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REVIEW

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Effect of corticosteroid therapy on mortality in COVID-19 patients—A systematic review and meta-analysis

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Abstract

The effect of corticosteroid therapy is still controversial on prevention of mortality in coronavirus disease-2019 (COVID-19). The objective of this study is to investigate the effect of corticosteroids on mortality. This systematic review was performed as per preferred reporting items for systematic reviews and meta-analyses guidelines. A systematic search was performed at different databases namely Medline/PubMed, Cochrane and Google scholar on 10 February 2022. A pooled estimate for effect of corticosteroid therapy on mortality was calculated as outcome of study. Risk bias analysis and Newcastle Ottawa Scale were used to assess the quality of randomized control trial (RCT) and cohort studies, respectively. Cochran's Q test and the I^2 statistic were conducted for heterogeneity and accordingly study model was applied. A total 43 studies were included, having sample size of 96,852 patients. Amongst them, 19,426 and 77,426 patients received corticosteroid therapy (intervention group) or standard treatment without corticosteroid (control group), respectively. Mortality observed in the intervention and control group was 14.2% (2749) and 7.1% (5459), respectively. The pooled estimate 2.173 (95% CI: 2.0690–2.2820) showed significantly increased mortality in intervention as compared to control. The pooled estimate of methyprednisolone 1.206 (95% CI: 1.0770–1.3500) showed significantly increased mortality while the pooled estimate of dexamethasone 1.040 (95% CI: 0.9459–1.1440) showed insignificantly increased mortality as compared to control. In conclusion, corticosteroid therapy produced a negative prognosis as depicted by increased mortality among COVID-19 patients. The possible reasons might be delay in virus clearance and secondary infections due to corticosteroids initiated at high dose in the early stage of infection.

KEYWORDS
corticosteroids, COVID-19, death, dexamethasone, fatality, methylprednisolone, mortality, SARS-CoV-2

Abbreviations: ARDS, Acute Respiratory Distress Syndrome; CI, confidence interval; COVID-19, coronavirus disease-2019; MARS, Middle East respiratory syndrome; NOS, Newcastle Ottawa Scale; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, Randomized control trial; RT-PCR, Reverse Transcription–Polymerase Chain Reaction; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; WHO, World Health Organization.

1 | INTRODUCTION:

World Health Organization (WHO) reported 505,817,953 confirmed COVID-19 cases and 6,213,876 fatality from COVID-19 till 22 April 2022.[1] COVID-19 infection can cause infection without any symptoms, moderate upper respiratory tract sickness, severe pneumonia condition, respiratory failure and even death.[2] In severe COVID-19 infection, symptoms deteriorate and become hypoxic after four to seven days and can advance to acute respiratory distress syndrome (ARDS) between eight and 12 days.[3] Immune-mediated cascades including increased proinflammatory cytokines levels and cytokine storm, rather than virus-induced damage, are equally important in the pathophysiology of multiple organ damage and mortality.[4] Therefore, corticosteroid therapy was proposed to suppress the immune-mediated cascades and cytokine storm-related complications and mortality in COVID-19.[5,6] Therefore, numerous of observational studies and randomized controlled trials (RCT) to investigate the effect of corticosteroids therapy in COVID-19 have been initiated and reported.

Recently, the RECOVERY study reported the rationale for the corticosteroid therapy in severe COVID-19 patients.[7] As per initial results from the RECOVERY study, dexamethasone reduced 28-daysfatality in severe COVID-19 patients.[7] Multiple randomized trials have been found that systemic corticosteroids therapy improve clinical results and lowers fatality in COVID-19 hospitalised patients those need of oxygen supplement.[7–16] Based on results from these clinical trials, WHO advised to utilization of corticosteroids for the management of severe COVID-19 patients.[17] Furthermore, the recent global Surviving Sepsis Guideline suggests to use steroids in the severe COVID-19 patients those on mechanical ventilation support with ARDS.[18]

In contrary, the Centres for Disease Control and Prevention (CDC), United States has not been specifically advice either for or against the utilization of corticosteroids in COVID-19.[19] It has been reported that corticosteroids usage causes the delay in viral RNA clearance in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MARS).[20] A recent study also indicated that corticosteroid therapy started at high dose or early stage (less than 3 days) of infection in critical COVID-19 patients delayed viral clearance and increased the risk of 28 days mortality.[21] The possible cause might be weakening of the immune response by corticosteroid therapy. The weakening of patients' immune systems from corticosteroid therapy leads to rarely occurring fungal infections (e.g. aspergillosis, mucormycosis), relapsing of dormant infections (e.g. herpesvirus infections, strongyloidiasis, hepatitis B virus infection, tuberculosis) and respiratory failure.[22–26] Recent study reported that corticosteroids use in SARS patients has been associated to significant consequences such as avascular necrosis, diabetes and psychosis.[20,27]

