DEKA IN MEDICINE

Review

Assessing corticosteroid utilization and mortality risk in septic shock: insights from network meta-analysis

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ABSTRACT

BACKGROUND: Despite current guidelines recommending corticosteroid administration in septic shock management, there is ongoing controversy regarding their impact on mortality rates and the most effective corticosteroid type.

OBJECTIVES: To assess corticosteroid use and mortality risk in septic shock via network meta-analysis.

METHODS: A comprehensive network meta-analysis was undertaken by retrieving articles from PubMed, Embase, and Scopus databases. Pertinent data encompassing baseline characteristics of articles, definitions of sepsis, types of corticosteroids employed, and mortality rates were systematically extracted from each article. The Manthel Hanzhel method alongside a network meta-analysis approach was employed to evaluate the influence of corticosteroid administration on mortality risk among individuals diagnosed with septic shock.

RESULTS: Our analysis comprised a total of 50 articles. While indirect comparison failed to yield statistically significant results regarding the reduction in mortality risk, direct comparison indicated that corticosteroid administration was linked to a decreased risk of mortality among septic shock individuals (OR: 0.80; 95%CI: 0.68, 0.93; p Egger: 0.0550; p Heterogeneity: 0.0010; p: 0.0040). Furthermore, among all the types of corticosteroids analyzed, only the hydrocortisone and fludrocortisone combination demonstrated an association with reduced mortality risk in septic shock patients. Individuals receiving this combination therapy exhibited decreased likelihood of mortality compared to those receiving a placebo (OR: 0.78; 95%CI: 0.64, 0.96; p Egger: 0.3082; p Heterogeneity: 0.8570; p: 0.0190).

CONCLUSION: Our study emphasizes the significance of corticosteroid therapy, particularly highlighting the hydrocortisone and fludrocortisone combination, for septic shock management.

KEYWORDS: corticosteroids; septic shock; mortality; treatment.

INTRODUCTION

Septic shock remains a substantial global concern, notably in the context of intensive care unit (ICU) patient care. With a documented prevalence of 10.4% (95% CI 5.9 to 16.1%) in ICUs worldwide and a mortality rate of 38%, the elevated fatality rate associated with septic shock poses a formidable clinical challenge.[1] Mitigating this challenge necessitates concerted efforts to diminish both the incidence and mortality rates of septic shock through the implementation of comprehensive strategies and interventions. Recommended therapeutic modalities for managing septic shock include empiric antimicrobial therapy, vasopressors, inotropic agents, corticosteroids, glycemic control, and venous thromboembolism prophylaxis.[2] However, amidst these

interventions, the role of corticosteroids remains a subject of debate due to its controversial efficacy in septic shock management.[3] Further scientific inquiry is imperative to elucidate the therapeutic efficacy and possible negative outcomes associated with corticosteroids administration in this critical condition, with the overarching goal of refining treatment protocols and optimizing patient outcomes. Therefore, while advancements have been made in comprehending and addressing septic shock,[4] continuous research efforts are essential for efficiently addressing this notable healthcare challenge.

Corticosteroids, comprising both endogenous adrenal cortex-derived hormones and synthetic derivatives, exert multifaceted effects on physiological processes, encompassing stress and immune responses, inflammation modulation, metabolic regulation, and behavioral modulation.[5] Widely utilized across diverse medical conditions such as rheumatic diseases, inflammatory disorders, allergic reactions, and infectious diseases, including septic shock, corticosteroids have garnered substantial clinical interest.[6] The pivotal CORTICUS trial, the first clinical investigation into corticosteroid therapy for septic shock, demonstrated comparable mortality rates between hydrocortisone-treated and placebo groups, despite the former exhibiting expedited shock resolution and reduced vasopressor requirement.[7] The therapeutic justification for administering corticosteroids in the treatment of septic shock is based on their anti-inflammatory and immunosuppressive characteristics, as demonstrated by hydrocortisone's ability to alleviate inflammation and suppress immune hyperactivity, which are crucial for addressing the hyperinflammatory environment typical of septic shock.[8] Accordingly, guidelines supporting the application of corticosteroids in the therapy of septic shock have been established,[2] although discussions persist regarding their effect on mortality rates associated with this condition. Moreover, the optimal corticosteroid formulation for septic shock management remains elusive, warranting further investigation. Therefore, this study sought to elucidate the role of corticosteroids in septic shock mortality and ascertain the most efficacious corticosteroid type in mitigating septic shock mortality.

