Effectiveness of Pulse Dose Methyl Prednisolone in Management of COVID 19: A Systematic Review and Meta-Analysis of Observational Studies

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ABSTRACT -- Purpose: To date, only systemic corticosteroids have demonstrated definite mortality benefit in management of COVID 19 in various studies. Still certain questions regarding the appropriate dose, duration and timing of corticosteroids remain unanswered. For this reason, the study was planned to determine the efficacy and safety of the pulse dose methyl prednisolone in management of COVID 19 from publicly available evidence. **Methods:** PubMed, the Cochrane library, ClinicalTrials.gov and medRxiv were searched for articles reporting the use of pulse dose methyl prednisolone in COVID 19 from inception until May 31st, 2021. Odds ratios (ORs) were calculated for estimation of pooled effect by using random effect model and heterogeneity was checked by using I^2 statistics. **Results:** Twelve studies (11 observational and 1 RCT) were included in the systematic review. A total of 3110 patients from 9 studies were included in the meta-analysis. Though the use of pulse dose methyl prednisolone demonstrated statistically significant mortality benefit in comparison to usual care (OR=0.71, 95% CI: 0.51 to 0.97, [P=0.03]), (I^2= 21%) with calculated Number Needed to Treat (NNT) of 23.5, there was no statistically significant difference between the use of pulse dose and low dose corticosteroid (OR=0.66, 95% CI: 0.44 to 1.01, [(P=0.05]), (I^2= 25%) and NNT 23.5. Incidence of adverse events were similar across all the groups. The grade of evidence for primary outcome was of moderate certainty. **Conclusion:** This meta-analysis concurs with the previous reports regarding the use of corticosteroid in COVID 19 in comparison to usual care. However, for both the primary and secondary outcome, the study did not find any statistically significant difference between the use of pulse dose methyl prednisolone and low dose corticosteroid to treat COVID 19 patients.

INTRODUCTION

Since December 2019, Coronavirus disease 19 (COVID 19) pandemic continues to be one of the leading cause of morbidity and mortality worldwide (1,2). It is now well documented that the pathogenesis of COVID 19 has 3 stages, namely, the viral stage, the pulmonary stage, and the hyper-inflammatory stage (3,4). The hyper-inflammatory stage is of major concern as it is associated with increased morbidity and mortality (5,6). Therefore, many anti-inflammatory and antioxidant agents have been tried for the management of COVID 19 with varying success (7,8). To date, systemic corticosteroids are the only class of drugs successfully used for treatment of COVID 19 and has demonstrated definite mortality benefit in various studies (9,10). The mortality benefit with use of corticosteroid is evident in COVID 19 patients requiring oxygen therapy or mechanical ventilation, i.e., the late pulmonary or hyper-inflammatory stage of the disease (9). Though the Randomised Evaluation of COVID-19 Therapy (RECOVERY Trial) reported the mortality benefit with use of low dose systemic corticosteroid, still certain questions regarding the appropriate dose, duration and timing of corticosteroids remain unanswered (11). A meta-analysis by Hasan *et al*, reported that a short course of pulse dose methyl prednisolone may be a probable alternative to low dose dexamethasone (12). Pulse dose corticosteroid has also been suggested in past for treatment of severe acute respiratory syndrome (SARS) (13). It is an accepted treatment modality in various rheumatologic diseases (14,15). There are a few case reports and case series which have reported the beneficial effect of pulse dose methyl prednisolone in management of COVID 19 (16-18). The rapid downregulation of immune system activation and pro-inflammatory cytokine production with pulse dose corticosteroid by a non-genomic mechanism, different from low dose corticosteroid makes it an attractive alternative therapy in hyper-inflammatory stage of different

diseases (19). As the evidence regarding the use of pulse dose methyl prednisolone in the management of COVID 19 is still equivocal, we planned to conduct this systematic review and meta-analysis to determine the efficacy and safety of the same from the publicly available evidence.

MATERIALS AND METHODS

Development and registration of protocol

The draft protocol was developed in accordance with PRISMA-P guidelines and Meta-analysis of Observational Studies in Epidemiology (MOOSE) (20,21). After review by all the authors, it was registered in the prospective register of systematic review (PROSPERO) database (Registration number: CRD42021259610) and made publicly available.

Types of studies, participants, intervention, and comparator:

All double/ multiple arm studies (randomized, non-randomized and observational cohort studies) reporting the use of pulse dose methyl prednisolone in management of COVID 19 along with usual care were included. The study inclusion was not restricted by year of publication, site of study or dose of the drugs. Case series, case reports, review articles and non-English language publications were excluded.

All human subjects of both gender with a diagnosis of COVID 19 (RT-PCR confirmed or clinically diagnosed) treated in hospital were included.

The intervention in all included studies was the administration of pulse dose methyl prednisolone in COVID 19 patients along with usual care. In the protocol, pulse dose methyl prednisolone is defined as ≥ 125 mg/day bolus infusion for a minimum of 3 days. The timing of pulse dose therapy in relation to disease onset was not a limiting factor. The comparators were either usual care alone or usual care with low dose systemic corticosteroid for management of COVID 19. Low dose systemic corticosteroid is defined as ≤ 1 mg/kg/day of methyl prednisolone or equivalent dose of dexamethasone. As there is no universally accepted usual care for management of COVID 19, the standard care followed in different studies as per local guideline without use of systemic corticosteroid is considered as usual care.

