WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 9, 01-18. Research Article ISSN 2277–7105

CORTICOTHERAPY AND COVID-19 HOSPITALIZED PATIENT MORTALITY - IMPACT OF STUDY DESIGN, TEMPORALITY AND PUBLICATION STATUS ON STUDY RESULTS: A META-ANALYSIS

Akunga Nahashon G.*[1], Murithi Mary K.[1]

[1]Department of pre-Clinicals and Pharmacognosy, School of Pharmacy, Kabarak University, Nakuru, Kenya.

Article Received on
06 March 2025,

Revised on 27 March 2025,
Accepted on 17 April 2025

DOI: 10.20959/wjpr20259-36171

***Corresponding Author**
Akunga Nahashon G.
Department of pre-Clinicals and Pharmacognosy, School of Pharmacy, Kabarak University, Nakuru, Kenya.

ABSTRACT

Background: COVID-19, a viral infection of the respiratory system causes inflammation that can compromise lung function. Corticosteroids have been used to treat this inflammatory response though the efficacy is still debatable. ***Objective***: To assess whether study design, temporality, and publication status influenced the reported efficacy of corticosteroids in reducing mortality among hospitalized COVID-19 patients.. ***Methods:*** Studies were retrieved from PubMed, Google Scholar and MEDRXIV. Eligible studies were those conducted between 2019 and 2024, had a clear endpoint (mortality), had a treatment group (corticosteroid group) and a control (no corticosteroids). The pooled risk difference in mortality between corticosteroid treated and corticosteroid-untreated was computed taking into account study design, publication status (i.e., peer-reviewed vs. preprint) and the timing (temporality) of when the studies were conducted. ***Results:*** Nineteen studies involving 21,583 participants were analyzed. The overall pooled risk difference in mortality between corticosteroid-treated and untreated patients was **0.01** (95% CI: -0.03, 0.05). Nine randomized controlled trials (RCTs) with 9,537 patients showed a pooled risk difference of **-0.05** (95% CI: -0.10, 0.01), while 11 cohort studies with 12,046 patients had a pooled risk difference of **0.05** (95% CI: -0.01, 0.11). The difference in effect between RCTs and cohort studies was statistically significant (**p = 0.02**). Thirteen published studies (11,362 participants) had a pooled risk difference of **-0.02** (95% CI: -0.08, 0.03), compared to six unpublished studies (10,221 participants) with a pooled risk difference of **0.05** (95% CI: -0.01, 0.12). The difference between published and unpublished

studies was not statistically significant (**p = 0.08**).Eight studies conducted during or before 2020 (10,438 participants) had a pooled risk difference of **0.00** (95% CI: -0.06, 0.07), while 11 studies conducted after 2020 (11,145 participants) had a pooled risk difference of **0.01** (95% CI: -0.05, 0.06). There was no significant difference between studies conducted during or before 2020 and those conducted after (p = 0.99).Corticosteroids do not significantly reduce the risk of mortality among hospitalized COVID-19 patients overall. However, a significant difference was observed between randomized controlled trials (RCTs) and cohort studies, with RCTs suggesting a possible benefit of corticosteroids compared to cohort studies. These findings underscore the influence of study design on treatment outcomes and highlight the need for cautious interpretation of non-randomized evidence.

KEY WORDS: COVID-19, Corticosteroids, Study Design, Mortality, Corticotherapy, Publication, Temporality, RCT, COHORT.

BACKGROUND

Coronavirus disease (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and primarily presents as a respiratory illness.[1] While many individuals experience mild to moderate symptoms and recover, others develop severe illness requiring hospitalization, and in some cases, the disease can lead to death.[2],[3] COVID-19 spreads mainly via person-to-person transmission, including asymptomatic carriers.[4] At the height of the COVID-19 Pandemic numerous therapeutic strategies were urgently adopted to reduce disease severity and mortality. These included antiviral agents like remdesivir and ritonavir[5] as well as antibiotics such as azithromycin to manage secondary bacterial infections.[6],[7] Corticosteroids—including hydrocortisone, methylprednisolone, and prednisolone—were widely administered to control the severe lung inflammation attributed to cytokine storms in critically ill patients.[8],[9] The other interventions included the administration of supplemental oxygen and mechanical ventilation.[10],[11] Corticosteroids suppress the release of pro-inflammatory cytokines and modulate the activity of T lymphocytes and macrophages, key mediators of inflammation.[12],[13] However, their efficacy in reducing mortality among hospitalized COVID-19 patients remains debated, with existing studies producing mixed results.[14], [15], [16]

Despite numerous trials and observational studies, there is limited clarity on whether factors such as study design, timing during the pandemic, and publication status influence the reported effect

of corticosteroids on mortality. Given this uncertainty, a meta-analysis offers a robust approach to synthesizing existing evidence and exploring the influence of these methodological variables.

This meta-analysis quantitatively assessed whether study design, temporality (time study was conducted), and publication status influenced the reported effect of corticosteroids on mortality in hospitalized COVID-19 patients with moderate to severe or critical illness.

METHODS

Search Strategy and Data Sources

A systematic literature search was conducted using PubMed, Google Scholar, and MEDRXIV to identify relevant studies published between 2019 and 2024. The search included both peer-reviewed and preprint articles. Keywords used in various combinations included: *"COVID-19," "SARS-CoV-2," "corticosteroids," "dexamethasone," "hydrocortisone," "methylprednisolone,"* and *"mortality."* Additionally, reference lists of included studies were manually screened to identify further eligible studies.

Eligibility Criteria

Studies were included if they met the following criteria: (1) involved hospitalized COVID-19 patients with moderate to critical illness, (2) reported mortality as an outcome, (3) used corticosteroids plus standard care as the intervention, and (4) included a comparison/control group receiving standard care alone. Moreover, studies had to provide sufficient data to compute the risk difference, including the sample sizes in both intervention and control groups. Only studies published in English between 2019 and 2024 were considered. Studies were excluded if they did not report mortality outcomes, lacked a comparison group, or were case reports, reviews, or editorials without extractable data.