METHODS

Study design

A network meta-analysis, adhering to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) protocols, was undertaken to evaluate the relationship between corticosteroids utilization and mortality risk in individuals diagnosed with septic shock.[9] To ensure a thorough comparison, pertinent articles were gathered from PubMed, Embase, and Scopus databases. The collected data encompassed information on mortality rates among septic shock patients treated with different types of corticosteroids. Through meticulous extraction and analysis of this data, insights into the potential impact of corticosteroids administration on mortality outcomes in septic shock cases were sought.

Eligibility criteria

Inclusion criteria for our analysis comprised articles that fulfilled two conditions: firstly, they evaluated mortality rates among septic shock patients who received different types of corticosteroids; and secondly, they furnished standardized data facilitating the determination of mortality rates among septic shock patients treated with diverse corticosteroid types. Articles excluded from consideration encompassed reviews, commentaries, letters to the editor, and duplicate publications.

Search methodology and data retrieval

On January 10, 2024, our search for potential articles commenced across PubMed, Embase, and Scopus databases databases. Before investigating primary outcomes, we identified the potential types of corticosteroids to be involved in our study. Using Medical Subject Headings (MeSH) based keywords, including " corticosteroid" or "hydrocortisone" or "dexamethasone" or "methylprednisolone" or "betamethasone" or "prednisolone" or "hydrocortisone + fludrocortisone" and "mortality" or "survival," we conducted the search, restricting results to articles published in English. In cases of duplicate publications, only articles with substantial sample sizes were incorporated. Additionally, we explored the reference lists of pertinent systematic reviews to identify further sources. Subsequently, two independent investigators extracted the following pertinent information from potential articles: (1) name of author, (2) publication year, (3) study design, (4) age of patients, (5) sample size, (6) sepsis definition, (7) type of corticosteroid, (8) outcome, (9) quality assessment, (10) duration of follow-up, and (11) mortality rate.

Methodological quality evaluation

Before being included in our analysis, articles underwent quality assessment using the modified JADAD scale for randomized controlled trial (RCT) studies and the Newcastle – Ottawa scale (NOS) for non-RCT studies. The modified JADAD scale utilized a scoring system ranging from 0 to 7, with scores falling within the ranges of 5–7, 3–4, and 0–2 indicating high-, moderate-, and low-quality papers, respectively.[10] Similarly, the NOS scores ranged from 0 to 9, with scores of 7–9, 4–6, and 0–3 indicating high-, moderate-, and low-quality papers, respectively.[11] Articles considered low-quality were omitted from the analysis. Evaluation of quality was conducted by two separate reviewers using a pilot form. Any inconsistencies between the two authors were reconciled through discussion, ensuring a thorough and consistent evaluation process.

Outcome measure

The primary focus of our study was the mortality risk among septic shock patients receiving treatment with different types of corticosteroids. The key predictors under investigation were the specific types of corticosteroids utilized in treatment. To determine the potential corticosteroids for inclusion, an initial assessment of the data accessible through PubMed, Scopus, and Web of Science databases was conducted. From the available literature, we identified hydrocortisone, dexamethasone, methylprednisolone, betamethasone, prednisolone, and the coadministration of hydrocortisone and fludrocortisone as the corticosteroids available for analysis in our study. These identified corticosteroids were considered as the focal points for evaluating their association with mortality outcomes in septic shock patients.