The results of multiple RCTs and observational studies are very diverse and contradictory, which arising difficulty in the clinical decision-making. Furthermore, these studies were performed with limited sample size. Therefore, there is need to review available studies with greater statistical power for concrete conclusion in relation to utilization of corticosteroids in the COVID-19 patients. The objective of this study is to assess relationship between corticosteroids therapy usage and mortality in the COVID 19 patients by a systematic review and meta-analysis of RCT and observational cohort studies.

2 | METHODS

2.1 | Data sources and search strategy

A systematic review was conducted as per the preferred reporting items for systematic reviews and meta-analyses guideline. This systematic review and meta-analysis was registered to PROSPERO (CRD42022304323). A comprehensive search was performed in PubMed/Medline, Cochrane and Google Scholar databases on 10 February 2022 by two persons independently (Dipanshi Patel; Krupanshu Parmar). All the probable combination of key words was included in the study such as 'corticosteroid therapy' 'methylprednisolone' 'dexamethasone' 'Prednisolone' 'COVID-19' 'SARS-CoV-2 infection' 'Corona infection' 'Mortality' 'fatality' 'death' (Supplementary 1). The cross-references from the screened studies were explored for more articles. The same study selection criteria were utilised for articles identified via forward/backward search.

2.2 | Eligibility

The studies were included on basis of the inclusion and exclusion criteria. The inclusion criteria considered in the selection of studies were adult COVID-19 patients (aged 18 years or above), infection of COVID-19 confirmed through rapid antigen test or RT-PCR, the corticosteroid therapy given in at least one arm of the treatment, mortality data reported as outcome in both arms. The exclusion criteria considered for selection of studies were specific population only included in the study such as pregnant women and paediatric patients, review articles, case reports, editorials, and studies having only in vitro or preclinical data and published in other than English language.

2.3 | Study outcome

The reporting of 28 days, 30 days or hospital death in the treatment arm and control arm was considered as outcome of study.

2.4 | Study selection

A total four reviewers (Krupanshu Parmar; Dipanshi Patel; Sandip Patel; Devang Sheth) were independently screened articles included via keyword search by title and abstract as per the study selection

criteria. Full-text content screening was performed for highly relevant studies by two reviewers (Krupanshu Parmar; Dipanshi Patel). The opinion from third reviewer (Sandip Patel) was taken wherever it was needed.

2.5 | Data extraction

A data extraction was performed by two persons (Krupanshu Parmar; Dipanshi Patel) and reviewed by two persons (Jayesh V. Beladiya; Chirag Patel). Full text and corresponding supplementary information of the following items were collected and recorded from each eligible study; first author name, publication year, country, study design, type of steroid used, sample size, number of patient in intervention (corticosteroid treated) and control (without corticosteroid treated) groups, mortality in intervention (corticosteroid treated) and control (without corticosteroid treated) groups. MS Office Excel worksheet was utilised to collect the extracted information from included studies (Supplementary 2).

2.6 | Study quality assessment

The quality of individual study was assessed. The risk of bias was assessed on six domains (random sequence generation, concealment of allocation, blinding, selective outcome reporting, incomplete outcome data and other).[28,29] The Newcastle Ottawa Scale (NOS) has been used to assess the quality of observational studies.[30,31] (Supplementary 3 and 4) The NOS score ranges from zero (low quality) to nine (high quality).

2.7 | Statistical analysis and reporting

Associations between corticosteroid therapy used in COVID-19 patients and mortality in COVID-19 patients were analysed using meta-analysis. A meta-analysis was performed for the obtained odd ratio values and 95% confidence interval (CI) from the articles. A pooled estimate was calculated for the effect of corticosteroid therapy on mortality and graphically summarised in a forest plot using Graphpad Prism software. Fixed effects model was used for meta-analysis. Cochran's Q test and the I^2 statistic were performed to assess the statistical heterogeneity using Microsoft Excel 2007. $P < 0.05$ was considered as statistically significant.

3 | RESULT

3.1 | Study selection

The flowchart represents the search and selection strategy for the study. The initial search resulted total 1365 studies, PubMed ($n = 65$), Cochrane Library ($n = 276$), Google Scholar ($n = 1000$) and articles identified through forward/backward search ($n = 24$). Twenty nine articles were excluded as duplicate and 1270 articles were excluded from title and abstract screening. From remaining articles, 24 articles were excluded due to lacking of mortality data in screening full-text content. A total 43 studies were considered in the systematic review (Figure 1). The publication bias data reported in the supplementary file-6.