Data Extraction and Management

Two independent reviewers screened titles and abstracts to assess eligibility. Full texts of potentially relevant studies were reviewed against the inclusion criteria. A standardized data extraction form was used to collect information on study design, sample size, type of corticosteroid, mortality outcomes, year of publication or posting, and publication status (published or preprint). Disagreements were resolved through discussion or by involving a third reviewer. All data were securely stored and organized for analysis.

Statistical Analysis

The primary outcome was the risk difference in mortality between corticosteroid-treated and control groups. A random-effects meta-analysis model was applied using the DerSimonian-Laird

estimator to account for between-study heterogeneity. Heterogeneity was assessed using the Q-test, I^2 statistic, and tau-squared (τ^2). When $\tau^2 > 0$, a prediction interval was also computed to indicate the likely range of the true effect sizes across studies. Forest plots were generated to visually represent individual and pooled effect sizes with corresponding 95% confidence intervals (CI).

Outlier and influence analyses were conducted using studentized residuals and Cook's distances. Studies were considered potential outliers if their studentized residual exceeded the Bonferroni-corrected threshold. Influential studies were identified if their Cook's distance exceeded the median plus six times the interquartile range of all Cook's distances. Publication bias and small-study effects were examined using funnel plots, along with the rank correlation test and regression test with the standard error as a predictor.

Subgroup and Sensitivity Analyses

Subgroup analyses were performed to compare pooled effect sizes based on study design (RCTs vs. observational studies), publication status (published vs. unpublished (Pre-Prints)), and study timing (conducted during or before 2020 vs. after 2020). Sensitivity analyses involved systematically excluding studies identified as outliers or influential and observing the impact of their removal on the overall risk difference estimates. These analyses were conducted to assess the robustness and consistency of the findings.

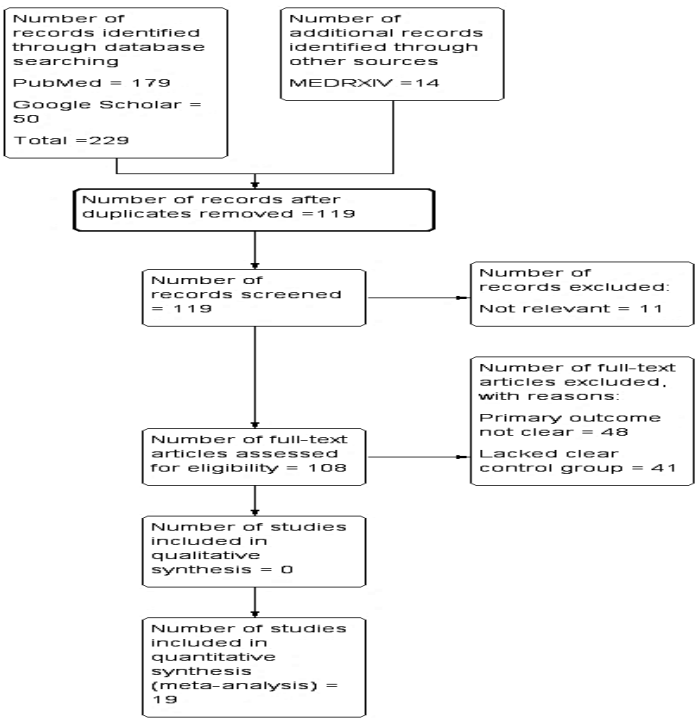

Figure1: ***Flow Chart: Selection of eligible Studies for Meta – Analysis.***

RESULTS

Table 1*: Characteristics of Included Studies.*

Variable	characteristic	Number (n)	Total (N)	Proportion (n/N)	p-value
Year of Publication/ Submission	2020	6	19	0.316	0.167
	2021	9	19	0.474	1.00
	2022	1	19	0.053	<0.001
	2023	2	19	0.105	<0.001
	2024	1	19	0.053	<0.001
Publication Status	Pre-Prints	6	19	0.316	0.167
	Published	13	19	0.684	0.167
Study Design	COHORT	10	19	0.526	1.00
	RCT	9	19	0.474	1.00

Note. *Proportions tested against value: 0.5 (H_0 =0.5).; RCT=Randomized Controlled Trial*

Table 2*: Summary of Included Studies.*

AUTHORS	YEAR	TITLE OF STUDY	DESIGN	EFFECT SIZE SUMMARY
Published Studies				
1.Emad R. Issak	March 2023	Timing of corticosteroids in non-severe non-hospitalized COVID-19 patients: open-label, two-center, randomized controlled study (TICS-COV19 study)	RCT	28-day mortality was significantly lower in the corticosteroid group (11.14%) compared to control (18.67%), OR = 0.55 (95% CI: 0.36, 0.83), p = 0.004
2.Jamaat et al	July 2021	No clinical benefit of high dose corticosteroid administration in patients with COVID-19: A preliminary report of a randomized clinical trial	RCT	There was no statistically significant difference in mortality between groups; 64% of patients in the dexamethasone group and 60% in the control group died (p = 0.500). The remaining patients were discharged during the 28-day follow-up period.
3.Munch et al	Nov. 2021	Low-dose hydrocortisone in patients with COVID-19 and severe hypoxia: The COVID STEROID randomized, placebo-controlled trial	RCT	The reported mortality was 6 out of 16 patients (37.5%) in the corticosteroid group compared to 2 out of 14 patients (14.3%) in the control group. No statistical significance was reported.
4.Salvarani et al	Oct. 2022	Intravenous methylprednisolone pulses in hospitalized patients with severe COVID-19 pneumonia:	RCT	There was no statistically significant difference in mortality. Death occurred in 20.0% of patients in the corticosteroid group versus

