Steroids use in non-oxygen requiring COVID-19 patients: a systematic review and meta-analysis

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Summary

Background: Corticosteroids have become the mainstay treatment in severe COVID-19. However, its role in mild disease is controversial due to lack of robust scientific evidence. This systematic review and meta-analysis were conducted to assess effect of steroids in mild COVID-19 patients.

Methods: PubMed, EMBASE, Web of Science and medRxiv were searched from 31 December 2019 to 14 May 2021 for studies that reported effectiveness of steroids in non-oxygen requiring COVID-19 patients in terms of progressing to severe disease, mortality, duration of fever, duration of viral clearance and length of hospital stay (LOHS). Studies on inhalational steroids, case reports and reviews were excluded. Risk of bias (ROB) was assessed by the Cochrane’s ROB tool and ROBANS tool. Quantitative data synthesis was done using the generic inverse variance method.

Results: A total of 6411 studies were identified, 2990 articles were screened after exclusion. Seven studies which fit the criteria (involving 2214 non-oxygen requiring COVID-19 patients) were included and analysed. Overall odds of progression to severe disease among the non-oxygen requiring COVID-19 patients receiving steroids was 5.97 [95% confidence interval (CI): 1.27–27.99, I2 = 0%] and odds of death (OR: 1.35, 95% CI: 1.01–1.79; I2 = 0%) as compared to the patients not receiving steroids. Mean duration of fever (7.4 days), duration to viral clearance (18.9 days) and LOHS (20.8 days) were significantly higher in the steroid arm, as compared to that in no-steroid arm (6.7, 16.5 and 15.2 days, respectively).

Conclusion: Steroids in non-oxygen requiring COVID-19 patients can be more detrimental than beneficial.

Protocol registration: The study was prospectively registered in PROSPERO (CRD 42021254951).

Introduction

The world has sustained COVID-19 pandemic for more than a year and epidemiological predictions suggest that it is expected to have a long haul.1 The therapeutic options for COVID-19 have evolved over a year with corticosteroids emerging as a steady medication in the treatment algorithms. As various studies have unravelled the effect of steroids in COVID-19, many questions still remain without any conclusive evidence, be it the better choice of steroid, dose of steroid, timing of administration in the course of the disease or the total duration of steroid use. The RECOVERY trial has shown robust evidence for mortality
benefit with the use of dexamethasone in patients of COVID-19 infection requiring supplemental oxygen or mechanical ventilation. However, the majority of COVID-19 infections result in mild illness. Based on the anti-inflammatory action of corticosteroids, many hypotheses have risen indicating that low-dose steroid administration during persisting symptomatic phase may be expected to be beneficial, by blunting the severity of inflammation and preventing systemic inflammatory response. Most studies to date have focussed on the role of steroids in severe illness and their use has been extrapolated in mild disease without robust evidence for or against it. Hence, we performed this meta-analysis with an aim to assess the effect of steroids in non-oxygen requiring or mild COVID-19 patients in terms of mortality, proportion of mild COVID-19 patients progressing to severe disease, duration of fever, duration of viral clearance and length of hospital stay (LOHS).

**Methods**

**Search strategy and selection criteria**

This systematic review was performed according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA guidelines). Databases including PubMed, EMBASE, Web of Science and Medrxiv were searched from 31 December 2019 to 14 May 2021. Two independent investigators (A.K. and R.B.) searched the databases using search terms [COVID-19 (or synonyms)] AND [corticosteroids (or synonyms) OR dexamethasone OR methylprednisolone OR hydrocortisone] without restrictions in terms of country or publication language. Reference lists of all relevant articles and ‘related citation’ search tool of PubMed were checked. Detailed search criteria are available in Supplementary Table S1.