3.2 | Basic characteristics of the selected studies

The studies were conducted in China ($n = 12$),[12,32–41] Spain ($n = 9$),[3,42–48] The United States of America ($n = 6$),[49–54] Italy ($n = 4$),[55–58] Iran ($n = 3$),[59–61] France ($n = 3$),[10,62,63] Brazil ($n = 2$),[8,64] Japan ($n = 1$),[65] Turkey ($n = 1$),[66] Netherlands ($n = 1$),[67] United Kingdom ($n = 1$)[7] (Supplementary 5). The majority of studies were retrospective cohort studies (32/43) while 11 studies were randomized controlled trials (Table 1).

A total 24 studies demonstrated the beneficial effects of the corticosteroid therapy on the prevention of mortality in the COVID-19 patients[3,7,8,10,12,34,42,43,45,46,48,50–55,57,59,61,63,64,66,67] while 17 studies were reported the increased mortality in the corticosteroid therapy received COVID-19 patients[32,33,35–41,44,48,56–58,60,65] while 2 studies reported the neutral effects of the corticosteroid therapy on the prevention of mortality in the COVID-19 patients.[49,62]

Four types of corticosteroid were used as single or multiple steroids individually including Methylprednisolone ($n = 24$), Dexamethasone ($n = 6$), Hydrocortisone ($n = 1$), Prednisone ($n = 1$), corticosteroid used individually including Methylprednisolone and Dexamethasone in the study ($n = 6$) unknown corticosteroid ($n = 5$) (Table 1).

In this review, total sample size was 96,852 patients. Amongst them, 19,426 patients were in the intervention group (Received corticosteroid therapy) while 77,426 patients were in the control group (Received standard treatment without corticosteroids). A total 8208 patients were died in both groups. Among them, 2749 (14.2%) patients were died in the intervention group and 5459 (7.1%) patients were died in the control group. 28.93% and 25.24% mortality was observed in the methylprednisolone and control group, respectively whereas 26.24% and 25.48% mortality was observed in the dexamethasone and control group, respectively (Table 1).

3.3 | Study quality assessment

The risk of bias for RCT is demonstrated in the Figure 2. The average NOS score was 7.03 (ranging: 6–9) for the observational studies (Supplementary 3 and 4).

3.4 | Meta-analysis

Collectively, 96,852 patients from 43 studies were included in the meta-analysis. A pooled fold change estimation of 2.173 (95% CI:

