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COVID-19

Corticosteroids in COVID-19: Is it Rational? A Systematic Review and Meta-Analysis

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Abstract

Due to a lack of definitive treatment, many drugs were repurposed for Coronavirus disease (COVID-19) treatment; among them, corticosteroid is one. However, its benefit or harm while treating COVID-19 is not fully studied. Thus, we conducted this meta-analysis to assess the rationality on the use of corticosteroids in COVID-19. Pubmed, Medline, Clinicaltrials.gov, Cochrane library, and Preprint publisher were searched. In the qualitative syntheses, 41, and quantitative studies, 40, were included using PRISMA guidelines. Assessment of heterogeneity was done using the *I*-squared (I^2) test and random/fixed effect analysis was done to determine the odds/risk ratio. We found severely ill COVID-19 patients almost 5 (OR 4.78, 2.76–8.26) times higher odds of getting corticosteroids during their treatment. Similarly, the odds for corticosteroids in addition to standard of care (SOC) were approximately 4 (OR 4.09, 1.89–8.84) times higher among intensive care unit (ICU) patients than non-ICU ones. A higher mortality risk with the corticosteroid-receiving group compared with the SOC alone (RR 2.01, 1.12–3.63) was observed. Neither increased discharge rate (RR 0.79, 0.63–0.99) nor recovery/improvement rate was shown among the corticosteroid-receiving group (OR 0.24, 0.13–0.43). Approximately, the overall 4-day longer hospital stay was found among the treatment groups (MD 4.19, 2.57–5.81). For the negative conversion of reverse transcription–polymerase chain reaction (RT-PCR), approximately a 3-day (MD 2.42, 1.31–3.53) delay was observed with corticosteroid treatment cases. Our study concludes that more severe and critically ill patients tend to get corticosteroids, and the mortality risk increases with the use of corticosteroids. With the use of corticosteroids, delayed recovery and a longer hospital stay were observed.

Keywords COVID-19 · Critical illness · Length of stay · Patient discharge · Survival rate

Background

An unprecedented outbreak of pneumonia of unknown etiology in Wuhan City, Hubei province in China emerged in December 2019. A novel coronavirus was identified as the causative agent and was subsequently termed Coronavirus disease (COVID-19) by the World Health Organization (WHO) and declared a pandemic in March 2020. The pandemic has spread all over the globe and created a public health catastrophe also dragging countries into economic crisis. The symptoms of infection range from sore throat, cough, fever to pneumonia, and acute respiratory distress syndrome (ARDS). As of June 2020, over 7 million cases have been confirmed, and more than 400,000 deaths have been recorded due to COVID-19 [1]. Lack of standardized care treatment makes the situation dreadful, and while several trials are being conducted everywhere, there are no specific answers yet. Among these treatment modalities being researched, corticosteroid is one of the most controversial drugs.

Corticosteroids (glucocorticoids) include steroid hormones that are naturally produced in the adrenal cortex of vertebrates and their synthetic analogs. Corticosteroids do not directly attack the viruses, rather act via anti-inflammatory and immunosuppressive properties to minimize the damage created all over the body. The anti-inflammatory activity of glucocorticoids is

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attributed to the repression of pro-inflammatory genes through signal transduction by their steroid receptors. Glucocorticoids inhibit nuclear transcription factor-κB (NF-κB) signaling and further inhibit the transcription and translation of inflammatory factors [2]. Thus, the anti-inflammatory mechanism is the basis for using it in various medical conditions including bacterial or viral pneumonia [3, 4]. Similarly, corticosteroids have been used in the past during severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreaks; although, the evidence of benefit has not been well established and is full of conflicting conclusions [5, 6]. The use of corticosteroid in the recent pandemic of COVID-19 is based on the genetic homology with the SARS and MERS coronaviruses. Although they are not identical, the exigency for standardized treatment drives clinicians around the world to use it in adjunct to various treatment forms.

With the rapid surge and lack of standardized treatment, the global health situation looks jeopardized. The use of steroids is varied on the geography and severity of patients, ranging from about 7–60% [7–11]. Ling et al. [7] showing 7.6% of the study participants receiving steroids while Lu X et al. [11] showed about 60% of critically ill COVID-19 patients getting steroids in their treatment. Among corticosteroid recipients, the mixed result was shown by studies published. Wu C et al. showed decrease mortality when used in COVID-19 patients with ARDS [9], while many other observational retrospective studies showed increased mortality among corticosteroid receiving groups [12–18]. Furthermore, COVID-19 patients taking steroids did not show the better result in clinical improvement and duration of hospital stay and viral clearance in some, and another study could not conclude towards or against significantly urging the current meta-analysis. Therefore, we conducted our study to analyze what patients are prone to receive steroids and determine the clinical outcome with the use of steroids among COVID-19 patients.

The objective of our study is to find the type of patients who are prone to get corticosteroids, overall change in mortality, overall improvement or deterioration among treatment groups in comparison with control, duration of virological clearance, length of hospital stay, the requirement of intubation, and mechanical ventilation.

Methodology

We used PRISMA guidelines for a systematic review of the available literature [19]:

Criteria for Considering Studies for this Review

Types of Studies

We included studies like observational studies, case series, and randomized controlled trials (RCTs) that focused on mortality, clinical improvement, and adverse events among COVID-19 patients taking steroid.

Types of Participants

We included patients diagnosed with COVID-19 who received steroids and standard of care in the treatment group and patients receiving standard of care (SOC) alone in the control group.

Types of Interventions

We included patients receiving steroids along with the SOC in the treatment group and standard of care like antivirals, antibiotics, and respiratory support only in the control group.

Types of Outcome Measures

We analyzed what group of patients were prone to receive steroids, the mortality, requirement for intubation and mechanical ventilation, clinical improvement/deterioration, and length of hospital stay among the patients in the treatment group compared with control.

Outcomes

Our outcomes were to find which type of patients are prone to get corticosteroids, the overall change in mortality, overall improvement or deterioration among treatment groups in comparison with control, the duration of virological clearance, length of hospital stay, and the requirement of intubation and mechanical ventilation.

Search Methods for Identification of Studies

Two reviewers (DBS and PB) accessed electronic databases like Pubmed, Medline, Clinicaltrials.gov, Cochrane library, Medxriv, Researchsquare, Google Scholar, and WHO clinical trial registry. Reviewers independently searched and evaluated the quality of the studies from January 1 to June 3, 2020. Studies were filtered using COVIDENCE, and data was extracted for quantitative and qualitative analysis. Another reviewer (SK) solved any potential conflict between the two reviewers concerning study selection. The assessment of risk of bias and cross-checking of all the selected studies were done by another reviewer (ER).

Electronic Searches

We have documented the detailed search strategy in additional file 1.

Table 1 Assessment of bias in the included cohort and observational studies using the NHLBI tool

SN	Study	Score	Percentage	Quality
1	Chen Q 2020[21]	6/14	42.8%	Poor
2	Chen TL 2020 [22]	8/14	57.1%	Fair
3	Chrobozcek 2020 [23]	10/14	71%	Good
4	Confalonieri 2020 [24]	12/14	85.7%	Good
5	Cruz 2020 [25]	12/14	85.7%	Good
6	Feng 2020 [26]	8/14	57.1%	Fair
7	Gong 2020 [27]	9/14	64.2%	Good
8	Guan 2020 [28]	7/14	50%	Fair
9	Hong Y 2020 [29]	7/14	50%	Fair
10	Hong KS 2020 [30]	6/14	42.8%	Poor
11	Hou 2020 [31]	8/14	57.1%	Fair
12	Hu 2020 [32]	8/14	57.1%	Fair
13	Huang C 2020 [12]	7/14	50%	Fair
14	Huang M 2020 [33]	8/14	57.1%	Fair
15	Jiang 2020 [34]	8/14	57.1%	Fair
16	Lei 2020 [35]	8/14	57.1%	Fair
17	Li 2020 [36]	8/14	57.1%	Fair
18	Ling 2020 [7]	9/14	64.2%	Good
19	Liu T 2020 [37]	8/14	57.1%	Fair
20	Liu Y 2020 [38]	8/14	57.1%	Fair
21	Lu Xiaofan 2020 [11]	11/14	78.6%	Good
22	Sun L 2020 [39]	6/14	42.8%	Poor
23	Wang K 2020 [14]	9/14	64.2%	Good
24	Wu C 2020 [9]	9/14	64.2%	Good
25	Wu J 2020 [16]	12/14	85.7%	Good
26	Xu Yonghao 2020 [40]	7/14	50%	Fair
27	Yang L 2020 [41]	7/14	50%	Fair
28	Yang X 2020 [42]	8/14	57.1%	Fair
29	Yu H 2020 [17]	10/14	71.4%	Good
30	Zha L 2020 [43]	10/14	71.4%	Good
31	Zhao X 2020 [44]	7/14	50%	Fair
32	Zhou F 2020 [18]	8/14	57.1%	Fair

Good if they fulfilled 60–100% of the tool items, Fair if 50–59% or Poor if 0–49%.

