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Corticosteroids In COVID-19 Management- A Systematic Review and Meta-Analysis Based on Recent Evidence

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ABSTRACT

Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 has become a Public Health Emergency of International Concern (PHEIC) causing mortality due to cytokine storm syndrome and multiorgan failure. Corticosteroids have shown considerable efficacy in studies conducted on COVID-19 patients but the relative efficacy and safety for its compassionate use remain unclear. This meta-analysis aimed to evaluate available evidence on the efficacy of corticosteroids in the management of COVID-19 patients at various stages of the disease. In this meta-analysis, we included seven trials, and their pooled analysis revealed COVID-19 patients in the treatment group (n=3334) was lower as compared to the control group (n=5585). The overall pooled analysis among COVID-19 patients showed corticosteroids could decrease mortality (OR = 0.587, CI = 0.36-0.95, and p-value 0.029). Corticosteroids had an insignificant effect on viral clearance. Findings suggest that corticosteroids are helpful in managing COVID-19 patients although further research is required.

Abbreviations: COVID-19: Coronavirus disease 2019, PHEIC: Public Health Emergency of International Concern (PHEIC), OR: odds ratio, CI: confidence interval, SARS: Severe acute respiratory distress syndrome, MERS: middle east respiratory syndrome, RT-PCR: real time polymerase chain reaction, MDs: mean differences, HR: Hazard Ratios, IV: intravenous, ICU: intensive care unit, COPD: Chronic obstructive pulmonary disease, ARDS: Acute Respiratory Distress Syndrome, CRP: C-reactive proteins

Background

Coronavirus disease-19 (COVID-19), a respiratory viral disease caused by SARS-COV-2, enveloped, and single-stranded coronavirus belongs to subgenus Sarbecovirus. The first case of COVID-19 turned up in Wuhan, a city of China. It spread rapidly and became the global epidemic affecting more than 213 countries across the globe [1]. According to the World Health Organization, the number of cases across the world reaches 23 million, and the number of death is 805,902 as of August 24, 2020 [2]. Some studies reported that most of the patient shows no symptoms at all or very mild symptoms and only 20 percent of patients develop respiratory problems and need hospitalization [3]. The morbidity of the patients is due to the progression of the respiratory infection to the hypoxemic respiratory failure and cytokines releasing syndrome, often requiring prolonged mechanical ventilation. The fatality rate reaches 26% in the United Kingdom and more than 37% in ventilation requiring patients [4]. According to available literature the corticosteroids were widely used in previous SARS pandemic in 2003-4 in China and Hong Kong, and this leads to the usage of corticosteroid in COVID-19 in clinical trials [3,4]. Previously COVID-19 has been treated with drugs from various classes like antivirals, immune-modulating therapies, and anti-inflammatory drugs, and corticosteroid is an attractive option because of its potent anti-inflammatory mode of action and its previous regular usage in other respiratory conditions like severe acute respiratory distress syndrome. [5] But the use of systemic corticosteroid treating COVID 19 disease still contend because one of the recent meta-analysis

showed that patients treated without hydrocortisone show a low viral load in plasma and decreased viral shedding time than those treated with hydrocortisone [6].

According to some experts, corticosteroids increase viral shedding in lung damage and shock induced by a coronavirus and hence should not be used. [7] Various other trials showed promising results like recently in one of pre-published study, a randomized trial is conducted using a sample size of 11,303 patients in the different stage of COVID-19, show a reduction in 28 days mortality in the patients on oxygen therapy and mechanical ventilation using dexamethasone and their results lead to the global use of dexamethasone in COVID-19 patients [8]. Retrospective studies showed promising results of corticosteroid in SARS patients while in MERS patients, the usage of corticosteroids is not satisfactory, and patients require ventilation and renal replacement therapy. [9] In a nutshell, various trials and case studies showed a wide range of results. As the literature is rapidly expanding and continuously refilled every day, an updated meta-analysis featuring the latest literature is required. The aim of this systematic review and meta-analysis to assess the strength of evidence of usage of dexamethasone and other corticosteroids in the treatment of COVID-19. The study aims to obtain a single summary to quantify the results.