Study selection was performed by two independent investigators (A.K. and R.M.). Randomized controlled trials (RCT) or controlled observational studies that adjusted patients’ backgrounds between the steroid treatment group and the control group using propensity score matching (PSM) were included. We included studies that reported the comparison of the effectiveness of steroids in terms of number of non-oxygen requiring/mild COVID-19 patients progressing to severe disease, mortality, duration of fever, duration of viral clearance and LOHS; in the study arms with or without steroid use. To avoid clinical heterogeneity, studies on inhalational steroids were excluded. Case reports, duplicate publications, letters, editorials and reviews were also excluded. Discrepancies between reviewers were resolved in the presence of a third reviewer (P.A.).

Non-oxygen requiring patients were defined as any lab confirmed COVID-19 patients, who were mild or moderate (classification according to National Health Commission of China—NHCC), i.e. not requiring any supplemental oxygen therapy, at the time of recruitment in the study. Studies using WHO definitions were also scrutinized to extract the appropriate data (only mild category of COVID-19 according to WHO definitions were included). Studies investigating the role of steroids irrespective of the type, route of administration (except inhalational or intranasal route), dose and duration were extracted. Severe disease was defined according to NHCC or WHO as the presence of any of the following: (i) respiratory distress, respiratory rates >30/min; (ii) pulse oxygen saturation <93% in the resting state; (iii) oxygenation index i.e. P/F ratio <300 mmHg; (iv) require mechanical ventilation; (v) shock; (vi) combined with other organ failures and needed treatment in the intensive care unit (ICU). Classification according to any other international standard guidelines was also considered if recategorization to NHCC was possible. Any type of mortality data, such as inhospital or any duration specific mortality, were considered for analysis. Duration of viral clearance was defined as number of days from illness onset to two consecutive negative tests for SARS-CoV-2 with at least 24 h interval.

Data collected included study characteristics, such as authors, publication date, study type, study inclusion criteria; information on both study arms (steroid vs. no-steroid group) about sample size (in case of PSM, only 1:1 matched sample size taken), age, male gender (%), number of non-oxygen requiring/mild COVID-19 patients progressing to severe disease, in-hospital mortality, 28-day mortality or any other type of mortality, duration of fever (in days), duration of viral clearance (in days) and LOHS (in days). Information regarding details of steroid arm like type of drug used, dosing, time from symptom onset to start of steroids, route and duration were also extracted. One reviewer (R.M.) extracted the data, and the second reviewer verified the data independently (A.K.).

The methodological quality, i.e. risk of bias (ROB) of the randomized trials was assessed by the Cochrane Collaboration’s tool for assessing ROB in randomized trials, and that of non-randomized studies (controlled observational studies that adjusted patients’ backgrounds between the steroid treatment group and the control group using PSM) was determined by ROBANS (Risk of Bias Assessment Tool for Non-randomized Studies) tool. Risk-of-bias VISualization (robvis) tool was used to visualize the risk of bias assessment of the included studies. Two authors (R.M. and R.B.) performed the quality assessment separately, and disagreements were resolved by consensus in the presence of a third reviewer (A.K.).

**Data analysis**

Odds ratios (ORs) were calculated to study the effect of steroids on severe disease progression and mortality in non-oxygen requiring COVID-19 patients. OR were then meta-analysed by Der-Simonian and Laird method (random-effects pooling). If the number of deaths or patients progressing to severe disease was zero in both arms, the study was excluded for quantitative analysis. If a single arm had zero value, continuity correction of 0.5 was applied to the zero cells. Continuous data (like duration of fever, duration of viral clearance and LOHS) if presented in median and interquartile range (IQR) were transformed to mean and standard deviation (SD) using methods described by Luo et al. and Wan et al. only after ruling out the presence of skewness. The effect of steroids on the above-mentioned continuous outcome (steroid vs. no-steroid arm) were summarized in terms of standardized mean difference (SMD) by Cohen’s method using generic inverse variance method (random-effects pooling). To assess the heterogeneity among studies, inconsistency statistics ($I^2$) were calculated. Significant heterogeneity was considered to be present when $I^2$ was greater than 50%. Publication bias was assessed visually by constructing funnel plots and calculating Egger’s regression equation. The $P$ values for Egger’s regression coefficient less than 0.10 was considered as significant publication bias. Subgroup analysis, according to the type of study, type and dosage of steroids administered, duration of steroid administration (<1 week or >1 week), time from symptom onset to steroids, mean age of the patients in steroid arm (<65 years or >65 years), initiation and day of mortality were planned. All data were collected in Microsoft Excel Spreadsheet (Office 365). Random-effects analysis, generation of forest plot, assessment of heterogeneity and publication bias
were performed with the METAN, METABIAS and METAFUNNEL platform for STATA (version-14.2; StataCorp, College Station, TX, USA). This study was prospectively registered in PROSPERO database (CRD 42021254951).