Data Collection and Analysis

Data extracted from COVIDENCE for quantitative synthesis was analyzed using REVMAN 5.4 software. I^2 was used for the assessment of heterogeneity. Random/fixed effect was used for the pooling of studies appropriately. For the length of hospital stay and negative conversion of RT-PCR, the mean differences (MD) was measured between the treatment and control group.

Selection of Studies

Due to the paucity of RCTs, we included case reports, case series, and observational cohorts for qualitative analysis. For quantitative synthesis, we selected case series and observational studies being there were no published randomized studies comparing the treatment and control of our interest. The studies selected had patients being treated with steroids in addition to other treatment modalities. We excluded reviews, in vitro studies, editorials, letters to editors, simulation studies, molecular docking studies, commentaries, and viewpoints in our synthesis.

Table 2 Assessment of bias in included case series using the NHLBI tool

SN	Study	Score	Percentage	Quality
1	Cao 2020 [45]	8/9	88%	Good
2	Chen Xu 2020 [46]	7/9	77.7%	Good
3	Lo 2020 [47]	6/9	66.6%	Good
4	Wan 2020 [48]	7/9	77.7%	Good
5	Wang D 2020 [49]	7/9	77.7%	Good
6	Wang D2 2020 [13]	7/9	77.7%	Good
7	Wang Z 2020 [15]	7/9	77.7%	Good
8	Xu Y 2020 [50]	7/9	77.7%	Good
9	Zhang G 2020 [51]	5/9	55.5%	Fair

Good if they fulfilled 60–100% of the tool items, Fair if 50–59% or Poor if 0–49%.

Data Extraction and Management

The quality of the studies was thoroughly evaluated and outcomes of importance for our studies were selected.

Assessment of Risk of Bias in Included Studies

The National Heart, Lung, and Blood Institute (NHLBI) tool [20] was used for the assessment of the risk of bias for observational studies and case series illustrated in Tables 1 and 2 (details of bias assessment of every single study are available in additional files 2 and 3).

Assessment of Heterogeneity

We assessed the heterogeneity of our included studies using the I^2 test. The Cochrane Handbook for Systematic Reviews of Intervention was used for the interpretation like 0 to 40% (might not be important, 30 to 60% (moderate heterogeneity), 50 to 90% (substantial heterogeneity), and 75 to 100% (considerable heterogeneity). The importance of the observed value of I^2 depends on (i) the magnitude and direction of effects and (ii) the strength of evidence for heterogeneity (e.g., P value from the chi-squared test, or a confidence interval for I^2).

Assessment of Reporting Biases

Prefixed reporting of the outcome was done for checking the reporting bias.

Data Synthesis

We used Revman 5.4 for performing statistical analysis and used Risk Ratio (RR)/ Odds Ratio (OR) for estimation of outcome whenever appropriate with 95% Confident Interval (CI). We used the fixed/random-effects model as per the heterogeneity. We analyzed the MD between the two groups for the duration of virological clearance and length of hospital stay calculated using the median, sample size, and inter-quartile range when mean and standard deviation were not provided in study [52].

Subgroup Analysis and Investigation of Heterogeneity

For cases of heterogeneity, we used the random effect model, inverse variance, and excluded the study with the most weight.

Sensitivity Analysis

We excluded the significant outlier studies with the most weight and applied the inverse variance method to assess the effect on the results and re-run the analysis to check for sensitivity analysis.

Results

A total of 2716 articles were identified after database searching, out of which 477 duplicates were removed. We screened the title and abstracts of 2239 articles and excluded 2156 articles. Full texts of 83 articles were reviewed, and 41 articles were extracted after 42 were excluded with various reasons mentioned in Fig. 1. We included 41 studies for qualitative and 40 studies for quantitative analysis. The qualitative analysis of 41 studies is done in Table 3.

PRISMA 2009 Flow Diagram

Qualitative Analysis

Clinical definition

- Mild type: The clinical symptoms are mild, with no abnormal radiological findings