Materials and Methods

Search Strategies

In our study, we collected data by searching published articles in peer-reviewed journals by doing online search on article search engines like PubMed, Google Scholar, EMBASE, and Cochrane database from June 15th to July 31th, 2020. We searched articles by searching keywords "Coronavirus", "SARS-CoV-2", "Corticosteroids", "Dexamethasone", "treatment", and "effectiveness". We also searched these databases with individual drug names of corticosteroid family like, prednisolone, methylprednisolone, betamethasone, cortisone, and hydrocortisone. We also searched for the articles mentioned in the references of these articles.

Study Selection

We included randomized control trials and cohort studies investigating the effect of corticosteroid therapy among COVID-19 patients provided that: the medium of the reported article was English, the participants of the study were 18 years old or older, COVID-19 testing was done through RT-PCR, and analysis & outcome measures were given. We included the articles published in peer review journals from June 15th to July 31th 2020. The articles like editorials, perspectives, commentaries and short reviews were excluded.

Data Extractions

Two authors (SA and A) screened the rest of the articles independently. The articles on which two authors were of different views, whether to include them or not, the opinion of the third author (MASC) was obtained, and thus, the articles were screened out without any bias. The data we extracted and tabulated were the name of the articles, publication date, interventional drugs, number of participants, and any co-interventions used. Screening of the articles yielded a total number 14 articles following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, as shown in Figure 3.

Data Analysis

We conducted meta-analysis on the factors: effect of corticosteroid therapy on mortality, length of stay, ICU admission, adverse events, and risk of infection. Data analysis was conducted on RevMan 5.4. We analyzed pooled mean differences (MDs) and pooled adjusted Odds Ratios (OR), Hazard Ratios (HR), with 95% CIs , using the generic inverse-variance approach. The pooled analysis is shown graphically by forest plot. $\chi 2$ Cochran's Q test was employed to assess the statistical heterogeneity of studies. p value of 0.05 less was considered significant. For assessment and graphical representation of the heterogenicity and bias, we plotted the funnel plot using individual studies.

Results

Search Results

Our database searches yielded 768 relevant articles. After removing 79 duplicated articles and screening titles and abstracts, 675 articles were excluded because of irrelevance. Full-text articles for 14 articles are assessed for eligibility, and 7 articles are included for final meta-analysis. Among 14 articles, 9 were observational cohort studies, 2 clinical trials (open label, randomized), and 3 were case series involving 8632 patients.

Study Characteristics

As 6 articles did not report relevant data on mortality, we reported outcomes on 7 studies (3334 patients receiving steroids and 5585 patients in the control group or not receiving steroids). The patient's mean age in the selected studies was 61.93 year and 63.61% are males and 36.69% are females. Seven studies reported mortality. 9 studies showed participants receiving other cointerventions. Hypertension and diabetes were common in 11 studies. Corticosteroid most commonly used was methylprednisolone, but 2 studies included dexamethasone for treating COVID 19 patients. Seven articles included patients with severe SARS CoV-2 infection, 4 studies with COVID 19 pneumonia, one study included patients at all stages of COVID, and one study with non-severe patients. Among 14 articles, 13 specified dosing and duration with corticosteroid treatment.

Viral Clearance

Among the 14 studies included in the metanalysis, 3 of them discussed the differential outcomes of corticosteroid therapy on

viral clearance in treatment and control groups. showed that in both treatment and control groups, the difference in the viral clearance was insignificant (p = 0.252), which means that the time from onset of illness to viral clearance had no significant difference between two groups. studied the effect of methylprednisolone treatment on time taken for viral clearance. The results were insignificant in this trial (p = 0.713). Collectively, corticosteroids show no significant effect on viral clearance.