		a double-blind, randomized, placebo-controlled trial		16.1% in the control group (HR = 1.26, 95% CI: 0.74–2.16, p = 0.176). Similarly, overall mortality was 10.0% in the corticosteroid group compared to 12.2% in the control group (HR = 0.83, 95% CI: 0.42–1.64, p = 0.584).
5.Edalatifard et al	Dec. 2020	Intravenous methylprednisolone pulse as a treatment for hospitalized severe COVID-19 patients: results from a randomized controlled clinical trial	RCT	There was a highly statistically significant reduction in mortality in the methylprednisolone group, with a mortality rate of 5.9% compared to 42.9% in the control group (p < 0.001).
6.Dequin et al	July 2020	Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19: A Randomized Clinical Trial	RCT	The study reported 11 deaths in the hydrocortisone group compared to 20 deaths in the placebo group. The primary outcome was treatment failure on day 21, although statistical significance for mortality was not reported.
7.RECOVERY Collaborative Group	July 2021	Dexamethasone in Hospitalized Patients with Covid-19	RCT	There was a highly statistically significant reduction in 28-day mortality in the dexamethasone group, with 22.9% (482/2104) of patients dying compared to 25.7% (1110/4312) in the usual care group (age-adjusted rate ratio = 0.83, 95% CI: 0.75–0.93, p < 0.001).
8.Sen et al	July 2021	Inhaled corticosteroids do not adversely impact outcomes in COVID-19 positive patients with COPD: An analysis of Cleveland Clinic's COVID-19 registry	RCT	There were no statistically significant differences in in-hospital outcomes between patients receiving inhaled corticosteroids (ICS) and those who did not. ICU admission occurred in 36.8% (74/201) of ICS users versus 31.2% (53/170) of non-users (p = 0.30); endotracheal intubation in 21.9% (44/201) vs 16.5% (28/170), respectively (p = 0.24); and mortality in 18.4% (37/201) vs 20.0% (34/170), respectively (p = 0.80).
9.Piniella-Ruiz et al	July 2021	Impact of Systemic Corticosteroids on Mortality in Older Adults with Critical	RCT	In-hospital mortality was significantly lower in the corticosteroid group (68.2%) compared to the non-

		COVID-19 Pneumonia		corticosteroid group (81.8%). Corticosteroid treatment was identified as an independent survival factor (HR = 0.61, 95% CI: 0.41–0.93, p = 0.006), indicating a statistically significant association with improved survival.
10.RECOVERY Collaborative Group	July 2023	Higher dose corticosteroids in patients admitted to hospital with COVID-19 who are hypoxic but not requiring ventilatory support (RECOVERY): a randomised, controlled, open-label, platform trial	RCT	There was a statistically significant increase in 28-day mortality among patients receiving higher dose corticosteroids, with 19% (123/659) deaths compared to 12% (75/613) in the usual care group (rate ratio = 1.59, 95% CI: 1.20–2.10, p = 0.0012).
11.Albani et al	July 2021	Effect of corticosteroid treatment on 1376 hospitalized COVID-19 patients. A cohort study.	COHORT	Among 559 patients (39%) exposed to corticosteroids during hospitalization, 30.6% (171/559) died, compared to 21.7% (183/844) in the non-corticosteroid group. The difference in mortality was statistically significant (unadjusted p < 0.001).
12.Cusacovich et al	July 2021	Corticosteroid Pulses for Hospitalized Patients with COVID-19: Effects on Mortality	COHORT	Among 124 patients receiving corticosteroid pulses (250 mg of methylprednisolone for three days), 30.3% (37/122) died compared to 42.9% (57/133) in the non-corticosteroid group. The difference in mortality was statistically significant at 12.6% (95% CI: 8.54–16.65), with a log-rank test statistic of 4.72 (p = 0.03).
13.Li et al	Nov. 2021	Adverse Outcomes Associated with Corticosteroid Use in Critical COVID-19: A Retrospective Multicenter Cohort Study	COHORT	A total of 68 patients were treated with corticosteroids (CS group), while 28 were not (non-CS group). Multivariable logistic regression was used to assess the association between corticosteroid use and treatment outcomes. Mortality was notably higher in the CS group, with 68% (46/68) deaths compared to 21% (6/28) in the non-CS group. Statistical significance was not reported.

Pre-Prints (Unpublished Studies)				
1.Jianfeng Wu et al	May 2020	Systemic corticosteroids show no benefit in severe and critical COVID-19 patients in Wuhan, China: A retrospective cohort study	COHORT	In-hospital mortality was reported in 15.6% (83/531) of patients in the corticosteroid group and 2.6% (26/983) in the non-corticosteroid group. Statistical significance was not reported.
2.Jianfeng Wu et al B	May 2020	Systemic corticosteroids show no benefit in severe and critical COVID-19 patients in Wuhan, China:	COHORT	In-hospital mortality occurred in 44.0% (70/159) of patients in the corticosteroid group compared to 15.6% (14/90) in the non-corticosteroid group. Statistical significance was not reported.
3.RECOVERY Collaborative Group	Sept. 2024	Higher dose corticosteroids in hospitalized COVID-19 patients requiring ventilatory support (RECOVERY): a randomised, controlled, open-label, platform trial	RCT	In-hospital mortality was reported in 35.0% (86/246) of patients in the corticosteroid group and 37.7% (87/231) in the non-corticosteroid group. Statistical significance was not reported.
4.Kristina Crothers et al	July 2021	Early initiation of corticosteroids in patients hospitalized with COVID-19 not requiring intensive respiratory support: cohort study	COHORT	In-hospital mortality occurred in 12.9% (441/3,406) of patients in the corticosteroid group compared to 10.4% (356/3,419) in the non-corticosteroid group. Statistical significance was not reported.
5.Gallay Laure et al	Nov. 2020	Corticosteroids are associated with increased survival in elderly presenting severe SARS-Cov2 infection	COHORT	In-hospital mortality was 40.6% (39/96) in the corticosteroid group and 53.2% (91/171) in the non-corticosteroid group. Statistical significance was not reported.
6.The COCORICO Collaborative Group	Sept. 2020	Association between corticosteroids and intubation or death among patients with COVID-19 pneumonia in non-ICU settings: an observational study using of real-world data from 51 hospitals in France and Luxembourg	COHORT	In-hospital mortality occurred in 8.9% (18/203) of patients in the corticosteroid group compared to 6.7% (46/688) in the non-corticosteroid group. Statistical significance was not reported.