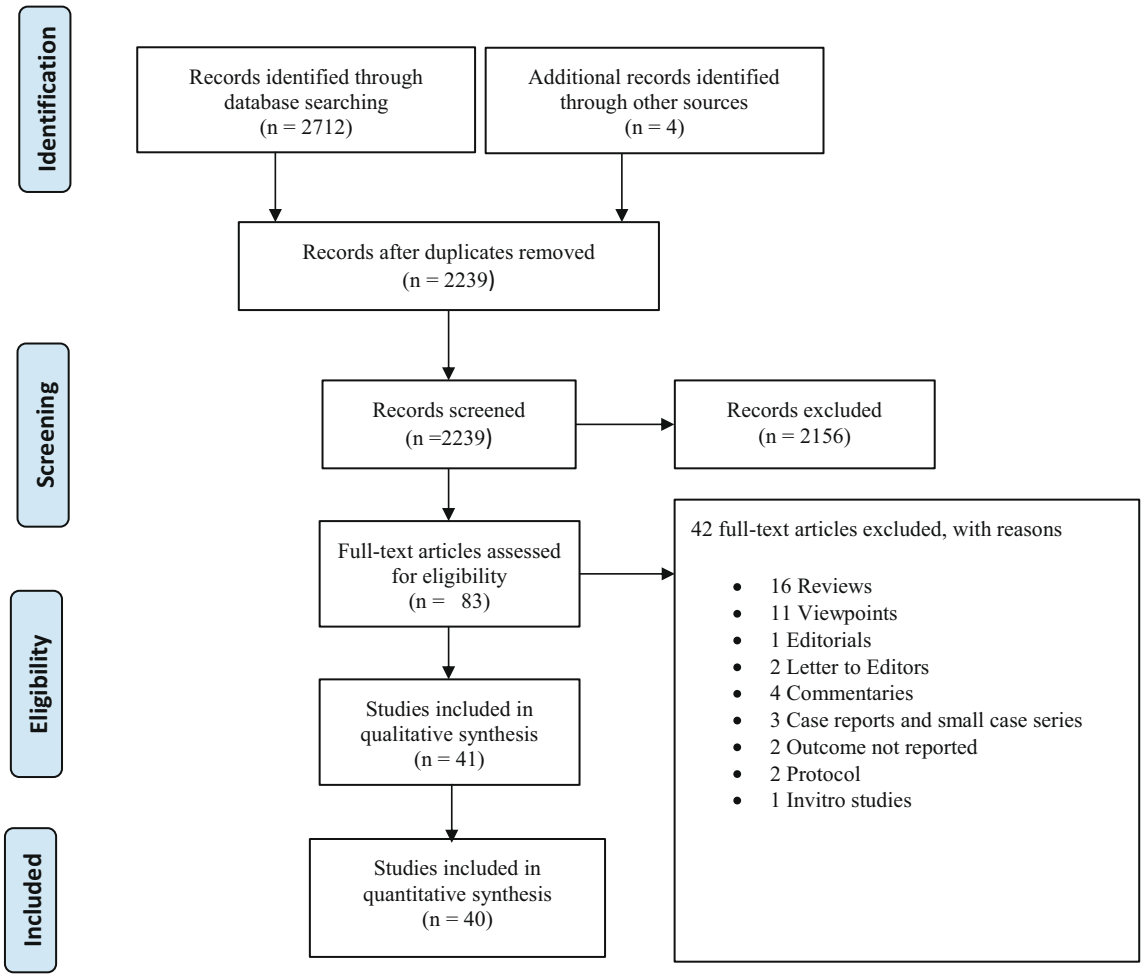


Fig. 1 Flow chart for study design

Table 3 Qualitative analysis of included studies

SN	Study	Study type	Study place and duration	Population	Intervention	Concomitant treatment	Outcome
1	Cao 2020 [45]	Retrospective case series	China January 3–February 1, 2020	102 T: 51 C: 51	51 Patients received corticosteroid therapy	Antiviral, antibiotics, Chinese medicine, and immunoglobulin therapy along with respiratory support	At the end of the study ICU T = 11/51 C = 7/51 Non-ICU T = 40/51 C = 44/51
2	Chen Q 2020 [21]	Retrospective observational study	China January 1–March 11, 2020	145 T: 47 C: 98	47 Patients received corticosteroid therapy	Antiviral, Chinese medicine, antibacterial, immunoglobulin therapy	At the end of the study Severely ill T: 38/47 C: 5/98 Non-severely ill: T: 9/47 C: 93/98
3	Chen TL 2020 [22]	Retrospective study	China January 1–February 20, 2020	203 T: 107 C: 96 Age < 65: 148 Age > 65: 55 T: 34 C: 21	107 Patients received corticosteroid 34 Patients received treatment at age group > 65	Antiviral, immunoglobulin, and respiratory support	At the end of study Death Age > 65: 19 Age < 65: 7 Among Age > 65 Death T: 14/34 C: 5/21 Survival T: 20/34 C: 16/21
4	Chen Xu 2020 [46]	Observational study	China January 23–February 14,2020	T: 67 C: 224	67 Patients received corticosteroid	Antiviral, Chinese medicine, chloroquine, and respiratory support	At the end of study Death: 2 Discharge: 159 Hospitalized: 130 Mild cases T: 13/67 C: 16/224 Moderate cases T: 46/67 C: 166/224 Severe cases T: 8/67 C: 42/224
5	Chrobozcek 2020 [23]	Retrospective study	France March 10–April 9, 2020	70 T: 21 C: 49	32 Patients received corticosteroid	Hydroxychloroquine, azithromycin, and lopinavir	At the end of study Non-intubated T: 18/21 C: 17/49 Intubated T: 3/21 C: 32/49
6	Confalonieri 2020 [24]	Prospective Cohort	Italy March 23–May 20, 2020	173 T: 83 C: 90	Standard of care plus methylprednisolone (MP) 80 mg/kg IV bolus, followed by MP infusion of 80 mg/day in 240 ml normal saline at 10 ml/h for 8 days and until achieving either a PaO_2:FiO_2 > 350 mmHg or a CRP < 20 mg/l	Empiric antibiotics and respiratory support	Admission to ICU, need for invasive

Table 3 (continued)

SN	Study	Study type	Study place and duration	Population	Intervention	Concomitant treatment	Outcome
					Treatment is then switched to oral administration of methylprednisolone 16 mg or 20 mg IV twice daily until CRP returns to <20% of normal range and/or PaO_2:FiO_2 > 400 or $SatHbO_2 \geq 95\%$		ventilation, and death by day 28 Mortality T: 6/83 C: 21/90 ICU admission T: 15/83 C: 27/90 Invasive ventilation T: 15/83 C: 26/90
7	Cruz 2020 [25]	Retrospective cohort study	Spain March 2020	463 T: 396 C: 67	Patients received 1 mg/kg/day methylprednisolone or equivalent, and steroid pulse in the treatment group	Hydroxychloroquine, azithromycin, antivirals, immunomodulators, and respiratory support	At the end of study ARDS T: 240/396 C: 58/67 Mortality T: 55/396 C: 16/67
8	Feng 2020 [26]	Retrospective study	China January 1–February 15, 2020	476 T: 127 C: 349	Patients received corticosteroids in the treatment group.	Antiviral, antibiotics, and antifungal	At the end of study Discharge: 403 Death: 38 Remained in hospital: 23 Lost to follow up: 12 Outcomes in critical patients (T = 52/127, C = 18/349) Discharge T = 13/52; C = 10/18 Death T = 21/52; C = 8/18 Remained in hospital T = 13/52; C = 0/18 Among 3 CAT Moderate T = 47/127 C = 305/349 Severe T = 28/127 C = 26/349 Critical T = 52/127, C = 18/349 Severe + critical T = 80/127 C = 44/349
9	Gong 2020 [27]	Retrospective comparison study	China	34 T: 18	Patients received methylprednisolone in the treatment group.	Antivirals and respiratory support	

Table 3 (continued)

SN	Study	Study type	Study place and duration	Population	Intervention	Concomitant treatment	Outcome
			January 30–February 20, 2020	C: 16			20 Days after methylprednisolone case Complete absorption in 2 cases Partial absorption in 14 cases Enlargement of lesion in 2 cases Nucleic acid negative period T = 29.11 ± 6.61 C = 24.44 ± 5.21
10	Guan 2020 [28]	Retrospective study	China December 11–January 29, 2020	1099 T: 204 C: 895	Patients received systemic glucocorticoid in the treatment group.	Antibiotics, antivirals, antifungal, and respiratory support	At the end of study Disease Severity Non-severe (N = 926); T = 127/204 C = 799/895 Severe (N = 173) T = 77/204, C = 96/895 Presence of composite primary end point (admitted to the ICU, invasive mechanical ventilation, and death) = deterioration Yes (N = 67) T = 35 /204 C = 32/895 No (N = 1032) T = 169/204 C = 863/895
11	Hong Y 2020 [29]	Retrospective study	China January–February 20, 2020	75 T: 17 C: 58	Patients received corticosteroid in the treatment group.	Antiviral, Antibiotics, corticosteroid, and respiratory support	Prolonged length of stay T: 9/17; C: 16/58 Non-prolonged length of stay T: 8/17; C: 42/58
12	Hong KS 2020 [30]	Retrospective study	Korea March 2020	98 T: 18 C: 80	Patients received corticosteroid in the treatment group	Antiviral, antibiotic, hydroxychloroquine, and respiratory support	At the end of study ICU T: 10/18; C: 3/80 Non-ICU T: 8/18; C: 77/80
13	Hou 2020 [31]	Retrospective cohort study	China January 21–March 9, 2020	101 T: 32 C: 69	Patients received corticosteroid in the treatment group.	Antiviral, hydroxychloroquine,	Improvement T: 18/32; C: 66/69 Progression

Table 3 (continued)

SN	Study	Study type	Study place and duration	Population	Intervention	Concomitant treatment	Outcome
						and respiratory support	T: 14/32; C: 3/69
14	Hu 2020 [32]	Retrospective study	China January 8–February 20, 2020	323 T: 196/323 C: 127/323	Patients received corticosteroid in treatment group.	Antiviral, antibiotic, and, respiratory support	At the end of study Favorable T: 142/196; C: 118/127 Unfavorable T: 54/196; C: 9/127 Non-severe T: 87/196; C: 64/127 Severe T: 86/196; C: 60/127 Critical T: 23/196; C: 3/127 Critical + severe = 172 T = 109/196 C = 63/127
15	Huang C 2020[12]	Prospective cohort study	China December–January 2020	41 T: 9 C: 32	Patients received corticosteroid in the treatment group	Antiviral, antibiotic, and respiratory support	At the end of the study ICU T: 6/9; C: 7/32 Non-ICU T: 3/9; C: 25/32 Hospitalized T: 0/9; C: 7/32 Discharge T: 5/9; C: 23/32 Death T: 4/9; C: 2/32 ARDS T: 6/9; C: 6/32
16	Huang M 2020 [33]	Retrospective cohort study	China January 24–February 23, 2020	60 severe cases Among severe cases T: 34 C: 26	Patients received corticosteroid in the treatment group.	Antiviral, antibiotics, antifungal, interferon, and, respiratory support	At the end of the study Improvement T: 27/34; C: 25/26 Deterioration T: 7/34; C: 1/26
17	Jiang 2020 [34]	Retrospective observational study	China January 31–February 16, 2020	60 T: 9 C: 51	Patients received corticosteroid in the treatment group.	Antiviral, antibiotics, interferon, and, respiratory support	At the end of study Non-severe T = 1/9 C = 51/51 Severe T = 8/9 C = 0/51
18	Lei 2020 [35]	Retrospective study	China January 1–February 5, 2020	34 T: 16 C: 18	Patients received corticosteroid in the treatment group.	Antiviral, antibiotics, immunoglobulin, and respiratory support	At the end of the study ICU T: 9/16; C: 6/18 Non-ICU T: 7/16; C: 12/18

Table 3 (continued)