Length of Hospital Stay/ ICU days

Several studies investigated the effect of corticosteroid therapy on the length of hospital stay. [10, 11] showed that the patients taking corticosteroids stayed admitted to the hospital for a longer time than the control group. The length of stay in the treatment group on average was 25 days, while the untreated group remained admitted on an average of, and these results are significant (p = 0.016). (Table 1) showed that the length of stay in the treatment group was less than that of the duration of hospital stay in the usual care group. Herrero et al. showed an insignificant relationship between a hospital stay and corticosteroid therapy (p = 0.091). in subgroup analysis, compared the timing of initial steroid dosing with ICU stay days when given less than 48 hours, mid between 48 hours and 7 days, and greater than 7 days after ICU. The association between use of corticosteroids and length of hospital stay was insignificant.

Table 1: Descriptive characteristics of included studies of corticosteroids and COVID-19.

Id	Article	Study Design	Date of Publishing	Participants (Sample Size) N	Type of Corticosteroid	Dose of Drug	Cointerventions
1	Ramiro, et al. [10]	Case control	13 july,2020	172	Methylprednisone	250mg on day 1 followed by 80mg on days 2–5	Tocilizumab Ceftriaxone Chloroquine
2	Keller, et al. [11]	Case-control	22-Jul-20	1086 (Treatment group had 140 patients, the control group had 1666 patients)	glucocorticoid	N/A	N/A
3	Sheianov, et al. [12]	Case series	07-Jul-20	3	methylprednisolone	125 mg daily IV in first 2 patients/ 1000 mg IV in the third patient	Antimicrobial therapy IV immunoglobulin
4	Hu, et al. [13]	Retrospective cohort study	03-Jul-20	28	Methylprednisolone	140 mg per day intravenously	Intravenous immunoglobulin Interferon alpha Oral antivirals Antibiotics
5	Hu Y, et al. [14]	Retrospective Study	11-Jul-20	104 (86 receiving glucocorticoids and 18 not receiving Glucocorticoids)	Methylprednisolone Prednisolone	0.75–1.5 mg/ kg/d	N/A
6	Ruiz Irastorza ,et al. [15]	Comparative observational study	23-Jul-20	242 (61 receiving week 2-MP, 181 not receiving week 2-MP)	Methylprednisolone	125-250 mg/d	Hydroxychloroquine Lopinavir/Ritonavir
7	Fernández, et al. [16]	Single centre retrospective cohort study	22-Jun-20	463 (276 in steroid cohort 41 in the control cohort)	Methylprednisolone	1mg/kg/day	Hydroxychloroquine Lopinavir/Ritonavir Azithromycin
8	Herrero, et al. [17]	Observational study	June 30.2020	72 (56 in the treatment group, 16 in the control group)	Methylprednisolone	250 mg administered intravenously daily on the first day followed by 40 mg every 12 h for 4 more days	Tocilizumab Lopinavir/ritonavir Interferon beta Hydroxychloroquine and azithromycin
9	Albani et, al. [18]	Cohort study	18-Jul-20	1403 (559 in the treatment group, 844 in the control group)	Methylprednisolone, Prednisolone	0.13 mg·kg-1	N/A

10	Horby P, et al. [19]	Open-label trial	17-Jul-20	11303	dexamethasone	6mg once daily for 10 days	Azithromycin in both group Remdesivir in 3 patient of the dexamethasone group and 2 in the usual care group
11	DTB Team. [20]	Randomized trial	July 20, 2020	6425	Dexamethasone	6mg once daily for 10 days	N/A
12	Rahman O, et al. [21]	Observational study	30-Jul-20	136	prednisone	56mg	N/A
13	Wang K, et al. [22]	Case study	08-Jul-20	1	IV corticosteroids	80mg twice a day for 3 days followed by 40mg twice a day for 3 days	Nasal cannula oxygen therapy Initial treatment with oseltamivir
14	Kuzeva A, et al. [23]	Case report	20-Jul-20	1	IV methylprednisolone	0.5mg/kg	oxygen therapy