CS: Corticosteroid, RCT: Randomized controlled trial, COHORT: Cohort Study, OR: odds ratio, CI: confidence interval, HR: hazard ratio

Effect of corticosteroids on COVID-19 Mortality- Overall effect (Risk Difference)

A total of k=19 studies were included in the analysis. The observed risk differences ranged from -0.382 to 0.495, with the majority of estimates being negative (53%). The pooled average risk difference based on the random-effects model was 0.01 (95% CI: -0.030 to 0.05). Therefore, the average outcome did not differ significantly from zero (z = 0.3310, p = 0.7406), indicating no overall difference in mortality between corticosteroid-treated and untreated groups (Figure 2).

The Q-test revealed significant heterogeneity among the included studies ($Q(18) = 174$, $p < 0.0001$), with substantial between-study variability (**tau² = 0.001**, **I² = 90%**). A 95% prediction interval for the true effects ranged from **–0.1411 to 0.1545**, suggesting that while the average effect is slightly positive, true effects in individual studies may vary considerably, and in some cases may even be negative.

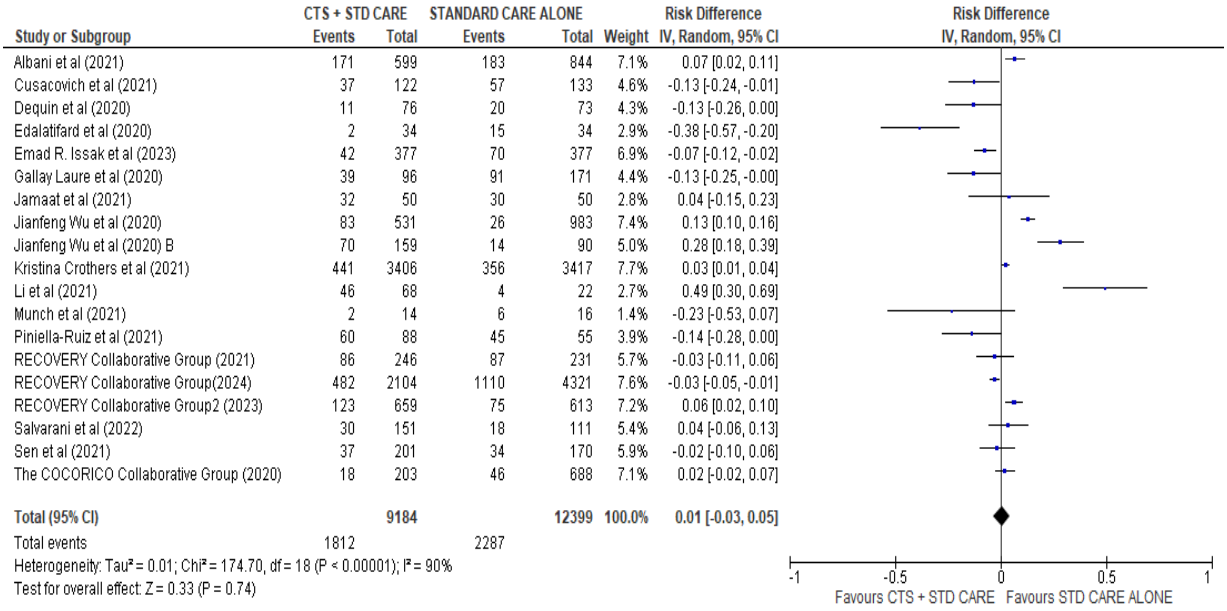

Figure 2*: Forest plot :- Effect of corticosteroids on COVID-19 mortality - Overall effect. CTS=Corticosteroids, STD CARE=Standard Care, IV=Inverse variance, Events = Mortalities; Total= Sample Size(n)*

Effect of Study Design on Risk Difference

A total of 19 studies were included in the subgroup analysis to assess whether study design influenced mortality outcomes in hospitalized COVID-19 patients. The nine randomized controlled trials (RCTs) yielded a pooled risk difference of –0.05 (95% CI: –0.10 to 0.01; p = 0.12), indicating that the effect was not statistically significant. There was significant

heterogeneity among the RCTs (Q, $p < 0.0001$).In contrast, the 10 cohort studies produced a pooled risk difference of 0.05 (95% CI: –0.01 to 0.11; p = 0.08), which was also not statistically significant. However, heterogeneity among cohort studies was similarly high ($p < 0.0001$). The overall pooled risk difference for both subgroups combined was 0.01 (95% CI: –0.03 to 0.05; p = 0.74), with substantial heterogeneity between the two designs ($p < 0.0001$). Notably, a chi-square test for subgroup differences revealed a statistically significant difference between RCTs and cohort studies ($\chi^2 = 5.45$, df = 1, p = 0.02) (Figure 3)