Results
The literature search flow diagram is summarized in the PRISMA format (Figure 1). Using our search criteria, we identified 6411 studies, of which 2845 were from PubMed, 1384 were from Web of Science, 1223 were from EMBASE, 956 were from preprint server Medrxiv and 3 were from searching of references and citations of the selected articles. A total of 2990 records were screened after removal of duplicates. A total of 145 full-text articles were assessed for eligibility, and 138 articles were excluded due to various reasons, as shown in Figure 1. Finally, seven studies were included in this meta-analysis, of which three were RCT and rest were PSM controlled observational studies.

A total of seven studies, consisting of 2214 non-oxygen requiring COVID-19 patients (steroid arm: 833, no-steroid arm: 1381) were included in this meta-analysis. Major contributions of the information in this meta-analysis were from the RECOVERY trial (steroid arm: 501, no-steroid arm: 1034). All the studies were published in the year 2020. We extracted the data from three studies which had separate subgroup of non-oxygen requiring COVID-19 patients, while the rest of the four studies reported information on non-severe COVID-19 patients according to NHCC classification (which were classified as non-oxygen requiring COVID-19 patients in this meta-
analysis. Mean age of the patients in both the arms was 56.2 years. Proportion of male patients were nearly similar in both the arms.

There were differences in the type of steroid used, its dose, time from symptom onset to steroid administration and duration of administration, among the included studies. Methylprednisolone (dose ranging from 20 mg/day to 2 mg/kg/day) was used in all the studies except in the RECOVERY trial where dexamethasone (6 mg/day) was used. Time from symptom onset to steroid administration was described in only two of the seven studies. Median time from symptom onset to steroid administration was 6 days in the RECOVERY trial and 9.7 in the study by Yuan et al.22 There were significant differences in the duration of steroid administration. Detailed characteristics of each of included studies and that of the steroid administered are listed in Table 1.

The detailed ROB analysis is available in Supplementary Figures S1 and S2. Among the RCTs (Supplementary Figure S1), RECOVERY trial2 and study by Jeronimo et al.23 had an overall unclear ROB, whereas study by Tang et al.20 had an overall high ROB. In these RCTs, there was low ROB in the domains like ‘random sequence generation’, ‘incomplete outcome data’ and ‘selective reporting’. Major sources of high risk of bias were found in the ‘blinding of participants and personnel’ and ‘blinding of outcome assessment’ domains.

All the included non-randomized studies21–24 had an overall high ROB (Supplementary Figure S2). Only in the domain of ‘confounding variables’, all the studies had low ROB because of utilization of PSM. Half of these studies23,24 had high ROB in the ‘measurement of exposure’ and ‘selective reporting’ domains. Three-fourths of these studies21,23,24 had high ROB in the ‘selection of participants’ domain. The presence of high ROB was there in ‘blinding of outcome assessment’ and ‘incomplete outcome data’ among all these non-randomized studies.

There was no publication bias in this meta-analysis (P values of Egger’s regression 0.11 for mortality, 0.53 for LOHS and 0.19 for viral clearance, as shown in the (Supplementary Figures S3–S5)). Egger’s regression was not possible for the outcomes like severe disease progression and duration of fever, as only two studies were included in data pooling.