Mortality Rate

Out of 14 studies, 7 studies, i.e., Ramiro et al., Fernandez et al., Rahman et al., Horby et al., Ruiz Irastoza et al., Herrero et al., and Albani et al. investigated effect of corticosteroid therapy on mortality rates (p-value=0.029). The pooled analysis among COVID-19 patients revealed significant effect of corticosteroids on mortality. Mortality rate was lower in the corticosteroid treated group. (OR = 0.587, CI = 0.36-0.95, and p-value 0.029). There was an evidence of significant heterogeneity between trials, i.e., I2 = 88% and p-value = 0.000.

Adverse Events

Hue et al. reported the effect of corticosteroid on fasting blood glucose before and after the intervention. Corticosteroids have no significant effect on fasting blood glucose (p = 0.845). There was a trend towards bacterial infections in the group treated with corticosteroids. Two studies reported nosocomial infections associated with steroid administration. According to Ruiz Irastorza et al. non-pulse glucocorticoids have increased risk for infections (OR=4.72, 95% CI 1.9-11.8, p < 0.001) as compared to week 2 MP (OR=1.04, 95% CI 0.40-2.70, p=0.938). According to [12]., pulmonary embolism risk was significantly greater in the treatment group as compared to the control group (p = 0.0590). In [13]. bacterial infections are reported in 15 patients (8 in the treatment group vs 7 in the control group p = 0.787). Shieanov et al. discussed a report of three clinical cases in tocilizumab resistant COVID-19 patients and reported pulse therapy with glucocorticoids and IV immunoglobulins could help reverse respiratory failure and CT changes Figure 1.

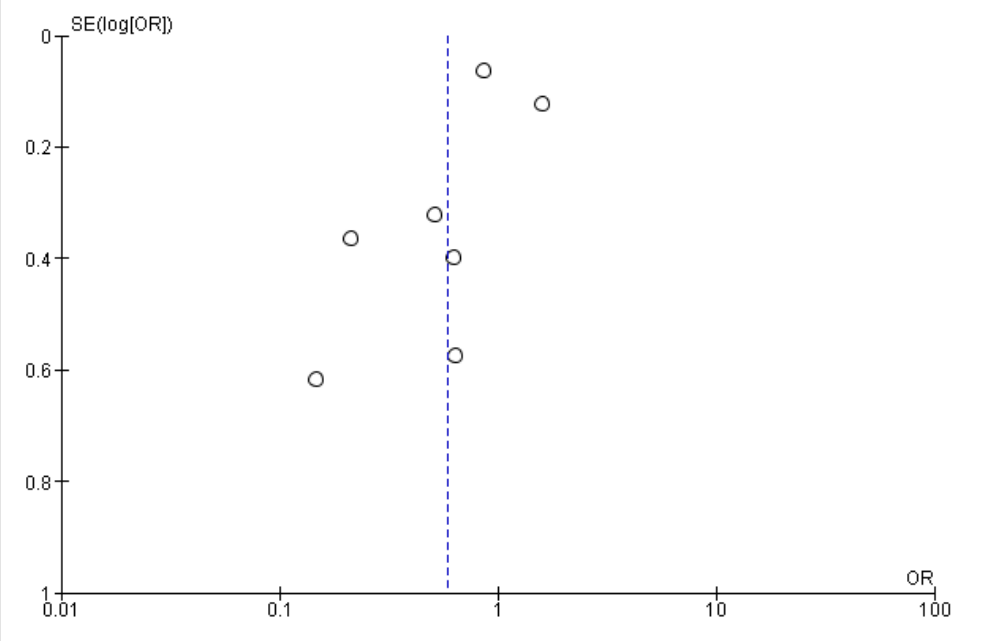

Figure 1: Funnel plot for the assessment of publication bias among included studies. There is no evidence of publication bias.