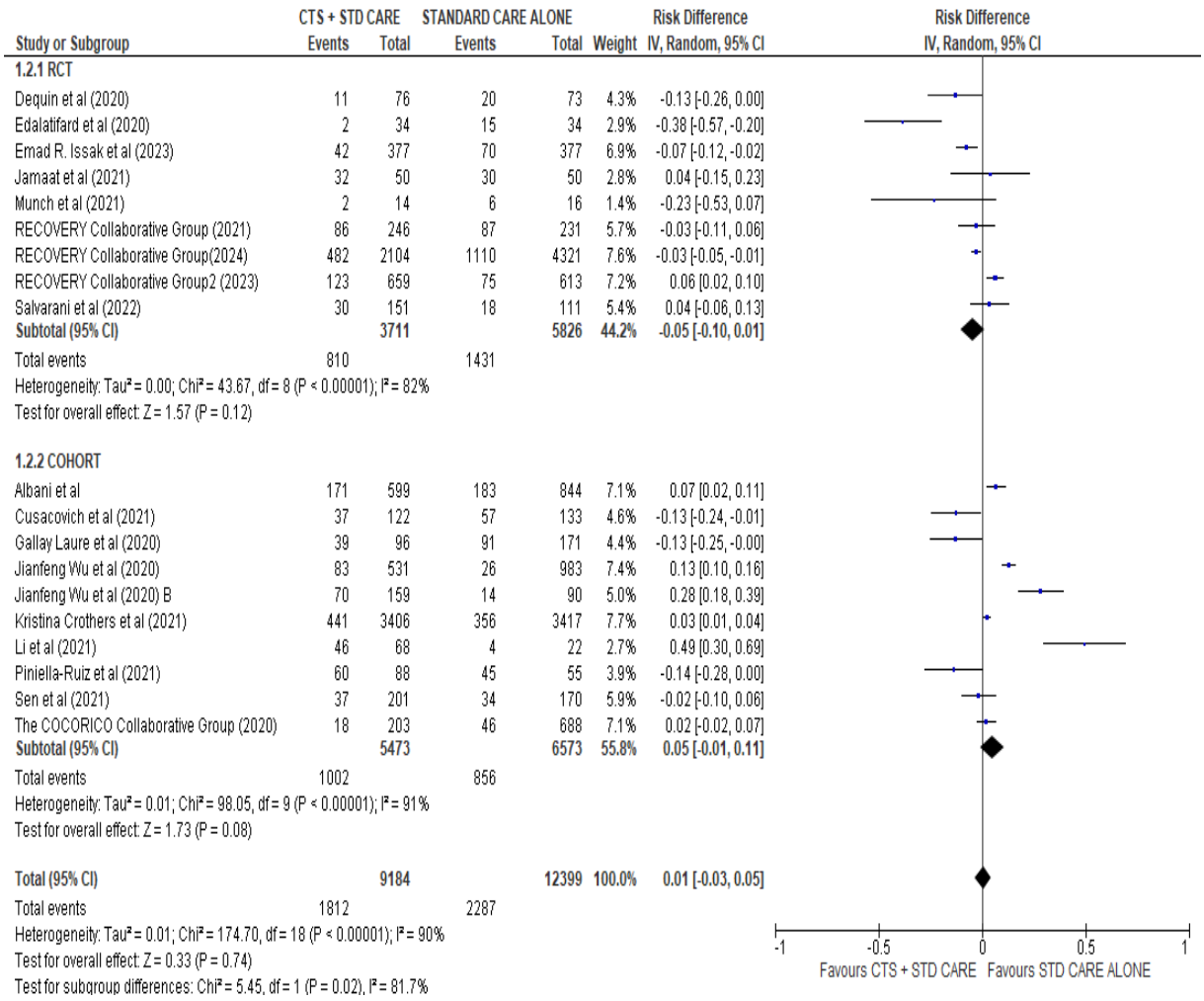

Figure 3*: Forest plot :- Corticosteroids and COVID-19 Mortality - RCTs vs COHORTS. CTS=Corticosteroids, STD CARE=Standard Care, IV=Inverse variance, Events = Mortalities; Total= Sample Size(n); Events = Mortalities*

Effect of Publication Status on Risk Difference

Thirteen published and six unpublished (preprint) studies were analyzed. The pooled risk difference from the published studies was –0.02 (95% CI: –0.08 to 0.03; p = 0.42). There was significant heterogeneity ($\tau^2 = 0.01$, $\chi^2 = 88$, $df = 12$, $I^2 = 86\%$, $p < 0.0001$). For the six

unpublished studies, the risk difference was 0.05 (95% CI: –0.01 to 0.12; p = 0.11), also not statistically significant. Heterogeneity remained high (τ^2 = 0.01, χ^2 = 62.7, *df* = 5, I^2 = 92%, *p* < 0.0001). The combined analysis of both groups yielded an overall risk difference of 0.01 (95% CI: –0.03 to 0.05; p = 0.74). A subgroup comparison showed no statistically significant difference between published and unpublished studies (χ^2 = 3.08, df = 1, p = 0.08).