SN	Study	Study type	Study place and duration	Population	Intervention	Concomitant treatment	Outcome
19	Li 2020 [36]	Ambispective cohort study	China January 26–February 5, 2020	548 T: 341 C: 207	Patients received corticosteroid in the treatment group	Antiviral, immunoglobulin, vasopressor, and respiratory support	At the end of the study Non-severe T: 145/341; C: 134/207 Severe T: 196/341; C: 73/207
20	Ling 2020 [7]	Retrospective study	China January 20–February 10, 2020	66 T: 5 C: 61	Patients received corticosteroid in treatment group.	Not mentioned	Negative RT-PCR median (IQR) T = 15 d (9.8–16.8) C = 8 d (6–11)
21	Liu T 2020 [37]	Retrospective Study	China January 21–February 16, 2020	80 T = 29 C = 51	Patients received corticosteroid in the treatment group.	Antiviral, antibiotic, antifungal, and, respiratory support	Severe cases: T = 29/29 C = 40/51 Non-severe cases: T = 0/29 C = 11/51 Recovery = 47 (Non-severe = 10; severe = 37) Hospitalization 33 (Non-severe = 1; severe = 32)
22	Liu Y 2020 [38]	Retrospective Study	China January 2–February 1, 2020	109 T = 72 C = 37	Glucocorticoid therapy	Antiviral, antibiotic, immunoglobulin, and respiratory support	Non-ARDS: T = 35/72; C = 21/37 ARDS: T = 37/72 C = 16/37 Death (31): ARDS = 26 Non-ARDS = 5
23	Lo IL 2020 [47]	Case series	China January 21–February 16, 2020	10 T = 3 C = 7	Patients received corticosteroid in the treatment group.	Antiviral, antibiotic, interferon, and respiratory support	Severe: T = 3/3 C = 1/7 Non-severe: T = 0/3 C = 6/7
24	Lu Xiaofan 2020 [11]	Retrospective Cohort Study	China January 25–February 25, 2020	244 T = 151 C = 93	Patients received corticosteroid in the treatment group	Antiviral, antibiotics and, immunoglobulin	ARDS: T = 81/151 C = 6/93 MV: T = 78/151 C = 4/93 Mortality: T = 79/151 C = 5/93 Subgroup mortality: T = 12/31 C = 5/31
25	Sun L 2020 [39]	Retrospective Observational Study	China January 20–February 15, 2020	55 T = 25 C = 30	Patients received corticosteroid in the treatment group	Antiviral, interferon, antibiotic, and respiratory support	Severe: T = 11/25; C = 4/30 Non-severe: T = 14/25; C = 26/30 Hospitalized: T = 19/25; C = 7/30 Discharged: T = 6/25; C = 23/30
26		Case Series	China	135	Patients received corticosteroid in the treatment group.		Severe:

Table 3 (continued)

SN	Study	Study type	Study place and duration	Population	Intervention	Concomitant treatment	Outcome
	Wan S 2020 [48]		January 23–February 8, 2020	T = 36 C = 99		Antiviral, antibiotic, oxygen support, traditional Chinese medicine, and respiratory support	T = 21/36; C = 19/99 Non-severe cases T = 15/36; C = 80/99 Hospitalization 120 Discharge 15 Death 1
27	Wang D 2020 [49]	Retrospective Case Series	China January 1–28, 2020	138 T = 62 C = 76	Patients received corticosteroid in the treatment group.	Antiviral and respiratory support	ICU T = 26/62; C = 10/76 Non-ICU T = 36/62; C = 66/76
28	Wang D2 2020 [13]	Retrospective case series	China December 2019–February 2020	107 T = 62 C = 45	Patients received corticosteroid in the treatment group.	Antiviral, antibiotic and, respiratory support	Survivors (S): 88 Non-survivors (NS): 19 S: T = 44/62; C = 44/45 NS: T = 18/62; C = 1/45
29	Wang Z 2020 [15]	Case series	China January 19–29, 2020	67 T = 10 C = 57	Patients received corticosteroid in the treatment group.	Antiviral, antibiotic, antifungal, and Arbidol	Hospitalization: T = 3/10; C = 41/57 Death: T = 4/10; C = 1/57 Discharged T = 3/10; C = 15/57
30	Wang K 2020 [14]	Ambispective Observational Cohort Study	China	T = 548	Patients received corticosteroid in the treatment group.	Antiviral including Arbidol	At the end of the study, D15; Survivors (n = 470), T = 276/341, C = 194/207 Non-survivors (n = 78); T = 65/341, C = 13/207
31	Wu C 2020 [9]	Retrospective cohort study	China December 25, 2019–January 26, 2020	201 T = 62 C = 139	Patients received corticosteroid in the treatment group.	Antiviral, antibiotic, oxygen therapy, immunomodulators, and antioxidant	ARDS = 84 Death among ARDS = 44/84 T = 23/50 C = 21/34 Discharged = 27/50 C = 13/34
32	Wu J 2020 [16]	Retrospective cohort study	China December 26, 2019–March 15, 2020	1763 Severe = 1514 T = 531 C = 983 Critical = 249 T = 159 C = 90	Patients received corticosteroid in the treatment group.		Severe cases Hospital stay: T = 15.2 d C = 11.5 d Progression to critical case: T = 149/531 C = 104/983 Death: T = 83/531 C = 26/983 Critical cases: Hospital stay, d: T = 12.9 C = 15.6

Table 3 (continued)

SN	Study	Study type	Study place and duration	Population	Intervention	Concomitant treatment	Outcome
							Death: T = 70/159 C = 14/90
33	Xu Y 2020 [50]	Retrospective multicenter case series	China February 7–28, 2020	69 T = 6 C = 63	Patients received corticosteroid in the treatment group.	Antiviral, antibiotic	Severe cases: T = 6/6 C = 19/63 Non-severe cases: T = 0/6 C = 44/63
34	Xu Yonghao 2020 [40]	Multi-centered retrospective observational cohort study	China	45 T = 21 C = 24	Patients received corticosteroid in the treatment group.	Antiviral, antibiotic, antifungal, convalescent plasma, and albumin	Intubation T = 10/21 C = 10/24 Non-intubated T = 11/21 C = 14/24
35	Yang L 2020 [41]	Retrospective study	China January 30–February 8, 2020	200 T = 112 C = 88	Patients received corticosteroid in the treatment group.	Antiviral, antibiotic	ICU: T = 20/112 C = 9/88 Non-ICU: T = 92/112 C = 79/88 Hospitalization: 143 Discharge: 42 Death: 15
36	Yang X 2020 [42]	Single-centered retrospective observational study	China Late December–January 26, 2020	52 T = 30 C = 22	Patients received corticosteroids in the treatment group.	Antiviral, oxygen therapy, antibacterial, immunoglobulin	Survivors: T = 14/30 C = 6/22 Non-survivors: T = 16/30 C = 16/22 ARDS: 35 MV:37
37	Yu H 2020 [17]	Retrospective cohort	China January–March 2020	775 T: 238 C: 537	Patients received corticosteroid in treatment group.	Antivirals and respiratory support	Overall mortality rate T: 44/238 C: 18/537 Recovery T: 161/238 C: 433/537 Undetectable viral RNA (Clearance) T: 83/238 C: 311/537 Duration of hospital stay days T: 18.7 ± 12.0 C: 15.0 ± 8.9 Duration of viral RNA (Clearance) days T: 11.9 ± 9.2 C: 9.4 ± 8.3 Mild–moderate T = 117/238 C = 437/537 Severe to critical

Table 3 (continued)

SN	Study	Study type	Study place and duration	Population	Intervention	Concomitant treatment	Outcome
							T = 121/238 C = 100/537
38	Zha L 2020 [43]	Observational study	China January 24–February 24, 2020	31 T = 11 C = 20	Patients received corticosteroids in the treatment group.	Antiviral, antibiotic	Viral clearance (days) median: T = 15 C = 14 Hospital stay (days) median: T = 20 C = 17 Recovered: T = 11/11 C = 15/20
39	Zhang G 2020 [51]	Retrospective case series	China January 2–February 10, 2020	221 T = 115 C = 106	Patients received corticosteroids in the treatment group.	Antiviral	Non-severe cases: T = 75/115 C = 91/106 Severe cases: T = 40/115 C = 15/106 Hospitalization (167) Severe = 36, Non-severe = 131 Discharge (42) Severe = 7, Non-severe = 35 Death (12) Severe = 12
40	Zhao X 2020 [44]	Retrospective study	China January 16–February 10, 2020	91 T = 79 C = 12	Patients received corticosteroid in the treatment group.	Antiviral, antibiotic	Non-severe: T = 54/79 C = 7/12 Severe: T = 25/79 C = 5/12
41	Zhou F 2020 [18]	Multi-centered retrospective cohort study	China December 29, 2019–January 31, 2020	191 T = 57 C = 134	Patients received corticosteroid in the treatment group.	Antiviral, antibacterial, oxygen therapy, immunoglobulin	Discharged: 137 Died: 54 Survivors: T = 31/57 C = 106/134 Non-survivors: T = 26/57 C = 28/134

C control group, *d* days, *T* treatment group, *ICU* intensive care unit

- Moderate type: Fever, cough, and other symptoms are present with pneumonia on chest computed tomography
- Severe type: The disease is classified as severe if one of the following conditions is met such as respiratory distress, respiratory rate > 30/min, oxygen saturation on room air at rest <93%, and $PaO_2/FiO_2 < 300$
- Critical type: One of the following conditions has to be met: d respiratory failure occurs and mechanical ventilation is required. d shock occurs. d other organ dysfunction is present, requiring ICU monitoring and treatment

Quantitative Analysis

Overall, 40 studies included in the quantitative synthesis. There is a constant debate about whether to give corticosteroids or not to COVID-19 individuals. Until now, no proper randomized study showed clear beneficence or harm of giving steroids to COVID-19 patients. In the present meta-analysis, we have compared findings among non-randomized studies to extract the outcome on which a type of patient is prone to get corticosteroids, the overall change in mortality, overall improvement or deterioration among treatment groups in comparison with control, duration of virological clearance, length of hospital stay, the requirement of intubation, and mechanical ventilation.