ICU Admission

In Albani et al. 56 patients (11.5%) were admitted to ICU in patients exposed to corticosteroids on the ward vs 131 (14.4%) in the control group (unadjusted p = 0.15). In Herrero et al., 31 out of 56 patients treated with methylprednisolone were admitted to ICU as compared to 12/16 in non-methylprednisolone group (p = 0.158) Figure 2.

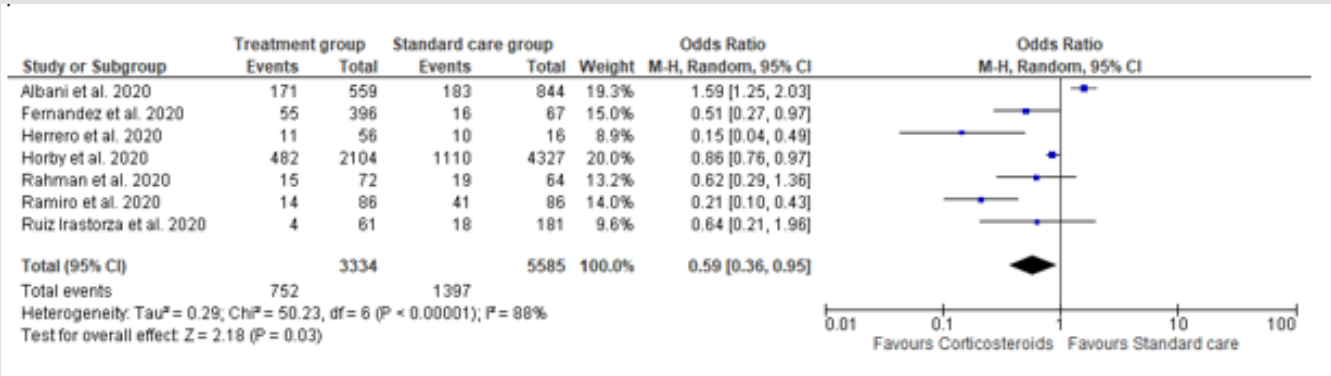

Figure 2: Corticosteroid vs. non-corticosteroid treatment group: mortality of studied subjects.

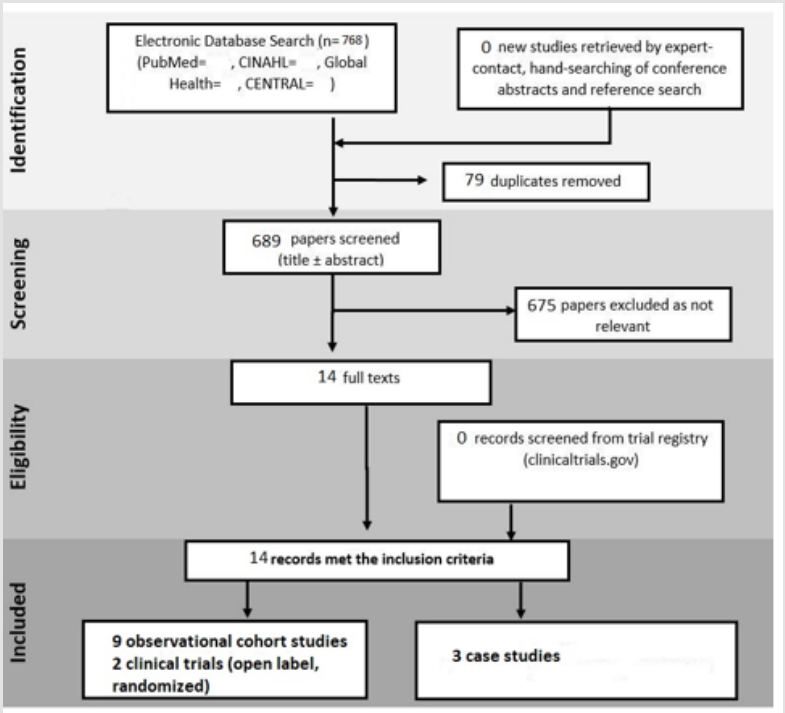

Figure 3: PRISMA Flow chart of literature search and selection of studies.