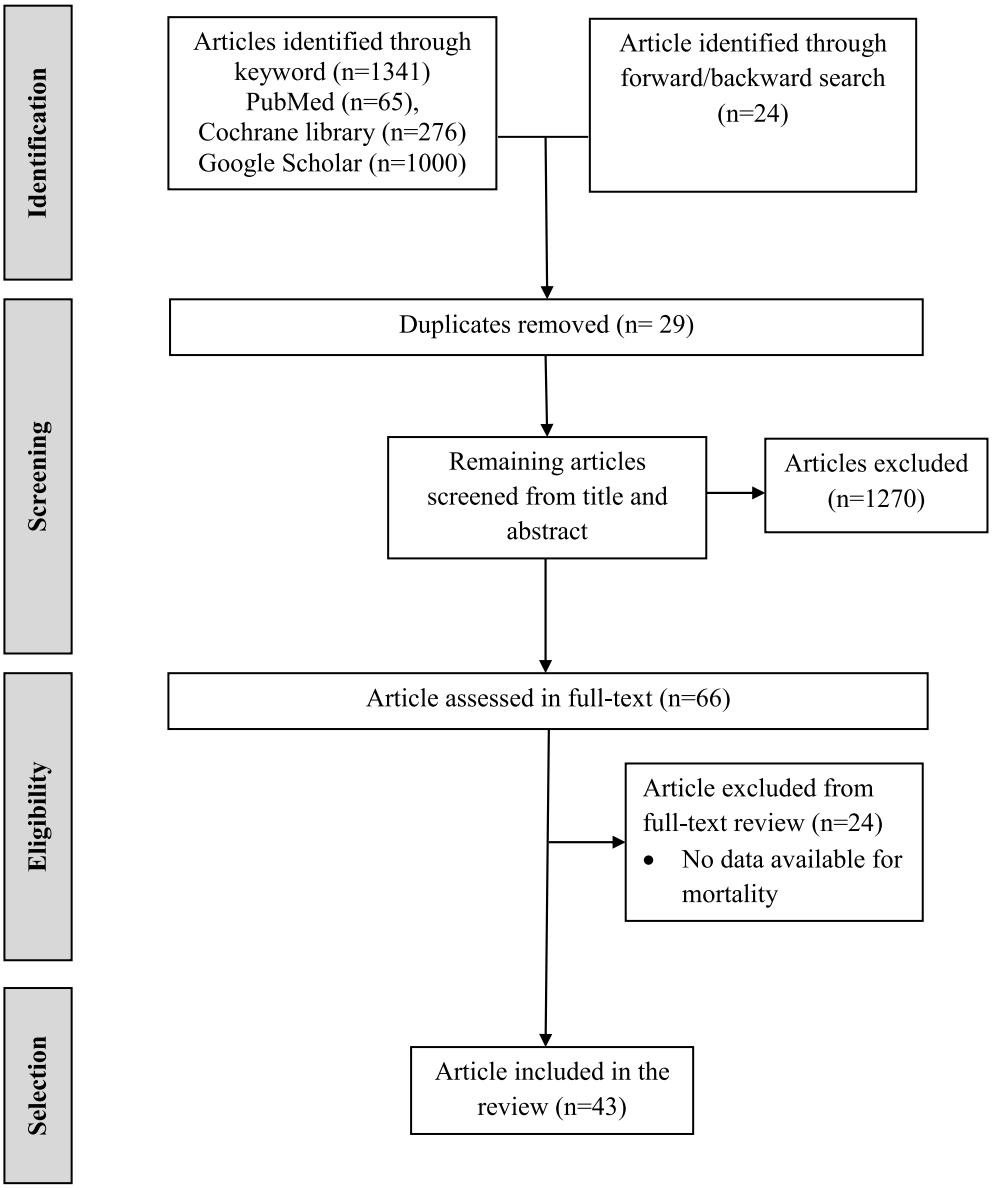

FIGURE 1 Flowchart for study selection

2.0690–2.2820) was calculated for mortality in corticosteroid therapy versus standard therapy. *p*-value = 0.0001 was obtained from a meta-analysis. Heterogeneity (I^2 values) was observed to be zero. The forest plot for primary meta-analysis of the pooled fold change estimation values along with the 95% CI from corticosteroid therapy, sample size, odd ratio and % weight of the individual study has been depicted in Figure 2.

A pooled fold change estimation of 1.206 (95% CI: 1.0770–1.3500) showed significantly increased mortality in methylprednisolone therapy as compared to control. *p*-value = 0.4 was obtained from a meta-analysis. Heterogeneity (I^2 values) was observed to be zero. Figure 3 represents the forest plot of the primary meta-analysis of the pooled fold change estimation values along with the 95% CI from methylprednisolone therapy.

A pooled fold change estimation 1.040 (95% CI: 0.9459–1.1440) was showed insignificantly higher for mortality in dexamethasone therapy as compared to control. Heterogeneity (I^2 values) was observed to be zero. Figure 4 represents the forest plot of the primary meta-analysis of the pooled fold change estimation values along with the 95% CI from dexamethasone therapy.

The graphical representation of the *x*-axis of the plot is the pooled fold change estimation, and 95% CI of the included studies. The blue square with the line represent the effect size of mortality in COVID-19 patients. If the pooled fold change estimation value is more than 1, it favours the increased mortality in the intervention treatment group as compared to control group while less than 1, favour the beneficial effect of corticosteroid on COVID-19 patients in intervention group as compared to control.