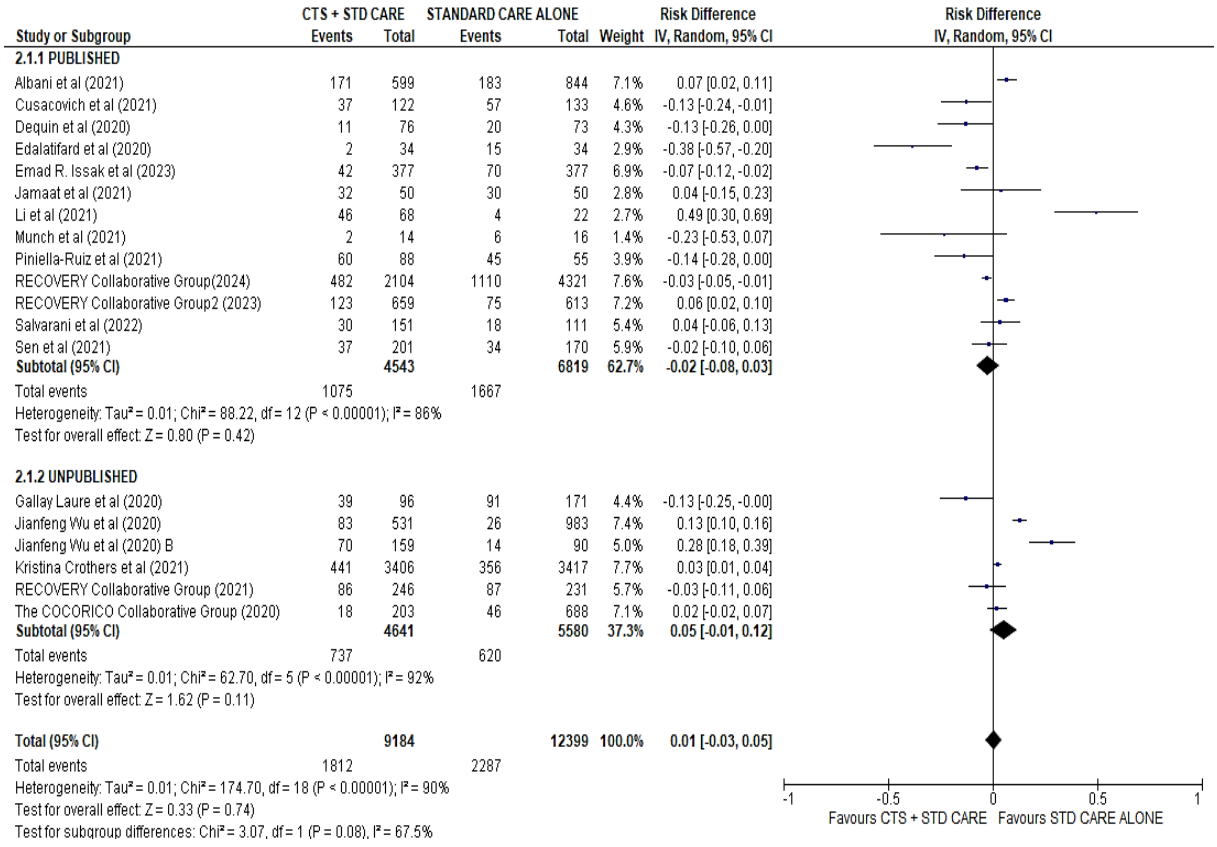

Figure 4*: Forest plot:- Corticosteroids and COVID-19 Mortality – Published vs Unpublished studies (pre-prints). Events= Mortalities; Total= Sample Size (n),CTS = Corticosteroids, STD CARE = Standard care.*

Impact of Study Timing (Temporality) on Risk Difference

Subgroup analysis based on the timing of the study included 8 studies conducted during or before 2020 and 11 conducted after 2020.The pooled risk difference for studies conducted during or before 2020 was 0.01 (95% CI: –0.07, 0.08; p = 0.87). Heterogeneity was substantial (τ^2 = 0.01, χ^2 = 87, *df* = 7, I^2 = 93%, *p* < 0.0001). For studies conducted after 2020, the pooled risk difference was 0.01 (95% CI: –0.05 to 0.06; p = 0.83), with continued significant heterogeneity (τ^2 = 0.01, χ^2 = 174, *df* = 10, I^2 = 90%, *p* < 0.0001).When all 19 studies were combined, the overall effect remained nonsignificant (0.01, 95% CI: –0.03 to

0.05; p = 0.83). The test for subgroup differences revealed no significant variation between earlier and later studies (χ^2 = 0.00, df = 1, I^2 = 0%, p = 0.99). (Figure 5)