Who Is More Likely to Get Corticosteroids?

For this, we did meta-analysis taking all studies comparing severity, baseline/overall ICU admission, and ARDS-diagnosed COVID-19 cases. Among the included studies in the meta-analysis, we found that there is moderate–high heterogeneity, which may be due to clinical and variability in study design and the risk of bias among studies that could not be omitted fully may be due to the acute surge in COVID-19 cases having diversity presenting and getting treatment due to the pandemic.

Severity of COVID Patients The meta-analysis of OR for severe and critical COVID-19 patients tending to get corticosteroids or standard of care compared using random effects model among non-randomized studies showed that there are significant differences between treatment and control arms (OR 4.78, 95% CI 2.76 to 8.26; participants = 4378; studies = 15; $I^2 = 89\%$). Severely ill COVID-19 patients have almost 5 times higher odds of getting corticosteroids during their treatment (Fig. 2). While non-severe individuals are less likely to get corticosteroids during their treatment (OR 0.21, 95% CI 0.12 to 0.36) (Additional file 4/ Fig. 1).

Sensitivity Analysis To evaluate the impact of inverse ORs as well as studies' weight on the meta-analysis results, we conducted sensitivity analyses as according to the substantial relative weight of 4 studies (Yu H 2020 [17], Guan W 2020 [28], Hu L 2020 [32], and Li X 2020 [36]) to the meta-analysis, by excluding these studies as they showed increases in the risk of getting steroid in treatment than observed (OR 7.64, 95% CI 2.85 to 20.43) (Additional file 4/ Figs. 2 and 3).

ICU Admitted COVID Patients Among studies comparing ICU admitted with non-ICU patients, overall odds for corticosteroids in addition to SOC are approximately 4 (OR 4.09, 95% CI 1.89 to 8.84; participants = 613; studies = 6; $I^2 = 64\%$) (Fig. 3). While non-ICU patients are having lesser odds for getting corticosteroids (OR 0.24, 95% CI 0.11 to 0.53) (Additional file 4/ Fig. 4).

COVID Patients with ARDS Our meta-analysis among studies reporting ARDS and non-ARDS showed about 3 (OR 2.99, 95% CI 0.66 to 13.64; participants = 1632; studies = 5; $I^2 = 95\%$) times the odds of getting corticosteroids but it is of no significance statistically (Fig. 4). Sensitivity assessment done after excluding a study with significantly high weight (Cruz AF 2020 [25]) showed significant odds for getting corticosteroids among ARDS (OR 5.64, 95% CI 2.02 to 15.70) (Additional file 4/ Fig. 5). Similar assessments among non-ARDS individuals showed non-ARDS have lower odds of getting steroids (OR 0.18, 95% CI 0.06 to 0.49) (Additional file 4/ Fig. 6).

Corticosteroids in Addition to Standard of Care: Mortality

The meta-analysis of death outcome among non-randomized studies with or without complete follow-ups showed significantly higher mortality risk with corticosteroids and standard of care group compared with standard of care alone (RR 2.01, 95% CI 1.12 to 3.63; participants = 4451; studies = 14; $I^2 = 92\%$; RD 0.10, 95% CI 0.02 to 0.17) (Fig. 5). Survival assessment among COVID-19 individuals with or without corticosteroids showed no survival benefits after adding corticosteroids, rather corticosteroid addition may decrease the survival rate (RR 0.88, 95% CI 0.78 to 0.98) (Additional file 4/ Fig. 7).

Sensitivity Analysis for Corticosteroids in Addition to SOC on Mortality Compared with SOC Alone To evaluate the impact of inverse RRs as well as studies' weight on the meta-analysis results, we conducted sensitivity analyses excluding Wu J 2020 [16] due to its substantial weight in the meta-analysis. Excluding Wu J 2020 [16] showed no significant changes (RR 1.76, 95% CI 1.03 to 3.02) (Additional file 4/ Figs. 8 and 9).

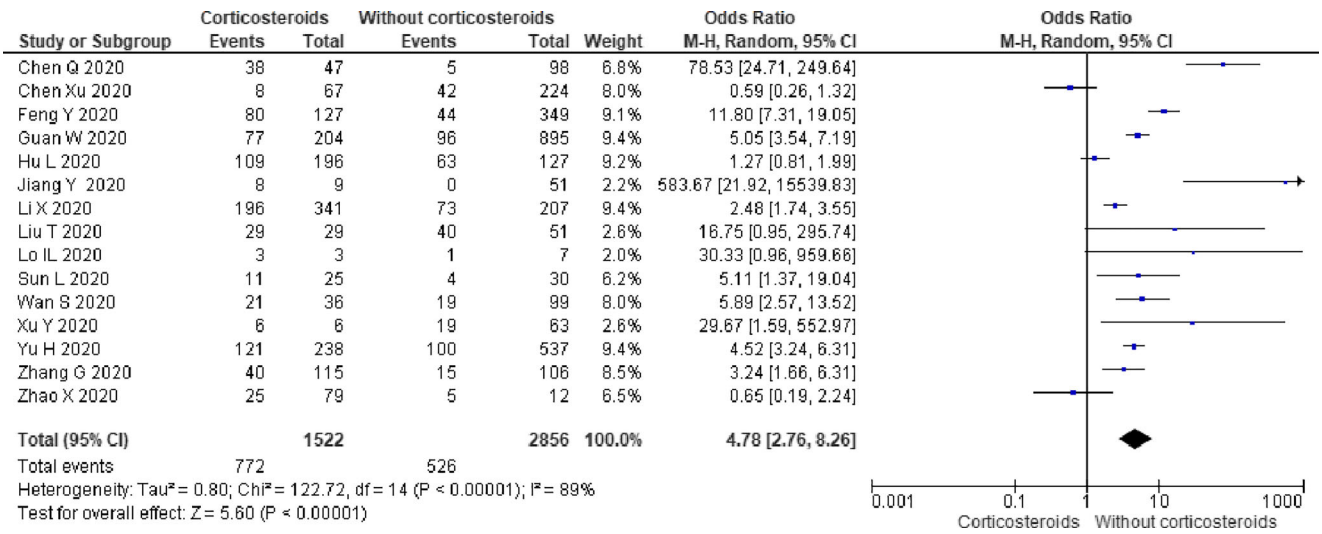


Fig. 2 Forest plot for odds ratios among severe and critically ill COVID-19 patient

Rate

The meta-analysis on discharge rate as an outcome among non-randomized studies with or without complete follow-ups showed a significant lower discharge rate with corticosteroids and standard of care group compared with standard of care alone at the point of data analysis of study included for analysis (RR 0.79, 95% CI 0.63 to 0.99; participants = 1390; studies = 9; I^2 = 62%, RD − 0.13, 95% CI − 0.26 to − 0.01) (Fig. 6).

Corticosteroids in Addition to Standard of Care in Studies with Incomplete Follow-Up: Hospitalization at the Point of Concluding Studies

The meta-analysis on hospitalization rate at the point of concluding studies including studies with incomplete follow-up, showed no significant differences between treatment and control groups (RR 1.28, 95% CI 0.27 to 6.17) (Fig. 7).

with Incomplete Follow-Up: On Recovery/Improvement

The meta-analysis on recovery/improvement rate at the point of concluding studies including studies with incomplete follow-up results showed significant delay in recovery/improvement among the treatment groups with added corticosteroids to SOC (OR 0.24, 95% CI 0.13 to 0.43; participants = 2555; studies = 9; I^2 = 71%) (Fig. 8). Rather, additional corticosteroids with SOC showed significant odds of deterioration (OR 3.79, 95% CI 1.93 to 7.46) (Additional file 4/ Fig. 10).

Corticosteroids in Addition to Standard of Care: Intubation and Mechanical Ventilation

Meta-analysis on overall mechanical ventilation among the included non-randomized studies showed no significant differences between corticosteroids and SOC versus SOC only about the odds of mechanical ventilation during treatment (OR 1.44, 95% CI 0.35 to 5.92; participants = 684; studies = 7; I^2 = 90%) (Fig. 9).