Five out of the seven studies had mentioned about mortality in both the arms.2,19,20,22,24 Variation in the day of mortality described among the included studies was noted. The 28-day mortality was described by the RECOVERY trial,2 Jeronimo et al.19 and Liang et al.22 whereas in-hospital mortality was described by Li et al.24 and Tang et al.20. A total of 91 deaths (12.3%) occurred in 738 patients taking steroids, whereas 145 deaths (11.3%) were observed in 1286 patients in no-steroid arm. Meta-analysis of these studies showed that odds of deaths was significantly higher in steroid arm (OR: 1.35, 95% CI: 1.01–1.79; with P = 0%). Figure 2A depicts the forest plot of mortality (studies by Tang et al.20 and Liang et al.22 were excluded in the forest plot as the mortality rate was zero in both the arms). Subgroup analysis showed that odds of 28-day mortality remained significantly higher in steroid arm as compared to no-steroid arm (OR: 1.34, 95% CI: 1.003–1.782).

Only three out of the seven included studies had described regarding the progression to severe disease among non-oxygen requiring COVID-19 patients.20,21,24 Study by Tang et al. showed none of the patients in any arm progressed to severe disease, hence was excluded from meta-analysis. A total of 11 out of 111 patients (9.9%) in the steroid arm progressed to severe or critical disease (according to WHO/NHCC definitions), which

| Study ID | Sample size | Eligibility criteria | Age (in years) | Male (%) | Steroid type (Dose) | Steroid duration (days) | Risk of bias (overall) | Male (%) | Steroid type (Dose) | Steroid duration (days) | Risk of bias (overall) |
|----------|-------------|---------------------|---------------|----------|---------------------|-------------------------|-----------------------|----------|---------------------|-------------------------|-----------------------|
| RECOVERY trial | 501 | No oxygen therapy | 71.1, 16.3 | 59 | Dexamethasone (6 mg/d) | 10 | Unclear | a, b, c, d, e |
| Li 2020 | 55 | No oxygen therapy | 68.5, 18 | NA | Methylprednisolone/prednisolone (20-40mg/day) | 5 | A | a, b, c, d, e |
| Jeronimo 2020 | 42 | No oxygen therapy | 58 (43-70) | NA | Methylprednisolone | 7 | Un unclear | a, b, c, d, e |
| Tang 2020 | 21 | No oxygen therapy | NA | NA | Methylprednisolone | 10 (8-2-12) | A | a, b, c, d, e |
| Yuan 2020 | 35 | Non-severe COVID-19 | 47.7 (41-57) | 46.6 | Methylprednisolone | 3 (minimum) | A | a, b, c, d, e |
| Ma 2020 | 60 | Non-severe COVID-21 | 47.9 (41-57) | 47.9, 14 | Methylprednisolone | 3 (minimum) | A | a, b, c, d, e |
| Liang 2020 | 131 | Non-severe COVID-21 | 59 (69-69) | 43.5 | Methylprednisolone | 3 (minimum) | A | a, b, c, d, e |
was significantly higher than that in the no-steroid arm (2 out of 114, 1.8%). Overall, the odds of progression to severe or critical disease among the non-oxygen requiring COVID-19 patients receiving steroids in the course of illness was 5.97 (95% CI: 1.27–27.99), as compared to the patients not receiving steroids (Figure 2B). The $I^2$ value for this meta-analysis was 0%.

The data on duration of fever in both the arms were provided by Li et al.\textsuperscript{21,24} and Yuan et al. In the study by Li et al., the median duration (IQR) of fever was 5 days (4–7 days) in steroid arm and 3 days (1–5 days) in no-steroid arm. In the study by Yuan et al., the median duration of fever was 9.5 days (6.5–12.2 days) in steroid arm and 10.2 days (6.8–14 days). On pooling these data, the average duration of fever was longer in steroid arm (7.4 days) as compared to that in no-steroid arm (6.7 days), with an SMD of 0.83 (0.61–1.05) (Figure 3A). Significant heterogeneity was detected in this meta-analysis ($I^2 = 91.6\%$).