Publication Bias

In order to check the publication bias, we plotted studies included in a literature on a funnel plot. Resultantly, no publication bias was founded (Table 2).

Table 2: Descriptives of corticosteroid intervention and outcomes in COVID-19 patients.

Id	Article	Stage of Covid	Outcome	Mean Age	Gender	Comorbidities
1	Ramiro, et al. [10]	Severe having cytokine storm syndrome	The treatment group had two-stage improvement in respiratory status, 65% lower hospital mortality rate, 71% lower chances of having mechanical ventilation as compared to the control group Bacterial infections due to immunosuppression were reported in 15 patients (8 in treatment, 7 in the control group)	67 years	Caucasians Male (79%)	The Control group contained more patients with diabetes. The treatment group had more patients with cardiovascular disease and arrhythmias
2	Keller, et al. [11]	Severe hospitalized COVID-19 patients	Patients having CRP level greater than 20mg/dl treated with glucocorticoids was associated with a low risk of mortality and mechanical ventilation Those having CRP less than 10mg/dl was associated with increased mortality rate and mechanical ventilation	62.2 ± 17.8	46% female 53% male	Treatment group had COPD (12%), asthma (19%), rheumatoid arthritis, lupus (2%)
3	Sheianov, et al. [12]	Severe Life-threatening COVID-19	Pulse therapy with corticosteroids and IV immunoglobulin improves patients respiratory status, eliminate clinically manifesting Cytokine storm syndrome and reverse pulmonary CT changes	64 years, 60 years old, 33 years old	Female Male	Obesity Asthma Pancreatitis
4	Hu, et al. [13]	Non-severe COVID 19 patients	All patients achieved an abatement of fever within 1 day, and 78.6% (22/28) of the patients achieved radiological remission when evaluated about 3 days later. Only one (3.6%) the patient progressed to severe COVID-19, and others were discharged. No effect on viral clearance compared to controls.	46 years	Female 55 % Male 44%	Hypertension (13%) Diabetes (5%)
5	Hu Y, et al. [14]	COVID-19 pneumonia	74/86 patients cured, 13 still hospitalized, no deaths. No specific effect on cure rate, clinical course, adverse events and outcome	53 years	Male 47% Female 52%	Hypertension (12%) Diabetes (7%)
6	Ruiz Irastorza, et al. [15]	Severe	Methylprednisolone for 3 consecutive days given on the second week of disease improved prognosis of patients with severe COVID 19 infection (4/61)	64 years	Male(62%)	Diabetic (21%) Hypertensive (48%)
7	Fernández et al. [16]	SARS COV 2 pneumonia	In the treatment group, mortality was reduced by 41.8% compared to the control group. Treatment with 1mg /kg/d compared steroid pulse treatment was not associated with in-hospital mortality	65 years	Male 69%	Hypertensive (46%) Diabetic (21%) COPD (17%)
8	Herrero, et al. [17]	SARS COV-2 pneumonia	The mortality rate is reduced in patients treated with methylprednisolone who were initially given tocilizumab for the treatment	67 years	Male 62%	Hypertensive (59%) Diabetic (26%) COPD (19%)
9	Albani, et al. [18]		Corticosteroid use was not associated with in-hospital mortality and reduces ICU admission (171/559 died in treatment group 183/844 died in the control group)	68 years	Female 33%	Hypertensive, Diabetic
10	Horby P, et al. [19]	An intensive trial involving patient of all stages	Mortality at 28 days in the dexamethasone group 482/2104 Mortality at 28 days in the usual care group 1110/4321	66.1+- 15.7	36% female	24% diabetes 21% chronic lung disease 27% heart disease
11	DTB Team. [20]	16% mechanical ventilation 60% oxygen therapy 24% neither	21.6% mortality in 28 days in dexamethasone receiving group 24.6% in the usual group	66	36% female	24% diabetes 21% chronic lung disease 27% heart disease

