life[18, 19].

Historically, before the advent of loop diuretics, glucocorticoids were used to manage heart failure associated with diuretic resistance [20-22]. Loop diuretics are a crucial part of the current treatment for ADHF patients who are hospitalized with congestion-related signs and symptoms. Despite minimal effectiveness and safety findings from extensive randomized trials support the broad clinical acceptance of diuretic therapy in AHF.[23] However, observational studies demonstrated that severe diuretic use resulted in hypotension, neurohormonal system activation, and impairment of renal function.[24–26] The administration of glucocorticoids in one of the above-included RCTs led to a notable decrease in the SCr from baseline, indicating that glucocorticoids enhanced renal function.[7]

To our knowledge, this is the most up-to-date comprehensive evidence synthesis on steroids among patients with AHF, conducted as per the standard guidelines. Despite these strengths, there are notable limitations. Only two RCTs contributed data to the meta-analysis, and the included studies employed

different dosing regimens and endpoints. While the meta-analysis found no significant differences between control and intervention groups, the heterogeneity in data for all-cause mortality highlights a lack of consistent findings across trials. Additionally, no statistically significant difference in NT-proBNP levels was observed between the groups, which however was clinically significant.

Overall, all-cause mortality evidence quality was rated as low. This indicates a lack of confidence in the effect estimates and some degree of uncertainty brought on by study heterogeneity, bias risk, and imprecision. However, it shows a better response on the other parameters. There is a need for more data on all-cause mortality, and adverse events, including time to worsening heart failure, and hospital re-admission.

Strength and limitations

Our study has several strong points that ought to be emphasised. This is the first meta-analysis to comprehensively characterise the efficacy of steroids in patients with heart failure. In this meta-analysis, we only include RCTs to warrant the synthesis of data from high-quality studies. We screened three primary databases Pubmed, Scopus, Google Scholar and the trial registry.

Nevertheless, our study had several limitations that should be acknowledged. The small number of included RCTs and their corresponding small sample sizes represent a major drawback. Further drawbacks include a significant level of heterogeneity for the reported outcomes and a lack of Detection of publication bias because of the number of included studies.

Future research directions

To consolidate the findings of this meta-analysis, future research should include large-scale, high-quality RCTs to evaluate the efficacy of steroids in AHF. Studies should also explore the impact of steroids on additional endpoints, including long-term mortality, adverse events, hospital readmission rates, and health-related quality of life.

Conclusion

Steroids have no significant effect on all-cause mortality or NT-proBNP levels in patients with AHF. While secondary outcomes suggest potential benefits, these findings require validation through further RCTs to confirm the therapeutic role of steroids in this population.

Conflict of interest: The authors declare no conflicts of interest.

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