Table 1. Baseline characteristics of articles included in our analysis

Study	Region	Design	SS	Sepsis definition	CS	FU	Outcome	QA
Aboab 2008	France	PC	23	ACCP/SCCM	HF	3d	M	M
Annane 2002	France	RCT	299	NA	HF	7d	SS, M	M
Annane 2018	France	RCT	1241	SOFA	HF	28d	SS, M	H
Arabi 2010	Saudi Arabia	RCT	75	NA	H	28d	SS, M	M
Blum 2015	Switzerland	RCT	785	SSCG	P	7d	SS, M	H
Bollaert 1998	France	RCT	41	NA	H	4d	SS, M	M
Bone 1987	US	RCT	381	SSG	M	14d	SS, M	H

Bosch 2023	US	RC	40	NA	HF	7d	M	M
Briegel 1999	Germany	RCT	24	NA	H	7d	SS, M	M
Briegel 2001	Germany	RCT	44	ACCP/SCCM	H	7d	M	M
Chawla 1999	US	RCT	29	NA	H	7d	M	M
Cicarelli 2007	Portugal	RCT	46	NA	D	28d	M	M
COIITSS 2010	France	RCT	335	ACCP/SCCM	HF	28d	SS, M	H
Confalonieri 2005	Italy	RCT	160	NA	H	7d	M	M
CSG 1963	US	RCT	61	NA	H	28d	M	M
Doluee 2017	Iran	RCT	408	NA	H	28d	M	M
Gordon 2014	UK	RCT	77	NA	H	28d	SS, M	M
Gordon 2016	UK	RCT	40	NA	H	14d	M	M
Hu 2009	China	RCT	341	NA	H	14d	M	M
Huang 2014	China	RCT	85	NA	H	14d	M	M
Keh 2016	Germany	RCT	44	GSS	H	14d	SS, M	H
Klastersky 1971	Belgium	RCT	44	NA	B	28d	M	M
Labib 2022	Egypt	RCT	26	SOFA	HF	14d	SS, M	H
Liu 2012	China	PC	48	NA	H	28d	M	M
Lucas 1984	US	RCT	75	NA	D	14d	M	M
Luce 1988	Canada	PC	118	NA	M	14d	M	M
Lv 2017	China	RCT	91	SOFA	H	28d	SS, M	H
Meduri 2007	US	RCT	304	ACCP/SCCM	M	7d	SS, M	H
Meijvis 2011	Netherlands	RCT	24	NA	D	7d	M	M
Mussack 2005	Germany	PC	41	ACCP/SCCM	H	7d	SS, M	H
Oppert 2005	Germany	PC	203	NA	H	7d	SS, M	M
Raurich 2007	Spain	RC	27	ACCP/SCCM	H	28d	SS, M	H
Rezk 2013	Egypt	RCT	52	NA	M	14d	SS, M	M
Rinaldi 2006	Italy	PC	80	NA	H	7d	M	M
Sabry 2011	Egypt	RCT	129	SOFA	H	7d	SS, M	H
Schumer 1976	US	PC	129	NA	D	14d	M	M
Slusher 1996	US	RCT	72	NA	D	3d	M	M
Snijders 2010	Netherlands	RCT	213	NA	P	7d	M	M
Sprung 1984	US	PC	38	NA	D	7d	M	M
Sprung 2008	Israel	RCT	37	SOFA	H	28d	SS, M	H
Tandan 2005	India	RCT	499	NA	H	7d	M	M
Tomazini 2020	Brazil	RCT	28	SOFA	D	28d	SS, M	H
Tongyoo 2016	Thailand	RCT	299	SOFA	H	28d	SS, M	H
Torres 2015	Spain	RCT	197	NA	M	7d	M	M
Valoor 2009	India	RCT	120	ACCP/SCCM	H	7d	SS, M	H
VASSCSG 1987	US	RCT	38	NA	M	14d	M	M
Venkatesh 2018	US	RCT	223	NA	H	28d	M	M
Wagner 1955	US	RCT	3681	NA	H	28d	M	M
Yildiz 2002	Turkey	RCT	113	NA	P	14d	M	M
Yildiz 2011	Turkey	RCT	40	NA	P	14d	M	M

Note, SS, sample size; FU, follow up; QA, quality assessment, CS, corticosteroids.

- Design; RCT, randomized controlled trial; PC, prospective cohort; RC, retrospective cohort.