12	Rahman O, et al. [21]	Increased severity of illness	Early use of corticosteroids show increase survival in non-mechanically ventilated patients and prevent intubation and decreased ICU stay	60.5	47% male 39% female	35% cardiovascular 44% diabetes 58% hypertension
13	Wang K, et al. [22]	Critically ill	Improved within 6 days and discharge on 17 days. A moderate dose of corticosteroid increased the chances of recovery of the critically ill patient	53	female	History of hypertension
14	Kuzeva A, et l. [23]	COVID-19 pneumonitis	Patient with critical condition and comorbidities should be rescued with high dose glucocorticoid therapy	77	male	Chronic obstructive pulmonary disease

Discussion

In this systematic review and meta-analysis of the effect of corticosteroid treatment on COVID-19 patients, a pool of 14 studies were included. Most of the studies showed the positive effect of corticosteroid therapy on the mortality of the patients but no significant effect on the viral clearance from the onset of illness. The mean time of viral clearance in treated and non- treated patients group was same. An increase hospital stay was observed in treated group as compared to control group [13]. Corticosteroid, as evident by a randomized trial study, decrease the "28-day mortality" [14] on invasive mechanical ventilation requirement. So, we can say that corticosteroids when administered in the COVID-19 patients shown marked improvement in their condition. However, there is an ambiguity about their effect on viral clearance and hospital stay duration. In comparison with other systematic reviews and meta-analysis, our study consists of a variety of studies with different study designs including case-control, observational studies, randomized and open trials, and even case studies, so it has a minimum risk of bias and increased evidence level. Our meta-analysis includes a recent constellation of literature on corticosteroids therapy and COVID-19 patients in a large number of recent recovery trials. Hence, it provides up-to-date and refined shreds of evidence.

In addition, all studies included in this meta-analysis provide evidence only on corticosteroid therapy for COVID-19 patients while some reported systematic reviews and meta-analysis, extrapolated, results from corticosteroid effect on MERS, SARS and non-viral Acute Respiratory Distress Syndrome (ARDS). With the high publication rate of COVID-19 articles in the past few months, it is necessary to include peer-reviewed articles as some of the most recent studies concluded that corticosteroid is not safe for administration in COVID-19 pneumonia with certain adverse reactions not included in the previous meta-analysis. Most of the included studies have large heterogeneity (the type of study, sample size, corticosteroid used in the study, dose, duration, cointerventions, comorbidities, and outcome measures, etc). Also, the reported meta-analysis included studies completed in one area or countries like China, so their results cannot be applied to the patients of other countries but we collected the evidence from studies carried out in different countries so, our results can be applied in every region of the world. [15-17] The optimal time for administration of steroids for better outcomes is the point of discussion in various reviews but none of the studies answered the mystery. But our results from included reports show that corticosteroid administration within 7 days after onset of illness is associated with better recovery, improved condition, and decrease ICU stay [18]. Methylprednisolone is the most commonly used steroid in the included studies.

And its administration on 1st, 2nd, 5th and 7th day from onset of illness show promising results. There are certain co-interventions along with corticosteroids including (tocilizumab, IV immunoglobulins and oseltamivir). The administration of corticosteroid with tocilizumab shows more promising results than corticosteroid alone. It reverse CT changes, decrease mortality but shows an increased risk of bacterial infection [10,17]. Co-administration of steroids with IV immunoglobulins in critical patients improves the severity of the disease, reverses cytokine syndrome, CT changes, and decreases mortality. Oseltamivir is administrated in a few patients as initial patient care prior to the administration of dexamethasone but no comment is given on its outcomes. [19] According to one negative study, that reports monotherapy with methylprednisolone having no effect on cure rate, death rate, clinical course, and adverse effects [14]. The studies included in this report have a variety of patients with different stages of COVID-19, so results concluded from these studies can be applied to any patient with any stage of disease not given by any other published systematic reviews and meta-analysis.