TABLE 1 Characteristics of included studies

Sr. No.	Author name	Year	Country	Study design	Type of steroid used	Sample size			Mortality		% Mortality	
						I	C	T	I	C	I	C
1	Jeronimo C.M.P	2020	Brazil	Randomized controlled trial	Methylprednisolone	194	199	393	72	76	37.1	38.2
2	Tang X	2021	China	Randomized controlled trial	Methylprednisolone	43	43	86	00	01	0.0	2.3
3	Jamaati H	2021	Iran	Randomized controlled trial	Dexamethasone	25	25	50	16	15	64.0	60.0
4	Edalatifard M	2020	Iran	Randomized controlled trial	Methylprednisolone	34	28	62	02	12	5.9	42.9
5	Dequin P.F	2020	France	Randomized controlled trial	Hydrocortisone	76	73	149	11	20	14.5	27.4
6	Ranjbar K.	2021	Iran	Randomized controlled trial	Methylprednisolone, dexamethasone	44	42	86	8	15	18.2	35.7
7	Solanich X.	2021	Spain	Randomized controlled trial	Methylprednisolone	27	28	55	03	04	11.1	14.3
8	Bruno M	2020	Brazil	Randomized controlled trial	Dexamethasone	151	148	299	85	91	56.3	61.5
9	Horby P	2020	UK	Randomized controlled trial	Dexamethasone	2104	4321	6425	482	1110	22.9	25.7
10	Ramiro S	2020	Netherlands	Randomized controlled trial	Methylprednisolone	86	86	172	14	41	16.3	47.7
11	Batirel A	2021	Turkey	Randomized controlled trial	Methylprednisolone, dexamethasone	63	63	126	11	15	17.5	23.8
12	Russo G	2021	Italy	Retrospective cohort study	Methylprednisolone	65	172	237	06	07	9.2	4.1
13	Albani F	2021	Italy	Retrospective cohort study	Dexamethasone	559	844	1403	171	183	30.6	21.7
14	Eynde E.V.D.	2020	Spain	Retrospective cohort study	Methylprednisolone	38	118	156	17	69	44.7	58.5
15	Ding C.	2020	China	Retrospective cohort study	Methylprednisolone	36	46	82	01	00	2.8	0.0
16	Li Q	2020	China	Retrospective cohort study	Methylprednisolone	55	55	110	01	00	1.8	0.0
17	Yang R	2020	China	Retrospective cohort study	Methylprednisolone	140	35	175	32	16	22.9	45.7
18	Nelson B.C	2020	USA	Retrospective cohort study	Methylprednisolone	48	69	117	10	20	20.8	29.0
19	Gragueb-Chatti I.	2021	France	Retrospective cohort study	Dexamethasone	84	67	151	14	11	16.7	16.4
20	Strauss R	2021	USA	Retrospective cohort study	Corticosteroid	10,187	61,960	72,147	231	1649	2.3	2.7
21	Gallay L.	2021	France, Luxembourg	Retrospective cohort study	Prednisone	98	166	264	43	84	43.9	50.6
22	Ruiz-Irastorza G.	2020	Spain	Retrospective cohort study	Methylprednisolone	61	181	242	06	25	9.8	13.8
23	Yaqoob H	2021	USA	Retrospective cohort study	Methylprednisolone	87	48	135	26	22	29.9	45.8

(Continues)

TABLE 1 (Continued)

Sr. No.	Author name	Year	Country	Study design	Type of steroid used	Sample size			Mortality		% Mortality	
						I	C	T	I	C	I	C
24	Fadel R.	2020	USA	Retrospective cohort study	Methylprednisolone	132	81	213	18	21	13.6	25.9
25	Moreno G	2021	Spain	Retrospective cohort study	Methylprednisolone	1117	463	1580	428	153	38.3	33.0
26	Ikeda S	2021	Japan	Retrospective cohort study	Methylprednisolone, prednisolone, dexamethasone	118	118	236	12	05	10.2	4.2
27	Chen Q	2020	China	Retrospective cohort study	Methylprednisolone	209	162	371	102	43	48.8	26.5
28	Fusina F	2021	Italy	Retrospective cohort study	Dexamethasone	480	831	1311	125	179	26.0	21.5
29	Majumdar M	2020	USA	Retrospective cohort study	Methylprednisolone, prednisone, hydrocortisone, dexamethasone	60	145	205	08	34	13.3	23.4
30	Ho KS	2021	USA	Retrospective cohort study	Methylprednisolone, dexamethasone, prednisone, hydrocortisone	574	3739	4313	153	1117	26.7	29.9
31	Piniella-Ruiz E.	2021	Spain	Retrospective cohort study	Methylprednisolone	88	55	143	60	45	68.2	81.8
32	You X.	2020	China	Retrospective cohort study	Methylprednisolone	225	118	343	14	01	6.2	0.8
33	Liu Z	2020	China	Retrospective cohort study	Methylprednisolone	158	488	646	72	56	45.6	11.5
34	Liu J	2020	China	Retrospective cohort study	Methylprednisolone, prednisone, dexamethasone, hydrocortisone	409	365	774	181	113	44.3	31.0
35	Marti M.C	2021	Spain	Retrospective cohort study	Methylprednisolone	72	70	142	20	39	27.8	55.7
36	Cruz A.F	2020	Spain	Retrospective cohort study	Methylprednisolone	396	67	463	55	16	13.9	23.9
37	Li Y.	2021	China	Retrospective cohort study	Methylprednisolone	68	28	96	46	06	67.6	21.4
38	Salton F	2020	Italy	Retrospective cohort study	Methylprednisolone	83	90	173	06	21	7.2	23.3
39	Ma Q	2020	China	Retrospective cohort study	Methylprednisolone	47	28	75	04	02	5.9	7.1
40	Rodriguez high dose	2021	Spain	Retrospective cohort study	Corticosteroid	117	344	461	22	41	18.8	11.9
41	Rodriguez pulse dose	2021	Spain	Retrospective cohort study	Corticosteroid	78	344	422	08	41	5.9	11.9
42	Wu J (critical cases)	2020	China	Retrospective cohort study	Corticosteroid	159	90	249	70	14	44.0	15.6
43	Wu J (severe cases)	2020	China	Retrospective cohort study	Corticosteroid	531	983	1514	83	26	15.6	2.6