- Sepsis definition; NA, not available; ACCP/SCCM, American College of Chest Physicians and the Society of Critical Care Medicine; SOFA, Sequential Organ Failure Assessment; SSCG, Surviving Sepsis Campaign Guidelines; SSG, Sepsis study group; GSS, German Sepsis Society.
- Steroid; H, hydrocortisone; D, dexamethasone; M, methylprednisolone; B, betamethasone; P, prednisolone; HF, hydrocortisone + fludrocortisone.
- Outcome: M, mortality; SS, septic shock.
- Quality assessment; M, moderate; H, high

Statistical analysis

Before proceeding with data analysis, we conducted an assessment to ascertain potential bias in publication and diversity among the studies. The presence of publication bias was assessed utilizing an Egger test, where a p-value < 0.05 indicated the presence of publication bias. Variability across the studies was evaluated through the implementation of the Q test, with a p-value < 0.10 indicating heterogeneity and suggesting the application of a random effects model for data analysis; alternatively, a fixed-effect model was utilized. The analysis of the data was conducted using R package software (R package, MA, US, RRID:SCR_001905). The cumulative mortality rates were synthesized in a forest plot. Comparison of mortality risk between different types of corticosteroids was conducted by calculating effect sizes, with the highest risk of mortality considered as the highest impact. To visually represent the comparison among different types of corticosteroids, the Confidence in Network Meta-Analysis software version 1.9.1 (Bern, Switzerland, RRID:SCR_016488) was utilized to construct the network diagram.

RESULTS

Study selection

A comprehensive search across databases yielded 19,754 potential papers, supplemented by an additional 28 articles from other sources. After identifying and removing 23 duplicate papers, we found that 19,670 papers were unrelated to our study's focus and were consequently excluded. Subsequently, 89 papers underwent further full-text reviews. Of these, 22 reviews and 17 papers with insufficient data were omitted from the analysis. Ultimately, a total of 50 papers were selected for detailed examination to assess the association between corticosteroids usage and mortality risk in individuals with septic shock.[7,12-60] The article selection process is depicted in Figure 1, while the details of the included papers are presented in Table 1.

The risk of mortality in individuals with septic shock receiving treatment with different types of corticosteroids

Fifty papers assessing the mortality risk among septic shock patients receiving various types of corticosteroids were gathered (Table 2). Overall, the administration of corticosteroids was linked to a reduced mortality risk in individuals with septic shock (OR: 0.80; 95%CI: 0.68, 0.93; p Egger: 0.0550; p Heterogeneity: 0.0010; p: 0.0040) (Figure 2). Among all the corticosteroids types analyzed, only the hydrocortisone and fludrocortisone combination exhibited an association with mortality risk reduction in septic shock patients, with those receiving this combination therapy demonstrating a decreased risk of mortality compared to placebo (OR: 0.78; 95%CI: 0.64, 0.96; p Egger: 0.3082; p Heterogeneity: 0.8570; p: 0.0190) (Figure 3). However, we could not establish the role of hydrocortisone (OR: 0.87; 95%CI: 0.71, 1.08; p Egger: 0.0842; p Heterogeneity: 0.0200; p: 0.2060), dexamethasone (OR: 0.60; 95%CI: 0.35, 1.04; p Egger: 0.7640; p Heterogeneity: 0.0880; p: 0.0680), methylprednisolone (OR: 0.60; 95%CI: 0.32, 1.13; p Egger: 0.1078; p Heterogeneity: 0.0020; p: 0.1170), betamethasone (OR: 0.35; 95%CI: 0.11, 1.14; p Egger: 1.0000; p Heterogeneity; 1.0000; p: 0.0830), or prednisolone (OR:

1.03; 95%CI: 0.63, 1.70; p Egger: 0.0894; p Heterogeneity: 0.5560; p: 0.9030) in reducing mortality risk among septic shock individuals.