Almost every patient included in these studies has one of the comorbidities (diabetes, hypertension, heart diseases, chronic obstructive pulmonary disease and pancreatitis, etc) so these patients tend to progress to the more severe stage of disease. Such patients should be rescued with a high dose of corticosteroid therapy.[24] Hence, the conclusion drawn from these studies cannot be applied to patients having mild symptoms and patients without any comorbidities. One of the major findings not reported in the previous analysis is the level of C-reactive protein (CRP) in plasma and its association with corticosteroid therapy. Patients having CRP levels greater than 20mg have a less need for mechanical ventilation and a decreased mortality rate. While Patients having CRP levels lower than 10mg tends to have the severe clinical course

of the disease and increase the mortality rate. [20] The age of most of the patients is in the range between 50- 80 years. So conclusions drawn from these patients cannot be applied to younger patients.

COVID-19 patients faced duel problems. First, the patients develop a hyperinflammatory response against the virus in later stages that may cause pulmonary thrombosis and progress to acute respiratory syndrome and secondly, there is a need for viral clearance. Corticosteroid has an anti-inflammatory effect to cope with inflammatory response and cytokines release but not with viral shedding and hence, have certain adverse reactions. One of the adverse reactions reported by other meta-analysis is fasting hypoglycemia. But corticosteroids have an insignificant effect on fasting glucose levels [21]. The major side effect faced by patients on steroids, is an increased risk of the bacterial infections [22]. Nosocomial infections associated with steroid therapy are reported by two studies. Non-impulse glucocorticoids have more risks for infections. Pulmonary embolism is another adverse effect associated with corticosteroids. Control groups have low chances of development of pulmonary embolism than the treatment groups. [23] Tocilizumab resistant COVID-19, treated with corticosteroids and IV immunoglobulins have an increased risk of respiratory failure and severe CT changes. [12] Our systematic review and meta-analysis have certain limitations too. What is lacking is the specific indications of corticosteroid administration. We comment on only one laboratory marker CRP [12], other radiological and laboratory markers levels which can indicate the timing and dose of corticosteroid administrations should be investigated. Further researches on steroids administration on younger patients, patients with mild symptoms, and without comorbidities are needed which are lacking in all of the previous studies. More randomized trials and open-label trials are needed to investigate viral clearance and viral shedding, dose, indications, and optimal time for administration of corticosteroids. Most trials used co-administration of other drugs with corticosteroid so having little authenticity on the outcomes of monotherapy of corticosteroids.

In conclusion, combination therapy of corticosteroids with tocilizumab or IV immunoglobulins are associated with surprisingly better outcomes, decreased rate of mortality, decreased in hospital stay, reversal of cytokine storm syndrome, and CT changes. Certain adverse effects are associated with them. Bacterial infection is the major risk. Interventions should be made to cope with them. Because of the expanding knowledge and easy and over the counter availability of the steroids by healthcare systems, and the rapid spread of coronavirus across the globe, the area of corticosteroid research should be emphasized.

Conclusion

Recent evidence on the corticosteroids shows that the use of corticosteroids in various stages of coronavirus disease cause a significant effect on mortality and insignificant effect on viral clearance. Anti-inflammatory action of corticosteroids does not improve the time of viral clearance. The mean time for viral clearance in the affected patients did not vary much in the corticosteroid treated and the untreated group. Corticosteroids therapy shows varying effect on the length of hospital stay. Corticosteroids may increase or decrease the hospital stay durations. Corticosteroids, due to their immune suppressive effect, significantly increase the risk of bacterial infections. Corticosteroids improve respiratory symptoms, and often reverse the adverse CT findings. Corticosteroids therapy increases the risk of pulmonary embolism. Recent evidence shows a weak link between corticosteroid therapy and admission in Intensive Care Unit (ICU).

Availability of Data and Materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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Not applicable.

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