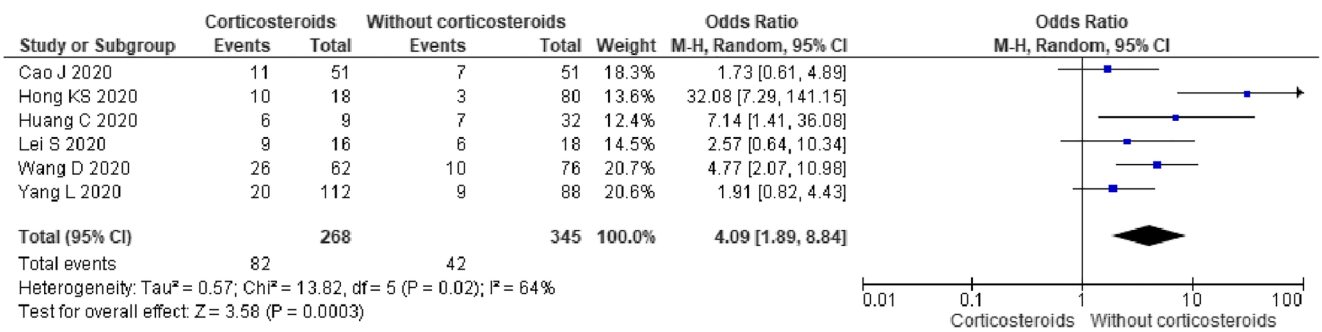


Fig. 3 Forest plot for odds ratios regarding getting corticosteroids among ICU-admitted patient

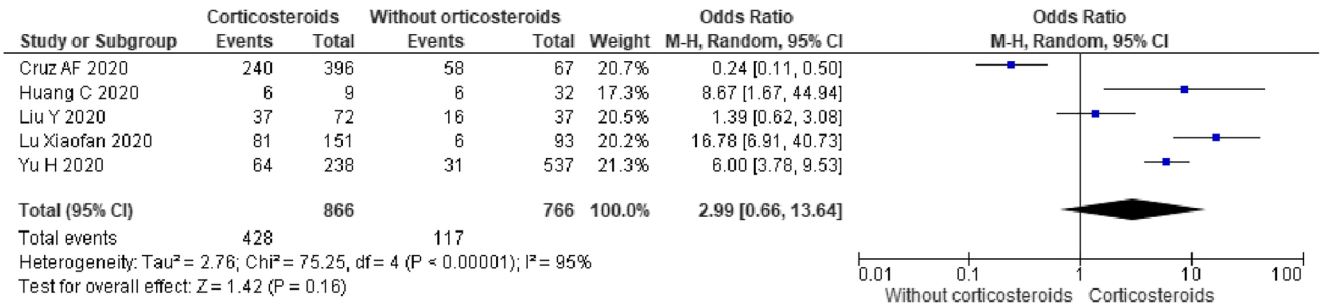
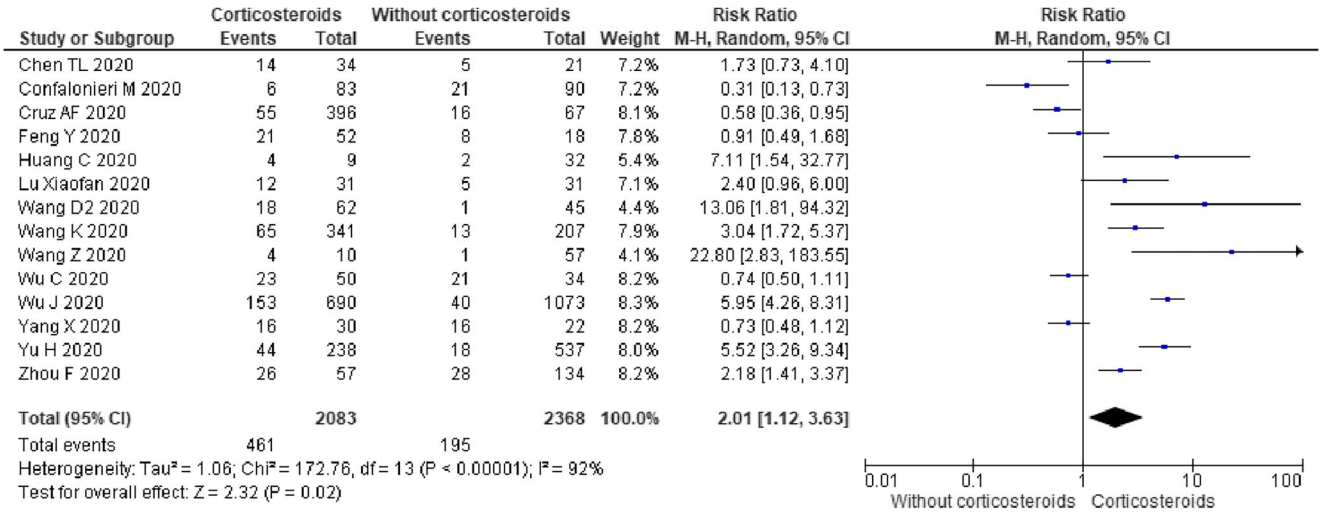


Fig. 4 Forest plot for odds ratios regarding getting corticosteroids among COVID-19 with ARDS patient

Length of Hospital Stay (LoHS)

Meta-analysis comparing the overall length of hospital stay between treatment and control groups showed approximately 4 days longer stay among treatments with corticosteroids (MD in days 4.19, 95% CI 2.57 to 5.81; participants = 2726; studies = 4; $I^2 = 70\%$) (Fig. 10).



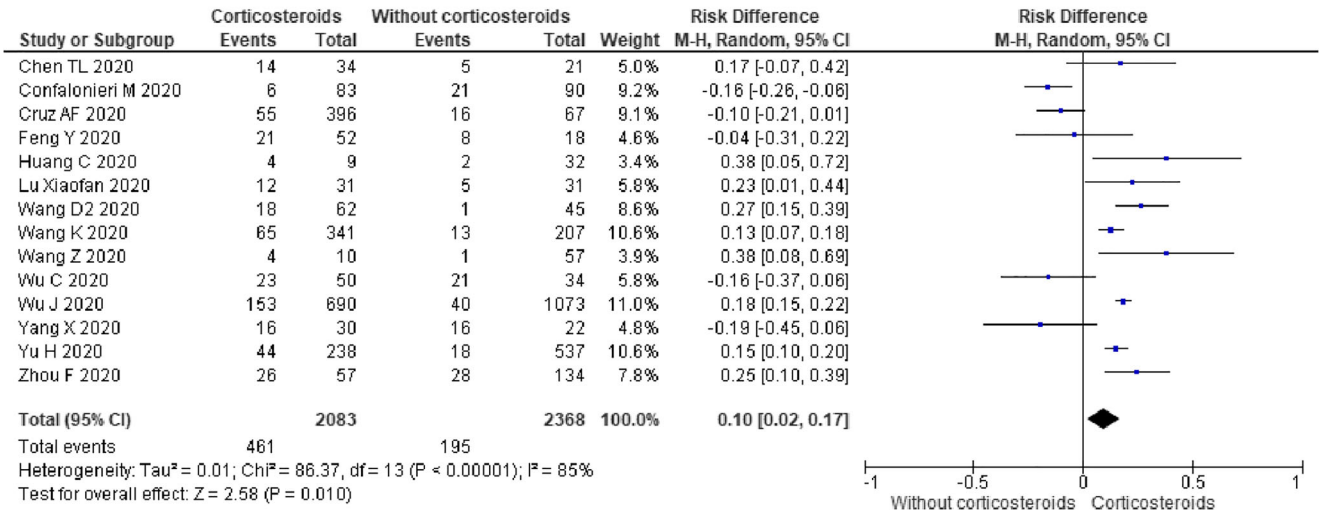


Fig. 5 Forest plot for risk ratios and risk differences regarding corticosteroids with SOC on mortality compared with SOC alone

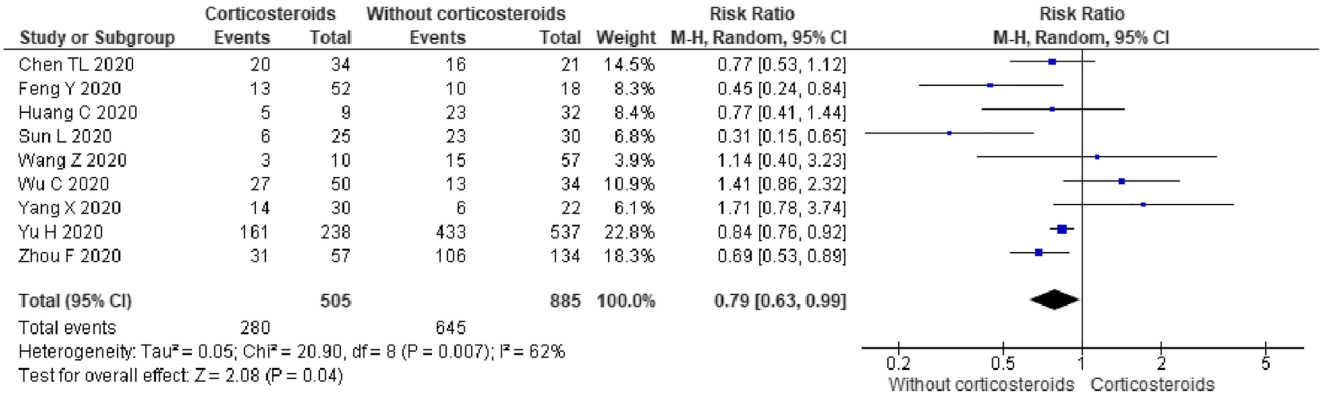


Fig. 6 Forest plot for risk ratios and risk differences regarding corticosteroids with SOC on discharge rate compared with SOC alone

Duration to Convert Negative RT-PCR

Our meta-analysis on negative conversion of RT-PCR demonstrated approximately 3 days (MD 2.42, 95% CI 1.31 to 3.53; participants = 906; studies = 4; $I^2 = 14\%$) more on treatment with corticosteroid than without corticosteroids (Fig. 11).