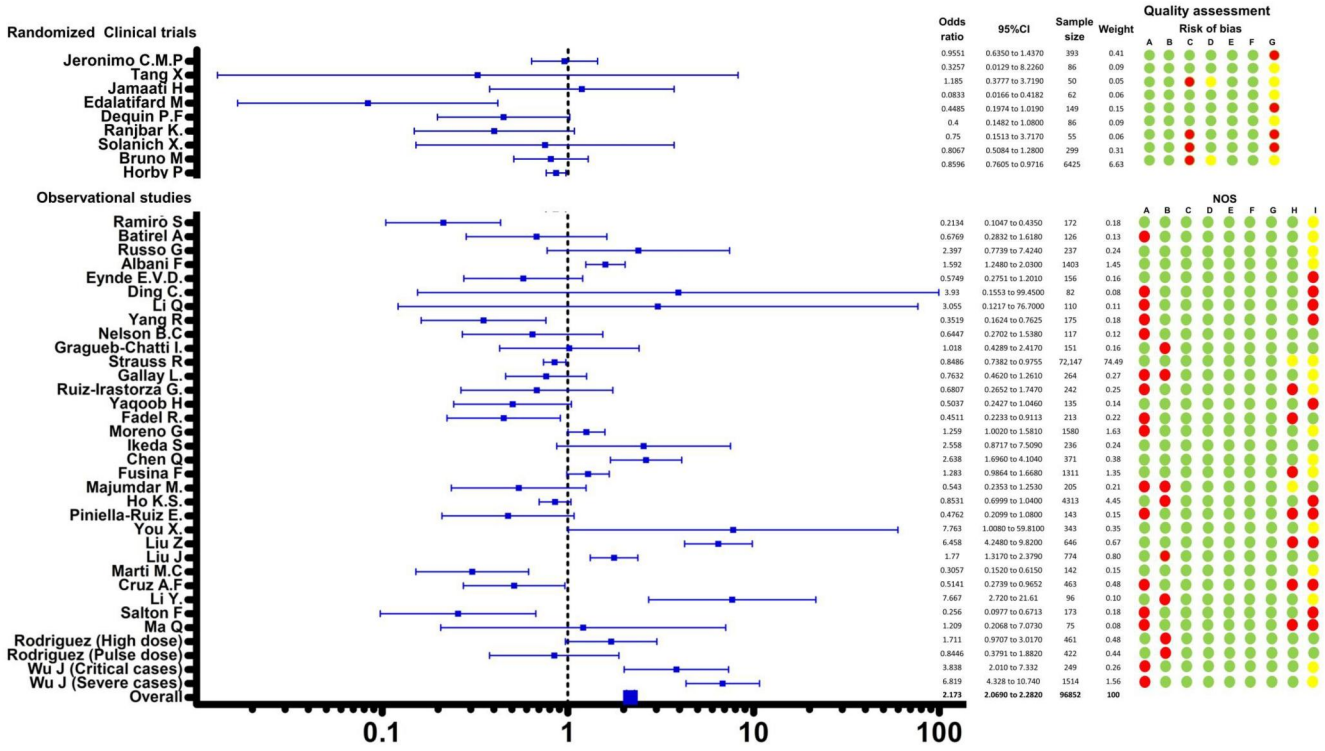

FIGURE 2 Effect of corticosteroids on mortality in COVID-19. Q-value: 88.60; Df: 42; I^2 value: 52.60; *p* value: $P < 0.0001$; Fixed model Z-value: 4.103; Random model Z-value: 2.90