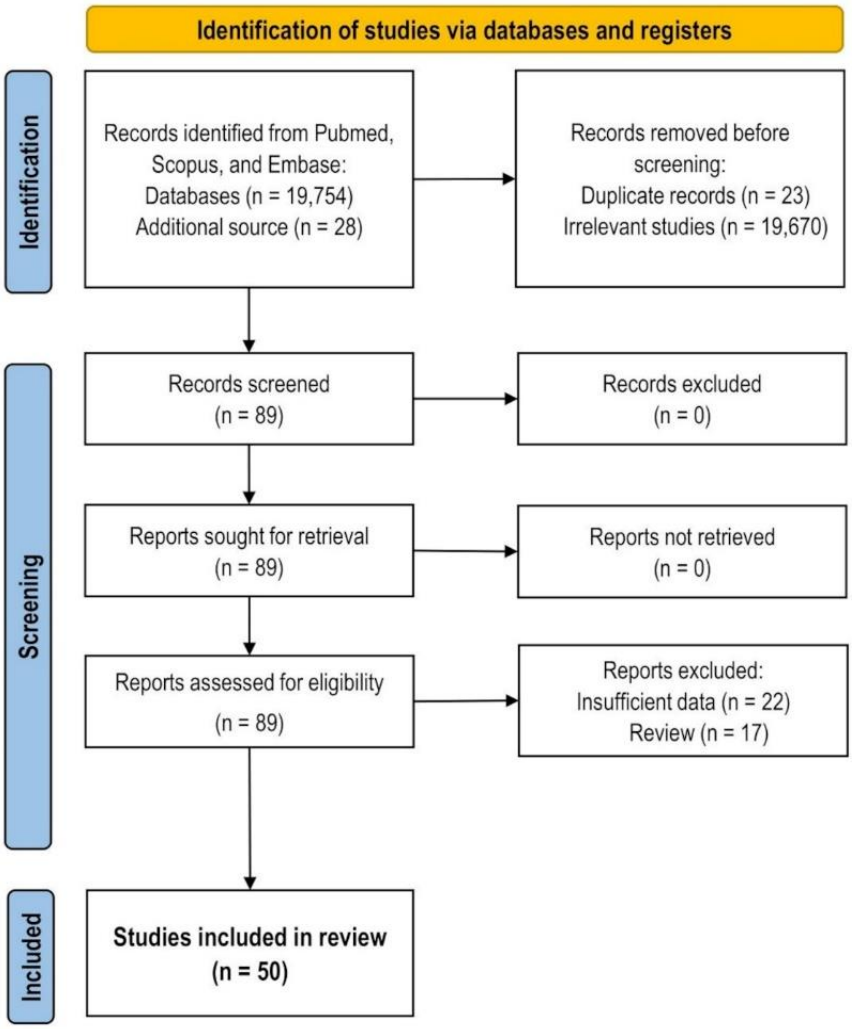

Figure 1. A flowchart of article selection in our study

The indirect comparison of mortality risk among septic shock patients treated with various types of corticosteroids

The diagram illustrating the indirect comparison of different corticosteroids and the associated mortality risk among individuals with septic shock is presented in Figure 4A. Our results indicated that the most significant reduction in mortality risk was observed with betamethasone (OR: 0.35; 95%CI: 0.10, 1.26), followed by dexamethasone (OR: 0.70; 95%CI: 0.46, 1.05), the hydrocortisone and fludrocortisone combination (OR: 0.78; 95%CI: 0.58, 1.04), hydrocortisone (OR: 0.89; 95%CI: 0.74, 1.08), and methylprednisolone (OR: 0.78; 95%CI: 0.54, 1.13). Conversely, prednisolone exhibited the least favorable reduction in mortality risk (OR: 1.01; 95%CI: 0.58, 1.77). However, our analysis suggested that the reduction in mortality risk through indirect comparison did not yield statistically significant results (Figure 4B).