Clinical Trials

There are right away 37 trials (details in additional file 5) registered for evaluation regarding the use of corticosteroids on COVID-19 [53]. Among these, 3 trials are already completed, while 9 trials are not yet recruiting participants. A total of 24 such trials are in recruiting status. These trials are run in different parts of the world. According to the location provided for the 33 trials, most of these are being managed in France (11 trials), followed by Spain (5 trials). A total of twenty-eight trials are of observational trials, and the rest are of an interventional type. Corticosteroids like prednisolone, methylprednisolone, dexamethasone, budesonide are used as drugs in such trials. Ranging from 12 participants in a trial conducted in Belgium, some trials are enrolling 12,000 participants in the UK to 13,770 in France. One trial among registered trials is in the active phase but not in the recruiting status.

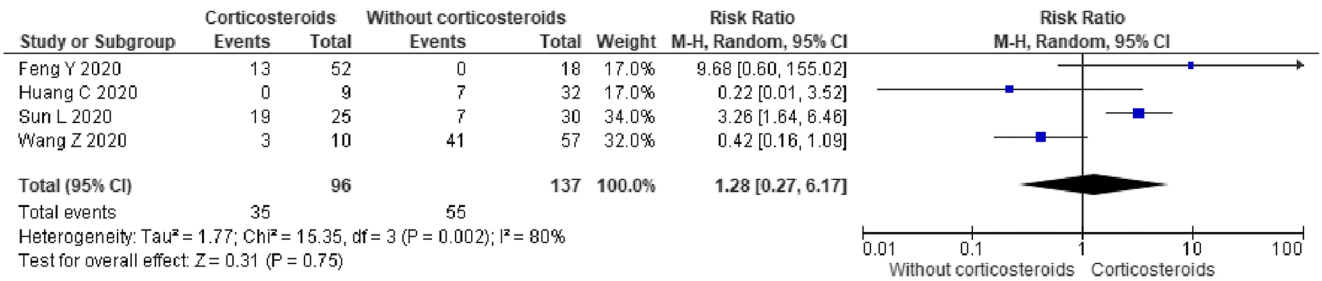


Fig. 7 Forest plot for risk ratios regarding corticosteroids with SOC for hospitalization

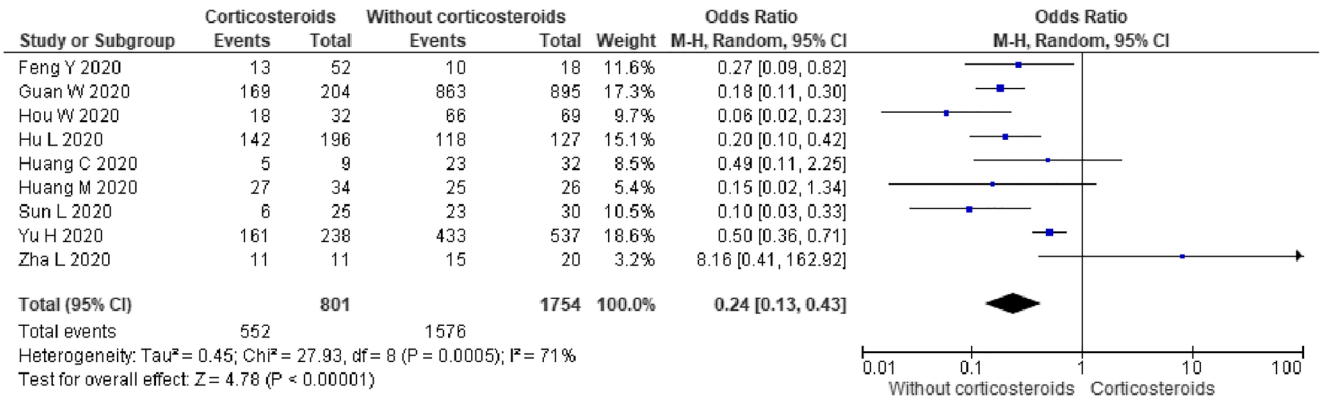


Fig. 8 Forest plot for odds ratios regarding corticosteroids with SOC on recovery/improvement

Discussion

The debate about how safe it is to use corticosteroids in critically ill patients is ongoing for many decades. The pathophysiology of previous coronavirus infectious outbreaks like SARS-CoV and MERS-CoV and the use of corticosteroids for treatment are still unclear. Earlier studies show that the increased amount of pro-inflammatory cytokines in serum was found in patients with SARS-CoV/MERS-CoV infections [54, 55]. Thus, the common ground of genetic homology might have attracted the clinician's attention to repurposing the drug in the treatment of ongoing COVID-19 pandemic. In this meta-analysis, we assessed which patients with COVID-19 are more likely to get corticosteroids in addition to standard of care and compared their outcomes including mortality, risk of intubation, viral clearance, recovery, hospital stay, and overall improvement compared with the standard of care alone.

The quantitatively synthesized data and their evaluation led to many significant findings. Critical patients and severely ill COVID-19 cases were likely to get the drug as the odds were almost 5 times higher in the treatment arm compared with the control arm (OR 4.78, 95% CI 2.69 to 8.48). ICU-admitted patients have higher odds of getting the drug as there was a significant difference between the ICU and non-ICU patients (OR 4.09, 95% CI 1.89 to 8.84). Among patients with ARDS, the odds were significantly higher following sensitivity analysis (OR 5.56, 95% CI 2.00 to 15.45), and non-ARDS patients showed lower odds of getting corticosteroids in their treatment (OR 0.18, 95% CI 0.06 to 0.50). As per the outcomes analyzed, there were few surprising findings regarding mortality caused by the drug. An earlier study showed that corticosteroids might decrease the risk of death in COVID-19 patients [9, 56, 57] but our meta-analysis derived contradicting answers. Higher mortality risk was observed with statistically significant numbers among the corticosteroid group, while

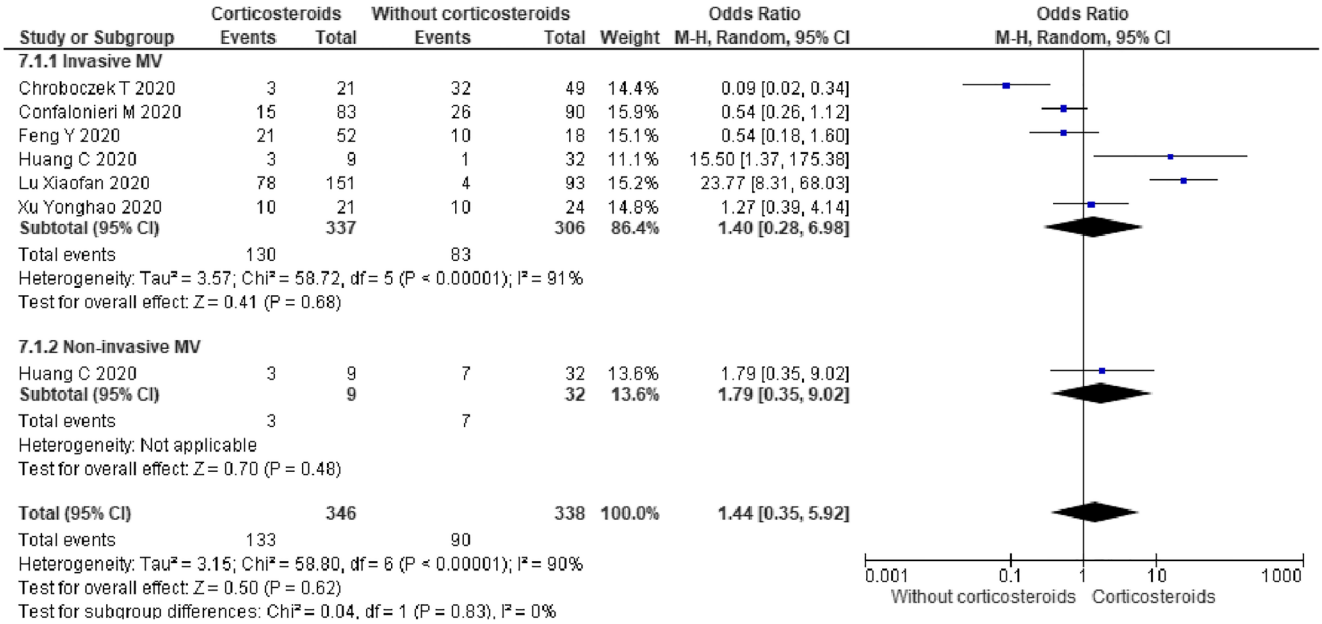


Fig. 9 Forest plot of corticosteroids in addition to standard of care on intubation and mechanical ventilation compared with SOC alone