Five out of seven studies described viral clearance in both the arms.\textsuperscript{20–24} The definition of viral clearance was consistent in all the studies, i.e. number of days from illness onset to two consecutive negative tests for SARS-CoV-2 with at least 24 h intervals. Overall, the mean duration of viral clearance was significantly higher in the steroid arm (18.9 days), as compared to that in the no-steroid arm (16.5 days), with an SMD of 0.20 (95% CI: 0.04–0.36, with $I^2 = 86.3\%$) (Figure 3B).

Data from four studies\textsuperscript{20,21,23,24} showed that non-oxygen requiring patients taking steroid had a significantly longer LOHS (average: 20.8 days) as compared to that of no-steroid group (average: 15.2 days). The SMD was 0.83 (95% CI: 0.61–1.05) and there was absence of any statistical heterogeneity ($I^2 = 0\%$) (Figure 3C). The summary of the quantitative syntheses for all the five outcome of this review is depicted in Figure 4.

As described above, there were differences in the type, dose and duration of steroid prescribed for COVID-19 management. The time from symptom onset to steroid administration was available in only two studies (RECOVERY trial\textsuperscript{2} and Yuan et al.\textsuperscript{21}). Hence, subgroup analysis could not be done.

We performed a leave out analysis excluding RECOVERY trial (for mortality outcome) and found that OR of 28-day mortality wasn’t significant in both arms (OR: 3.63, 95% CI: 0.37–35.61, $I^2 = 0\%$). (Supplementary Figure S6).

**Discussion**

This meta-analysis of three RCT and four PSM controlled observation studies evaluated the role of corticosteroids in non-oxygen requiring COVID-19 illness and found that early initiation of steroids in these subsets of patients could do more harm than good. There was higher odds of progression to severe...
illness and increased mortality in those who received steroids for non-severe illness. This study comes in the background of reported overuse of steroids in mild COVID-19 during the second wave of COVID-19. Steroids are easily available and low-priced drugs than all the other drugs approved for emergency use in COVID-19. This, compounded with rapid surge of cases in an already overwhelmed healthcare system, especially in developing countries, has led to over-prescription of steroids without proper evidence backing its use.

The use of steroids as a potential life-saving drug in COVID-19 was based on the RECOVERY trial which demonstrated its benefits in oxygen requiring patients. The study clearly shows the lack of evidence for its use in non-severe cases.

Figure 3. (A) Forest plot showing standardized mean difference of duration of fever in ‘Steroid’ arm versus ‘Non-steroid’ arm. (B) Forest plot showing standardized mean difference of duration of viral clearance in ‘Steroid’ arm versus ‘Non-steroid’ arm. (C) Forest plot showing standardized mean difference of length of hospital stay in ‘Steroid’ arm versus ‘Non-steroid’ arm. SD, standard deviation; SMD, standard mean difference; CI, confidence interval; IV, inverse variance.
mentions in its conclusions about the potential harm of using steroids in patients not requiring any oxygen support. In the 1534 patients with no oxygen requirement, the 28-day mortality was more in the dexamethasone arm (18% vs. 14%).

Corticosteroids are considered to have good antipyretic properties and have been found beneficial in community acquired pneumonia as adjunct to antibiotics. Previous meta-analyses in SARS CoV-1 and studies in Middle East respiratory virus syndrome also showed increased mortality and adverse events in patients treated with steroids. The higher duration to viral clearance in mild illness may have a risk of continued population transmission and had a longer duration of hospital stay.

Corticosteroids are considered to have good antipyretic properties and have been found beneficial in community acquired pneumonia as adjunct to antibiotics. Previous meta-analyses in SARS CoV-1 and studies in Middle East respiratory virus syndrome also showed increased mortality and adverse events in patients treated with steroids. The higher duration to viral clearance in mild illness may have a risk of continued population transmission and this along with prolonged duration of hospital stay may compound the burden on the healthcare system by increase in case load, risk of secondary infections and healthcare costs.