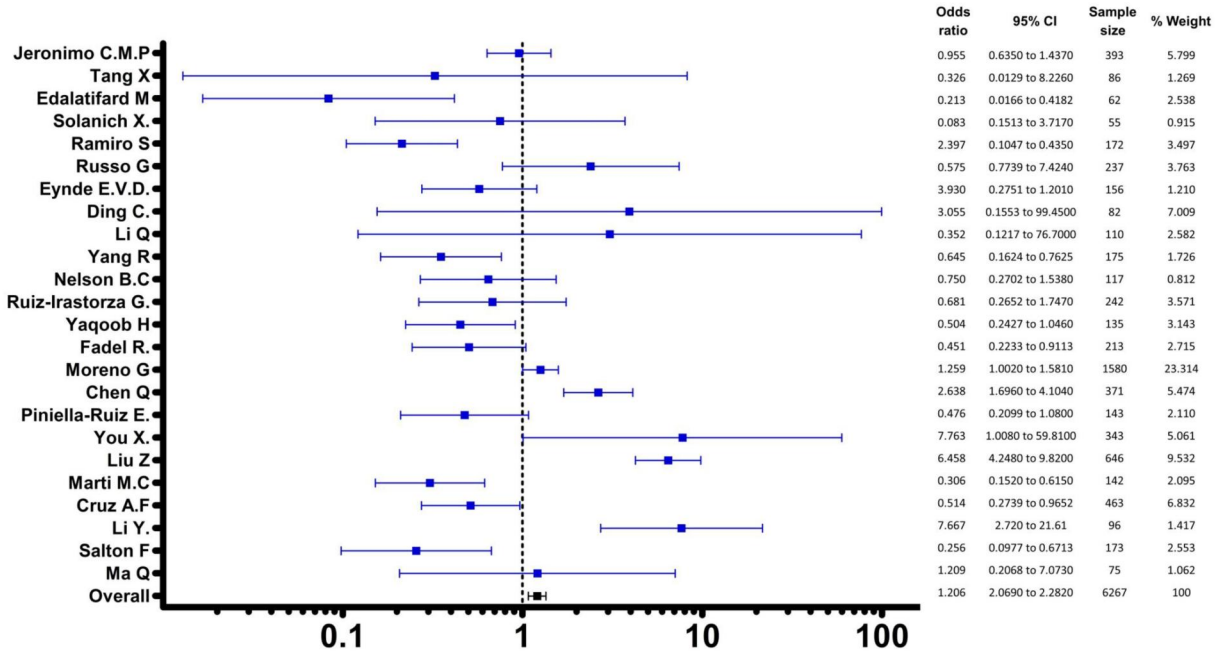

FIGURE 3 Effect of methylprednisolone on mortality in COVID-19. Q-value: 73.65; Df: 23; I^2 value: 68.77; *p* value: $P < 0.0001$; Fixed model Z-value: 2.93; Random model Z-value: 1.94

4 | DISCUSSION

The treatment approach for severe COVID-19 patients is facing dual challenges. First one is to suppress the hyper-inflammatory responses and cytokine storm while other one is the viral clearance.[68] This foremost theory hypothesises that corticosteroids could be used to alleviate the 'cytokine storm' and its lethal consequences. In a systematic review of 22 studies, Judith VP et al quantified the effect of corticosteroids on death rate in COVID-19 patients.[17] The results showed that corticosteroids therapy significantly reduced short-term

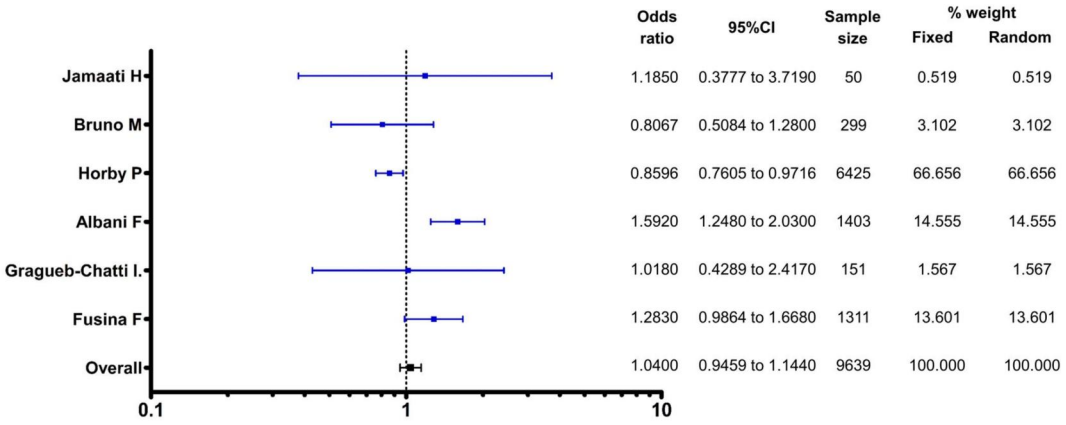

FIGURE 4 Effect of dexamethasone on mortality in COVID-19. *Q*-value: 0.188; Df: 5; I^2 value: 0; *p* value: $P < 0.0001$; Fixed model Z-value: 1.86; Random model Z-value: 1.86