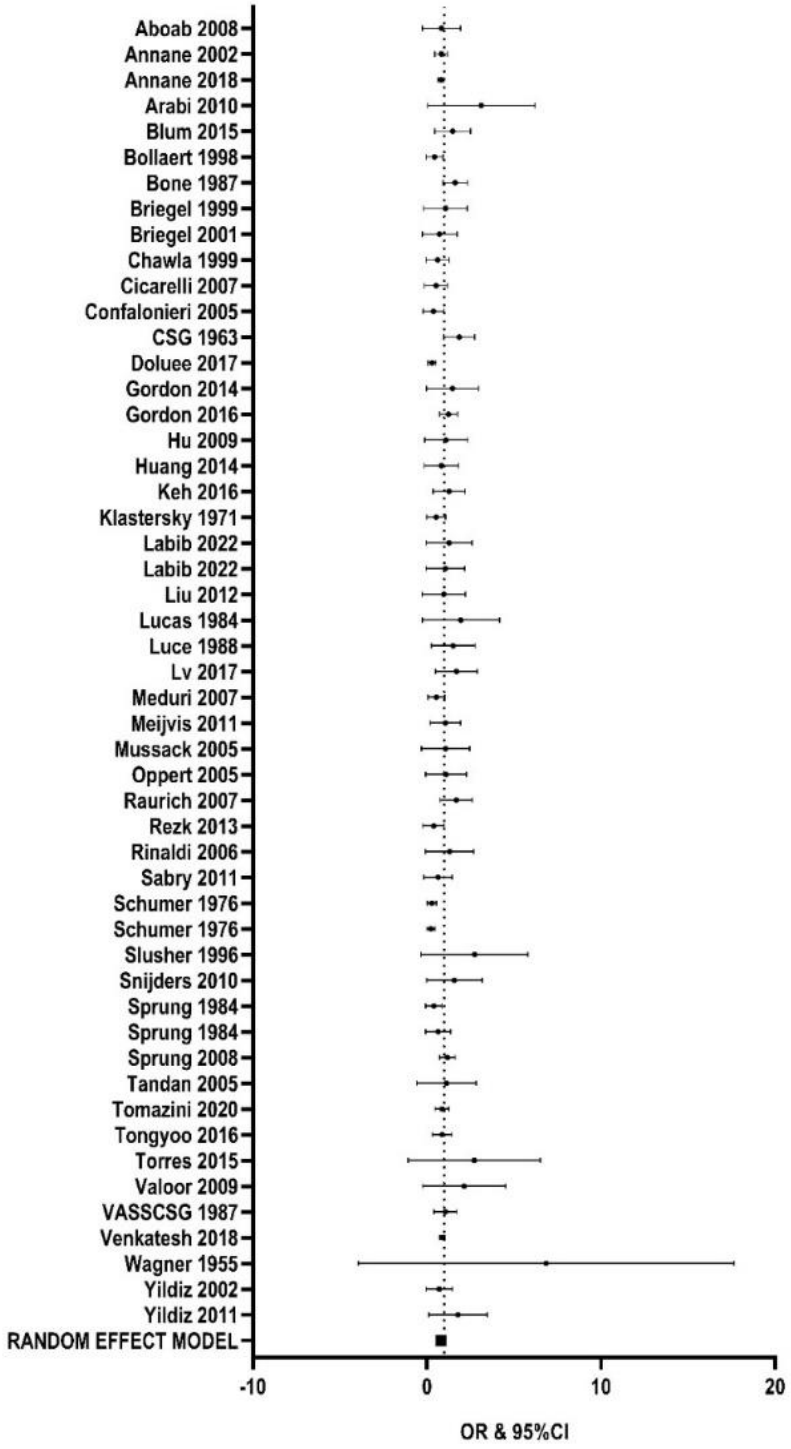

Figure 2. A forest plot of the association between corticosteroids and the risk of mortality among patients with septic shock (OR: 0.80; 95%CI: 0.68, 0.93; p Egger: 0.0550; p Heterogeneity: 0.0010; p: 0.0040)

Source of heterogeneity and publication bias

Our findings indicated that the variables all corticosteroids, hydrocortisone, dexamethasone, and methylprednisolone displayed heterogeneity ($p<0.10$). Consequently, these variables were analyzed utilizing a random effects model. In contrast, the variables betamethasone, prednisolone, and the combination of hydrocortisone and fludrocortisone were analyzed using a fixed effects model as they did not exhibit heterogeneity ($p>0.10$). Furthermore, regarding the assessment of

publication bias risk, the Egger test results revealed no evidence of bias (p>0.05) across all variables.

DISCUSSION

In our investigation, carried out within the framework of indirect comparison, we thoroughly explored the efficacy of corticosteroids in lowering mortality risk among individuals diagnosed with septic shock. Our findings revealed a lack of substantial evidence supporting the advantageous role of corticosteroids in this particular scenario. Consistent with earlier study, our results emphasized the minimal impact of various types of corticosteroids on reducing mortality risk in individuals with septic shock when subjected to rigorous networking analysis. Our study notably stood out for its thoroughness, employing a comprehensive methodology that analyzed a wide-ranging dataset comprising 50 articles. This approach differed from the more limited focus found in previous network meta-analysis, which included fewer publications.[61] This broader dataset bolstered the statistical robustness and generalizability of our findings, thereby enhancing confidence in the conclusions drawn from our study.