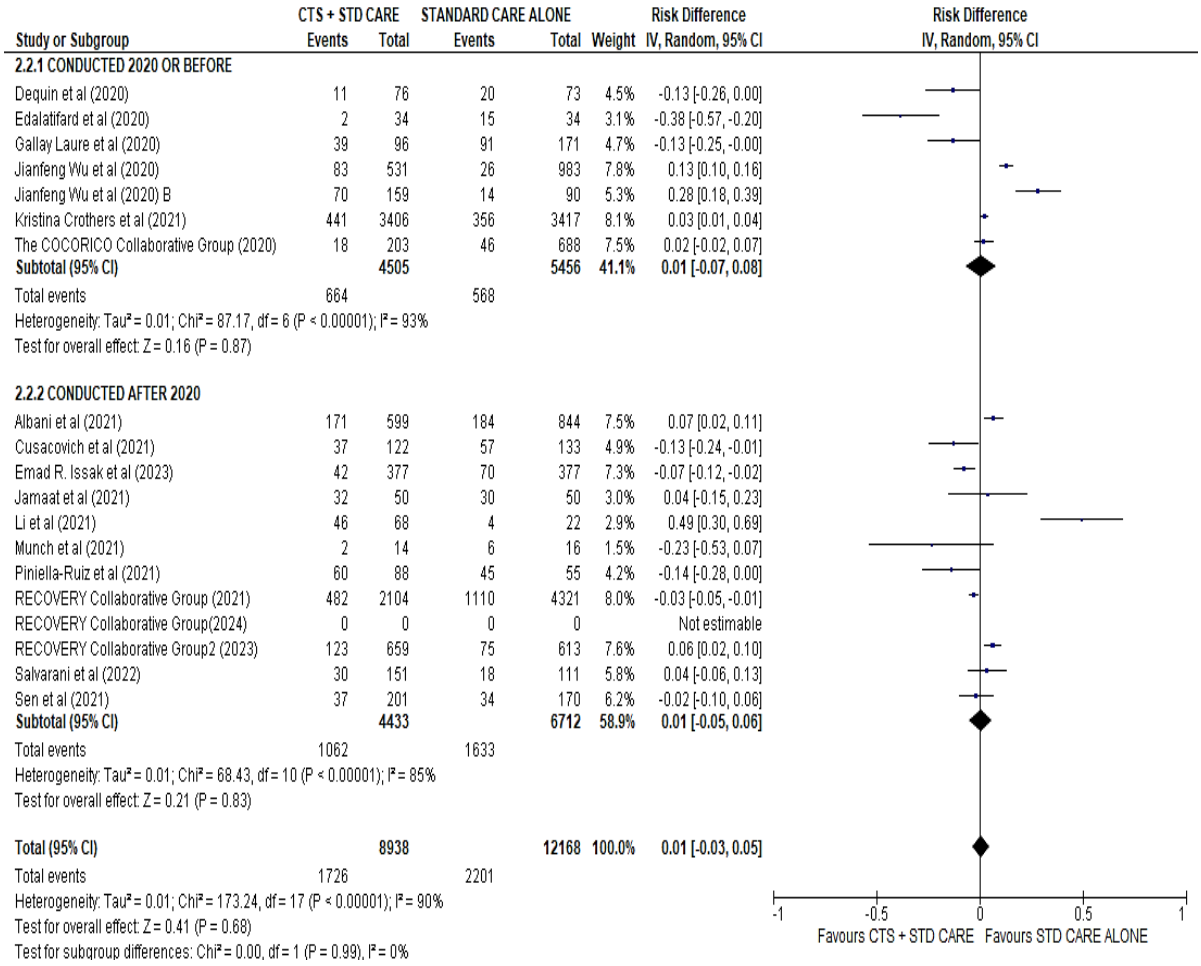

Figure 5*: Forest plot:- Corticosteroids and COVID-19 Mortality: Impact of time of the studies/temporality on effect size. Events= Mortalities; Total= Sample Size(n); CTS = Corticosteroid, STD CARE = Standard Care.*

Publication Bias Assessment

Neither the rank correlation nor the regression test indicated any funnel plot asymmetry (p = 0.45 and p = 0.18, respectively). A visual inspection of the funnel plot also did not reveal any obvious asymmetry that may be indicative of bias. (Figure 6)

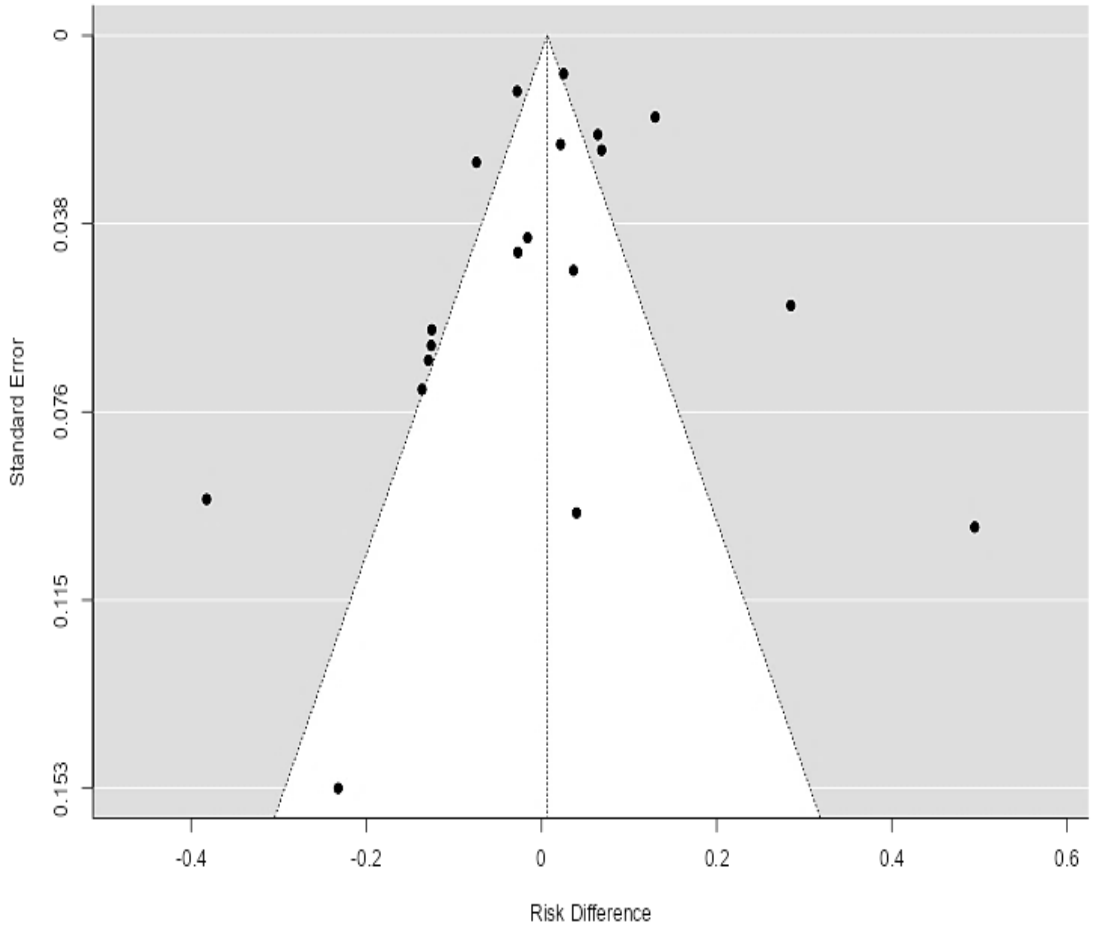

Figure 6*: Funnel plot of the effect of Corticotherapy on COVID-19 mortality (Standard error of the risk difference vs the risk difference of the studies).*

Sensitivity Analysis

Four studies—Edalatifard et al. (2020), Jianfeng Wu et al. (2020, B), Li et al. (2021), and Munch et al. (2021)—had studentized residuals exceeding ±1, suggesting potential outlier status. However, none of these studies were identified as overly influential based on Cook's distance. When these four studies were removed from the meta-analysis, the overall effect size changed slightly from 0.01 (95% CI: –0.03 to 0.05; p = 0.74) to –0.00 (95% CI: –0.04 to 0.04; p = 0.87). Similar results were observed across subgroup analyses. Heterogeneity remained significant before and after exclusion, indicating that these studies were not unduly influential on the overall findings. (Table 3)