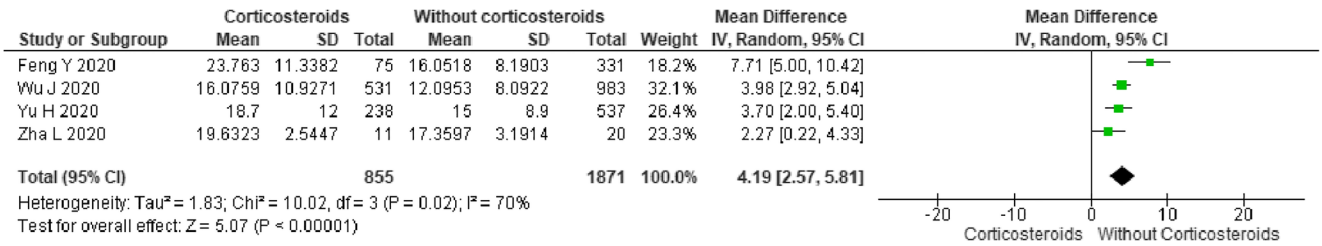


Fig. 10 Forest plot of corticosteroids in addition to standard of care on length of hospital stay

comparison was done between the treatment and control arm (RR 2.01, 95% CI 1.12 to 3.63) along with no survival benefit in the treatment group. Our meta-analysis alarms an increased risk of mortality among severe and critically ill COVID-19 patients and guides against the rampant use of corticosteroids in COVID-19 patients based on the present level of evidence.

The duration of viral clearance and length of hospital stay was higher in the treatment group as the result showed days required for conversion of RT-PCR to become negative took 3 days more in the treatment arm (MD in days; 2.70, 95% CI 1.03 to 4.37), and the patient in the treatment arm stayed 5 days longer in the hospital (MD 5.42, 95%CI 3.56 to 7.28). The discharge rate after the most studies was lower in the treatment group (RR 0.79, 95% CI 0.63 to 0.99), but there was no significant difference between the hospitalization rate of patients in the treatment and control arm (RR 0.80, 95% CI 0.33 to 1.94). Results showed delayed recovery among treatment groups (OR 0.24, 95% CI 0.13 to 0.43), although there was no significant difference between the cases in the two groups being mechanically ventilated or intubated (OR 1.44, 95% CI 0.35 to 5.92). Although meta-analysis in the past has extracted a similar result in the context of benefit, virus clearance, and hospitalization [58], the result regarding mortality may become a groundbreaking finding.

The overall mortality rate among ICU and severely critically ill patients is already higher irrespective of the disease condition. Our analysis of studies among COVID-19 patients showed getting corticosteroids in their treatment is higher in ICU and severely critically ill COVID-19 cases. Our main findings from the reported study raised questions towards the current practice of using corticosteroids in such a group of patients. Though the non-randomized nature of the included study and risk of bias is there, we need to rethink the use of corticosteroid in such COVID-19 patients because of no added benefit rather than having a poor outcome.

There are multiple trials going on around the world focusing on the efficacy of corticosteroid among cases of COVID-19 and the use of corticosteroid has been considered to be default [59, 60]. The WHO welcomed the results of the clinical trial in the UK which showed decreased mortality with dexamethasone in both patients requiring ventilator and on oxygen therapy [61]. Despite the optimism from WHO about the preliminary findings of the Oxford trial, there are doubts among clinicians which can only be answered as more clinical trials are completed and their results are analyzed.

Strength and Limitations of the Meta-Analysis

This meta-analysis has pooled data from 40 studies done among cases of COVID-19 solely. The sample size was remarkably increased with decreased probability of making Type II error in the study. The study has focused on the groups more likely to be treated with corticosteroids. Moreover, there were significant results under outcomes, which are an appreciable achievement regarding the current situation with inadequate evidence regarding the drug's use. The study has conducted subgroup analysis wherever applicable along with weighing out and sensitivity analysis for all outcomes which makes the results reliable.

Limitations of the study need to be acknowledged as there has been bias in many forms. There is moderate-to-high heterogeneity as various types of studies with methodological and clinical diversity were added to the pool; the dosing of the drug has not been uniform, and although the study has significant results, a cause–effect relationship cannot be derived in hands. Almost all studies have been conducted in China, which might affect the applicability to people with different ethnicity, and many variations of the drug efficacy and side effects have not been explored. This is why more controlled studies should be

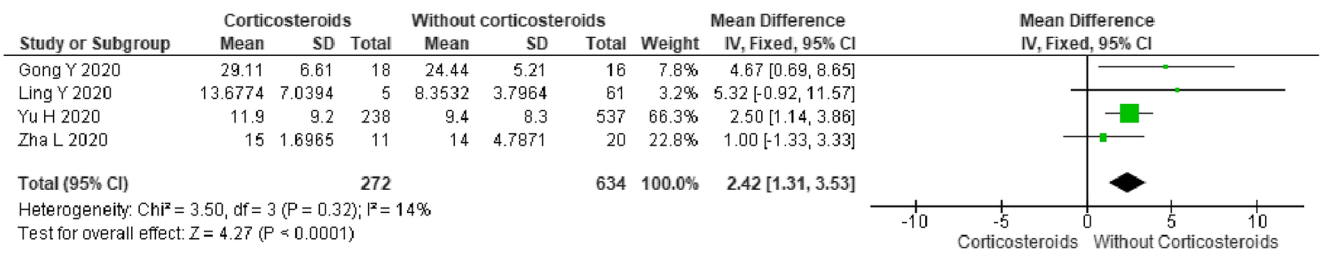


Fig. 11 Forest plot of corticosteroids in addition to standard of care on negative conversion of RT-PCR

dedicated to back up the use of this drug, being most of the studies for which we did meta-analysis were of retrospective observational type. To strengthen this result, the results of ongoing RCTs need to be explored when it will come out.

Conclusion

Our study concludes that more severe and critically ill patients tend to get corticosteroids, and the mortality risk increases with the use of corticosteroids. There were no survival benefits with the use of corticosteroids along with delayed recovery and longer hospital stay; this may be due to the tendency that more severe patients get corticosteroids. Corticosteroids have been effectively used for a long time in the field of medicine and in unprecedented times like these; little evidence of efficacy should be dealt with meticulously. Ongoing trials may answer unexplored questions about their safety and efficacy in the near future.

Acknowledgments Initially, this meta-analysis was submitted in Systematic Reviews; one of the title of Springer Nature but after completing the peer review process, they advise to transfer to SN Comprehensive Clinical Medicine. During prior submission, Systematic Reviews sent our manuscript to preprint to disseminate our findings as earlier as possible to the scientific community.

Availability of Data and Materials The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions PB and DBS contributed in the concept and design, analysis, and interpretation of data. ER and SK contributed in the literature search, data extraction, and review and assisted in analysis.

All authors were involved in drafting and revising the manuscript and approved the final version.

Compliance with Ethical Standards

Competing Interests The authors declare that they have no competing interests.

Ethics Approval and Consent to Participate Not applicable

Consent for Publication Not applicable

Abbreviations ARDS, Acute respiratory distress syndrome; C, Control group; CI, Confident interval; COVID-19, Coronavirus disease; d, Days; ICU, Intensive care unit; I^2, I-squared; LoHS, Length of hospital stay (LoHS); MD, Mean differences; MERS-CoV, Middle East respiratory syndrome coronavirus; NF-κB, Nuclear transcription factor-κB; NHLBI, National Heart, Lung, and Blood Institute; OR, Odds ratio; PRISMA, Preferred reporting items for systematic reviews and meta-analyses; RCTs, Randomized controlled trials; RD, Risk difference; RR, Risk ratio; RT-PCR, Reverse transcription–polymerase chain reaction; SARS-CoV, Severe acute respiratory syndrome coronavirus; SOC, Standard of care; T, Treatment group; WHO, World Health Organization

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