In our study, conducted within the context of direct comparison, the findings revealed that the utilization of corticosteroids was linked with a decrease in mortality risk among individuals with septic shock. Furthermore, our study indicated that among all types of corticosteroids, only the administration of hydrocortisone and fludrocortisone combination was linked with a decrease in mortality risk. These findings were consistent with several previous studies that had shown that, overall, corticosteroids played a crucial role in mitigating the risk of mortality in individuals with septic shock.[62-68] Regarding the type of corticosteroids, our results also aligned with previous studies that had revealed that the hydrocortisone and fludrocortisone combination had a beneficial impact on lowering the risk of mortality in individuals with septic shock.[69] However, our study had advantages over previous studies in that we had a larger sample size and evaluated all types of corticosteroids. Previous studies had a range of articles between 5 to 37, while our study involved 50 articles. Furthermore, our study evaluated all types of corticosteroids, including hydrocortisone, dexamethasone, methylprednisolone, betamethasone, prednisolone, and the combination of hydrocortisone with fludrocortisone, whereas previous studies were limited to corticosteroids in general.[62-69] Therefore, it could be concluded that the results of our study were more robust, comprehensive, and of higher quality.

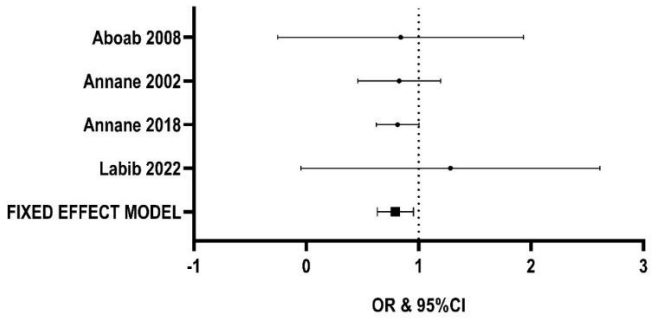

Figure 3. A forest plot of the association between hydrocortisone + fludrocortisone and the risk of mortality among patients with septic shock (OR: 0.78; 95%CI: 0.64, 0.96; p Egger: 0.3082; p Heterogeneity: 0.8570; p: 0.0190).

The mechanisms elucidated in our study were intricate and posed challenges in explication. However, several factors might underlie the mechanisms observed in our investigation. First, the enhanced survival associated with corticosteroids in our study

could have arisen from a reduction in shock duration, inflammation severity,[32] and organ dysfunction frequency.[21,32] Furthermore, previous study indicated that corticosteroids were linked to improved vascular contractility and hemodynamics, as well as inhibition of inflammatory cell recruitment, proliferation, and pro-inflammatory mediator release.[70] These phenomena likely accounted for the observed lower mortality rates among septic shock individuals treated with corticosteroids in our study. Conversely, the precise rationale behind the exclusive contribution of hydrocortisone-fludrocortisone combination therapy to mortality risk reduction in our study remained uncertain. It is notable that combining fludrocortisone with hydrocortisone aimed to bolster mineralocorticoid activity, which, in turn, influenced fluid balance regulation.[71] Moreover, the physiological effects of mineralocorticoids were regulated by the mineralocorticoid receptor (MR) present in various organs, suggesting potential non-renal immune effects. Animal models suggested a downregulation of MR in sepsis-associated endothelial cells, while clinical studies indicated improved survival and reduced IL-6 levels with mineralocorticoid supplementation.[72,73] Additionally, inadequate aldosterone levels observed in septic shock patients pointed towards adrenal insufficiency, potentially contributing to increased mortality.[74] This explanation was likely to have served as the basis for the mechanism underlying our study findings.

Our study emphasized the importance of corticosteroid use in cases of septic shock. Through this study, evidence from multiple studies could be synthesized to provide a comprehensive overview of the relationship between corticosteroid administration and mortality risk in individuals with septic shock. Additionally, the study could guide clinical decision-making regarding corticosteroid use in the management of septic shock, recommending the use of a combination of hydrocortisone and fludrocortisone. Furthermore, the study could help identify specific treatments that were more effective in reducing mortality risk among individuals with septic shock. Moreover, the study could have highlighted areas where further study was needed to understand the mechanisms underlying the relationship between corticosteroids use and mortality risk in septic shock. This could have stimulated future investigations to fill existing knowledge gaps and improve patient care.