mortality in the COVID-19 patients.[17] Furthermore, meta-analysis of seven RCTs involving 1703 disparagingly ill COVID-19 patients also revealed that systemic corticosteroids therapy reduced 28-day mortality when compared to standard care.[69] The RECOVERY trial found that dexamethasone therapy reduced 28-day mortality in individuals requiring oxygen therapy or mechanical ventilation as compared to standard care.[7]

Our systematic review and meta-analysis comprised 32 cohorts and 11 RCTs for investigating the outcome of corticosteroids treatment on the mortality in COVID-19 patients. Despite the fact that the several randomized trials found that corticosteroids medication was related to decreased mortality in COVID-19 patients, we were unable to find the similar result in our meta-analysis, having sample size 96,852 patients. Our study found that corticosteroids therapy didn't avert mortality in the COVID-19 patients, but it has increased the death in the COVID-19 patients as compared to usual care. Furthermore, we also found that both methylprednisolone and dexamethasone showed the higher mortality in the COVID-19 patients as compared to usual care. However, there was significant difference found in the mortality with respect to treatment of specific corticosteroid including methylprednisolone and dexamethasone.

The possible reasons may be considered for increasing the mortality with corticosteroid therapy like initiation of corticosteroid therapy in early stage of viral infection and higher dosage of corticosteroids, which delay the viral clearance and secondary infections. Consistent to our findings, the results of other meta-analysis on steroid treatment in COVID-19 patients showed the delay in viral clearance and enhance the mortality as compared to standard therapy.[70] Similar manner, another propensity score-based analysis study found that corticosteroids use significantly increased the period of hospital stay and majority of patients progress to more deteriorated critical conditions compared to the standard therapy.[71] Similarly, Li et al. described a significantly longer hospital stay in COVID-19 patients who treated with corticosteroids compared to standard care treatment.[37] Furthermore, patients who received corticosteroids for more than 5 days required an extended course of chemotherapeutic agents as compared to patients who received short-term treatment for 3–5 days.[37] Multi-organ malfunction is much more likely in critically sick COVID-19 patients who underwent corticosteroid treatment, according to Lu et al., and each ten-mg increase in dosage was linked with an extra four percent mortality risk.[72] Furthermore, another meta-analysis found that giving corticosteroids to patients with influenza increased death and hospital-acquired infections.[73] In a comprehensive evaluation of influenza pneumonia, glucocorticoid medication was found to be related with an increased risk of death, length of stay in the critical care unit and risk of secondary infections.[73] According to a meta-analysis of SARS, MERS and COVID-19, systemic glucocorticoids are not useful in lowering mortality.[74] In meta-analysis of observational studies and RCT, Tlayjeh et al. reported that corticosteroids therapy was not associated with a reduction in short-term mortality but may be associated with a delay in viral clearance in patients hospitalised with COVID-19.[75] Similarly, Wang J also reported that corticosteroid use in COVID-19 patients delayed viral clearance and didn't improve survival.[76]

5 | CONCLUSION

In conclusion, corticosteroid therapy did not show beneficial effect on prevention of mortality but it produced a negative prognosis as depicted by increased mortality among COVID-19 patients. The possible reasons for the increase in the mortality might be delay in virus clearance and secondary infection due to initiation of corticosteroid therapy at the early stage of the infection and at the high dose. There is need to conduct further clinical studies for development of the standard guideline to use corticosteroids in COVID-19 with considering factors such as initiation of the therapy with monitoring the virus load, dosage, route of administration and duration of the therapy as well as confounding antibiotics.

AUTHOR CONTRIBUTIONS

Conceptualisation: Jayesh Beladiya; Chirag Patel, Formal analysis: Jayesh Beladiya; Chirag Patel, Investigation: Krupanshu Parmar; Dipanshi Patel. Writing—original draft: Jayesh Beladiya; Chirag Patel;

Dipanshi Patel; Krupanshu Parmar, Writing—review & editing: Sandip Patel, Devang Sheth.

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Not Applicable.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study does not contain direct involvement of human participants or animals performed by any of the authors.

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