The previous published studies analysing the role of steroids in mild COVID showed no significant benefit, however Shuto et al. included heterogeneous population, that is patients on low flow oxygen too and no meta-analysis was done. The meta-analysis by Sarkar et al., had studies with significant heterogeneity ($I^2 > 50\%$) which may have impacted the validity of the meta-analysis. While the subgroup analysis by Sarma et al. on similar lines was methodologically robust, the inclusion criteria of cases was different.

The use of steroids for short term may be safe, but the potential side effect of developing hyperglycaemia and requirement for insulin therapy especially in COVID-19 patients can lead to progression to severe illness and increased in-hospital mortality. The inappropriate use, has a risk of tilting the balance of the overall wider effect of steroids from boon to bane, in terms of secondary outbreaks of various emerging infectious diseases, such as the epidemic of COVID-19 associated mucormycosis in developing countries.

Conversely, classifying the management of the disease black and white on the basis of a single parameter of oxygen requirement may be precarious. We noted that most studies which evaluated steroid use in mild COVID illness were based on resting oxygen saturation levels. Exertional hypoxia with normal resting oxygen saturation was found to have significant association with progression to moderate to severe disease and it preceded advanced oxygenation requirement by a median time of 54 h. Besides, the resource constraints that have arisen during the pandemic, in addition to limited scientific evidence has led to higher thresholds for initiating supplemental oxygen. It is worthy to note that, the RECOVERY trial showed benefit with dexamethasone use in patients of COVID-19 with more than 7 days of symptoms (RR 0.69, 95% CI 0.59–0.8, $I^2 = 12.4$), and in Asian-African ethnic groups (RR 0.7, 95% CI 0.51–0.95, $I^2 = 2.3$);
however, there was no explicit mention about patients being oxygen requiring or not. High C-reactive protein (CRP) levels in the early disease and computed tomography (CT) severity score on admission had been independently associated with increased risk of progression to severe illness. Setting individualized targets based on patients’ baseline oxygen saturation levels may be one of the unexplored areas which may be extrapolated in COVID-19 based on some evidence in other diseases. The reports of multisystem inflammatory syndrome in patients with COVID-19 is adding a new dimension to the disease which further stresses the need to find predictors for progression to severe illness.

With the anticipated third wave, the appropriate use of steroids has to be advocated and an objective criterion defined for its use, keeping in mind the potential benefits of steroids in preventing early cytokine storms and the harm caused by its overzealous use leading to secondary infections. While we strongly discourage the non-evidence-based use of corticosteroids in mild illness, we emphasize that it is necessary to demystify this grey zone of COVID-19 illness with further research, to capitalize on the lead time to prevent progression from mild to moderate or severe illness. In this pandemic, this can have a significant impact in easing the load on an already overwhelmed healthcare system.

Limitations of the study
Significant statistical heterogeneity was observed for outcomes like duration of fever and viral clearance. Newer studies might have been published between the completion of the literature review and when this article was completed. Publication bias could not be ascertained, as Egger’s regression was not possible for outcomes severe disease progression and duration of fever.

Conclusion
Steroid use in non-oxygen requiring COVID-19 patients is significantly associated with higher mean duration of fever, duration of viral clearance and LOH in addition to the higher odds of progression to severe disease and higher mortality. The above evidence should deter clinicians from unscrupulous use of steroids in non-oxygen requiring COVID-19 illness. However, further research is required to study predictive parameters other than oxygen requirement alone to myth bust role of steroids in COVID-19.

AUTHOR CONTRIBUTIONS
The Conceptualisation of the study: AK, JN, SG; Article searching and study selection: AK, RB; Data extraction: RB, RM; Quality assessment of the studies: RM, JN; Data analysis: AK; Manuscript writing: AK, RB, RM; and Overall conduct of the study: AK, JN, SG

Supplementary material
Supplementary material is available at QJMED online.

Conflict of interest. None declared.

Data sharing
All the relevant data are available in the manuscript and the Supplementary Appendix associated with this article. Any information or queries related to the study can be directed to the corresponding author. Our team is willing to clarify the queries and share the information.

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