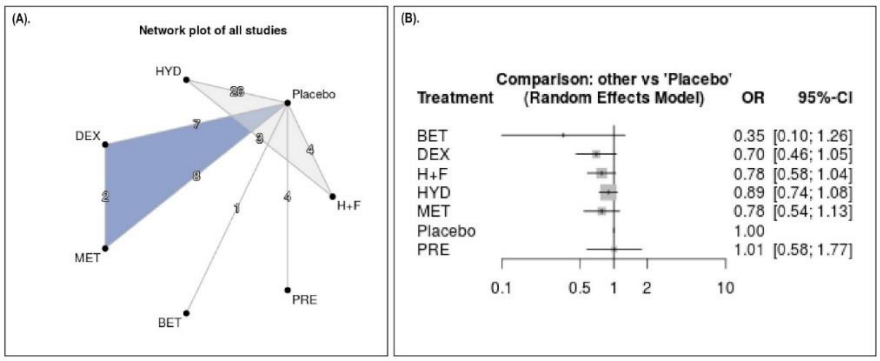

Figure 4. The indirect comparison of different corticosteroids and the risk of mortality among patients with septic shock. (A). A network plot of studies. (B). The comparison of the risk of mortality among corticosteroids.

We acknowledged several limitations in this study. First, we did not evaluate potential factors that could have increased the risk of mortality in individuals with septic shock, such as the type of underlying infection, timing of diagnosis, organ failure, and comorbidities. Therefore, the outcomes of this study should be approached with caution in interpretation. Second, there were differences in the definitions used to determine sepsis or septic shock across various studies. This raised concerns as one

criterion for sepsis and another may have differed in context. Third, there were differences in the length of follow-up periods across the studies. This could have potentially introduced a risk of bias due to the highly variable follow-up durations. Fourth, despite the study involving numerous articles, the sample size in each study was small, and there was an imbalance between cases and controls.

Table 2. Summary of the risk of mortality in patients with septic shock treated with corticosteroids.

Steroids (*vs*. placebo)	OR	95%CI	p Egger	P Het	p
All corticosteroids	0.80	0.68 – 0.93	0.0550	0.0010	0.0040
Hydrocortisone	0.87	0.71 – 1.08	0.0842	0.0200	0.2060
Dexamethasone	0.60	0.35 – 1.04	0.7640	0.0880	0.0680
Methylprednisolone	0.60	0.32 – 1.13	0.1078	0.0020	0.1170
Betamethasone	0.35	0.11 – 1.14	1.0000	1.0000	0.0830
Prednisolone	1.03	0.63 – 1.70	0.0894	0.5560	0.9030
Hydrocortisone + fludrocortisone	0.78	0.64 – 0.96	0.3082	0.8570	0.0190

Note, OR, odd ratio; CI, confidence interval; p Het, p Heterogeneity.

CONCLUSION

In conclusion, our investigation highlights the contrasting findings regarding the efficacy of corticosteroids in mitigating mortality risk among individuals with septic shock, as observed in indirect and direct comparison contexts. While indirect comparison revealed a lack of substantial evidence supporting the advantageous role of corticosteroids, direct comparison demonstrated a significant association between corticosteroids use, particularly hydrocortisone and fludrocortisone combination, and reduced mortality risk, emphasizing the importance of corticosteroids therapy in septic shock management.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

None.

CONFLICTS OF INTEREST

We have no conflict of interest

FUNDING SOURCES

We have no source of funding

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None

AUTHOR CONTRIBUTION

Conceptualization: WAS; Data Curation: WAS; Formal Analysis: WAS; Investigation: WAS; Project Administration: WAS; Resources: WAS; Methodology: WAS; Software: WAS; Visualization: WAS; Supervision: WAS; Validation: WAS; Writing – Original Draft Preparation: WAS, VD; Writing – Review & Editing: WAS, VD. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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