Table 3*: Studies With Studentized Residuals of More Than* **±1**

Study	year	Studentized residual
1.Edalatifard et al	2020	-2.508
2.Jianfeng Wu et al (B)	2020	1.843
3.Li et al	2021	3.368
4.Munch et al	2021	-1.108

DISCUSSION

Nineteen studies involving a total of 21,583 hospitalized COVID-19 patients were included in this meta-analysis. The overall risk difference in mortality between patients receiving corticosteroids (CTS) plus standard care and those receiving standard care alone was 0.00 (95% CI: –0.04 to 0.03; p = 0.74). This suggests that while the addition of corticosteroids may have reduced mortality by up to 4% in some patients, it may have increased mortality by up to 3% in others, resulting in a net effect of no statistically significant difference in mortality risk. These findings align with the conclusions of other studies that have similarly reported no definitive mortality benefit from corticosteroid use in hospitalized COVID-19 patients.[14],[16],[17] In essence, the addition of corticosteroids to standard care did not significantly impact the overall risk of death in this patient population.

In the subgroup analysis of nine randomized controlled trials (RCTs) involving 9,537 patients, the pooled risk difference in mortality was –0.05 (95% CI: –0.10 to 0.01; p = 0.12), indicating no statistically significant effect. While the point estimate suggests a 5% reduction in mortality with corticosteroid use, the confidence interval reflects variability across studies, ranging from a 10% reduction to a 1% increase in risk. In contrast, the 10 cohort studies, comprising 12,046 patients, yielded a pooled risk difference of 0.05 (95% CI: –0.01 to 0.11; p = 0.08). Although not statistically significant, the findings suggest a potential increase in mortality risk by up to 11% in some studies, while others reported a slight reduction of 1%.Importantly, a chi-square test for subgroup differences indicated a statistically significant difference between RCTs and cohort studies (p = 0.02), suggesting that study design may influence observed outcomes. This finding contrasts with the conclusions drawn by Wang et al.[18] who reported comparable results between RCTs and cohort studies in similar analyses. The discrepancy highlights the importance of considering methodological differences when interpreting evidence on the effects of corticosteroids in COVID-19 treatment.

Of the eight studies conducted during or before 2020, involving a total of 10,438 patients, the addition of corticosteroids (CTS) to standard care showed no significant effect on mortality

risk (risk difference = 0.00; 95% CI: –0.06 to 0.07; p = 0.94). During this early period of the pandemic, some studies reported up to a 6% reduction in mortality, while others indicated as much as a 7% increase. Similarly, 11 studies conducted after 2020, with a combined population of 11,145 patients, demonstrated a marginal 1% increase in mortality risk associated with corticosteroid use (95% CI: –0.05 to 0.06; p = 0.94). The variability across these studies ranged from a 6% reduction to a 7% increase in mortality, but this effect was also not statistically significant. A comparison of subgroup effects between pre-2020 and post-2020 studies showed no significant difference (p = 0.94), indicating that the timing of the studies—referred to as temporality—did not meaningfully influence the observed effect size. These findings are consistent with previous research spanning the 2020–2024 period[19], [20], [21], which similarly found no significant temporal trend in the impact of corticosteroid therapy on COVID-19 mortality.

In the 13 published studies comprising 11,362 patients, corticosteroid use was associated with a 2% reduction in the risk of mortality (risk difference = –0.02; 95% CI: –0.08 to 0.03), with the range spanning from an 8% reduction in some studies to a 3% increase in others. This effect was not statistically significant (p = 0.42).Similarly, the six unpublished studies, which included 10,221 patients, showed a 5% increase in mortality risk (risk difference = 0.05; 95% CI: –0.01 to 0.12), reflecting variation from a 1% reduction to a 12% increase. This effect was also not statistically significant (p = 0.74).Subgroup analysis revealed no significant difference in risk of mortality based on publication status (χ^2 = 3.08, df = 1, p = 0.08), suggesting that whether a study was published or unpublished (preprint) did not influence the reported treatment effect. These findings align with prior reviews indicating minimal evidence of publication bias in corticosteroid-related COVID-19 research.[22], [23], [24]

Limitations

This meta-analysis has several limitations. First, there was substantial heterogeneity across studies in terms of corticosteroid type, dosage, timing of administration, and patient characteristics, which may have influenced effect size estimates. Second, the inclusion of both randomized controlled trials and observational cohort studies introduces variability in methodological rigor and susceptibility to bias. Third, some included studies were preprints, not yet peer-reviewed, which may affect data quality. Fourth, the outcomes reported varied in follow-up duration and definition of mortality. Finally, while publication bias was not detected, the small number of unpublished studies limits the strength of that conclusion.

CONCLUSION

This meta-analysis found no statistically significant mortality benefit from administering corticosteroids (CTS) to hospitalized patients receiving standard treatment for COVID-19. While the overall risk difference was neutral, subgroup analyses revealed that study design had a significant influence on the direction of outcomes—randomized controlled trials (RCTs) tended to show reduced mortality, whereas cohort studies suggested an increase in risk, although neither subgroup alone showed statistically significant results. In contrast, temporality (the time studies were conducted) and publication status did not significantly impact the estimated overall treatment effect.

Given the statistically significant divergence between outcomes from RCTs and cohort studies, we recommend that future research and evidence syntheses carefully consider study design as a critical factor when interpreting and applying findings. Meta-analyses should emphasize results from high-quality RCTs, and guideline developers should weigh evidence accordingly when forming clinical recommendations for corticosteroid use in COVID-19 and similar respiratory conditions.

Declaration of conflict of interest

The authors have no conflict of interest to declare.

Funding

The study was funded by the authors.

Role of authors

Akunga N. G. – Concept development, data collection ,data analysis, edited manuscript.

Murithi M. K. – Concept development, data collection, developed and wrote manuscript.

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