Outcome measures

The primary outcome is all-cause mortality: death in COVID 19 patients due to any cause within the available period of follow up in the studies (maximum up to 30 days). The secondary outcome measures are the need for invasive ventilation or intensive care unit (ICU) admission and development of adverse events within the study follow up period.

Information source and search strategy

PubMed, the Cochrane library, International Clinical Trials Registry Platform (ICTRP) including ClinicalTrials.gov and Pre-print server medRxiv were searched for articles reporting the use of pulse dose methyl prednisolone in management of COVID 19 along with usual care from inception till May 31st, 2021.

Using PICO method, a combination of subject terms and keywords were used for appropriate adjustments of vocabulary and grammar between different databases. We used the search term (COVID 19) "AND" (pulse dose methyl prednisolone) "OR" (high dose methyl prednisolone) for literature search in PubMed. The reference list of all relevant articles obtained from electronic search were also reviewed for additional studies.

Data extraction and management

A pre-designed data extraction format including relevant information was used for data recording. Two review authors (RRM, BRM) independently extracted and assessed the data for quality following Cochrane Collaboration's guidelines. Any disagreement between them was resolved by the third author (BMP).

Assessment of risk of bias in included studies

Risk of bias for study validity was accessed for all the studies included in the meta-analysis using Risk of Bias in Non-Randomized Studies - of Interventions (ROBINS-I) for observational studies". Three authors (RRM, BRM, BMP) independently accessed the risk of bias in each study, and any disagreement was resolved by discussion.

Data analysis

Cochrane Program Review Manager 5.3 software was used for the meta-analysis. Systematic review was conducted for all the studies reporting the use of pulse dose methyl prednisolone in management of COVID 19. Studies reporting all-cause mortality as outcome measures were included in the meta-analysis. Odds ratios (ORs) were calculated and combined for estimation of pooled effect by using random effect model in accordance with Cochrane Handbook for Systematic Reviews of Interventions. Heterogeneity among eligible studies was checked by using I^2 statistics. $I^2 > 50\%$ was considered to be statistically significant.

Assessment of publication bias and Grade of evidence

We used funnel plot for visual assessment of asymmetry due to publication bias.

For certainty assessment of the evidence, Grading of Recommendations Assessment, Development and Evaluation (GRADE) profiler software (V 3.6.1) was used.

RESULTS

Description of studies

The search of all database and additional sources from the references of relevant publications retrieved 329 studies. Among them, 18 studies were selected for full text review after removing duplicates and studies not meeting the inclusion criteria. Finally, a total of 12 studies were included in the systematic review and meta-analysis (22-33). Six studies were excluded after full text review with reason (1 study was a case series with systematic review, 4 studies reporting use of only low dose methyl prednisolone and in 1 study, the comparator arm could not be identified). The PRISMA flowchart of study selection is depicted in Figure 1.

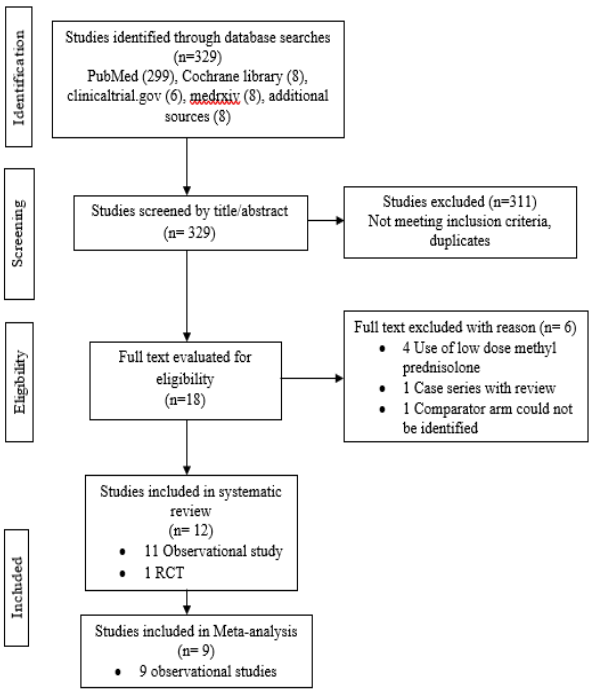


Figure 1. PRISMA flowchart of study selection process.

Out of 12 studies, 11 studies were observational cohort studies (8 retrospectives, 2 prospective, 1 ambispective studies) and 1 was a randomized controlled trial (RCT). The study by Cusacovich *et al* was published in pre-print server medRxiv and not peer reviewed (29). Though most of the studies included COVID 19 cases of severity ranging from moderate to critical, there were few mild cases in the studies by Pinzon *et al*, Cruz *et al* and Batirel *et al*. (25,27,32). The basic demographic profile, co-morbidities and other treatment received were comparable across the groups in all the studies. The lowest dose of methyl prednisolone administered in pulse dose group was 125 mg/day and the highest was 500 mg/day. Almost all patients received the pulse dose methyl prednisolone for at least 3 days in the intervention group. In most of the studies, the total duration of methyl prednisolone therapy was up to 7 days except in the study by Pinzon *et al*, where the pulse methyl prednisolone therapy for 3 days was followed by oral methyl prednisolone (50 mg/day) for 14 days (25). Though the follow up period varied across the studies, in most of them, it was up to 30 days. The characteristics of the 12 selected studies are summarized in Table 1.

The RCT by Edalatifard *et al* reported statistically significant survival benefit in COVID 19 management with use of high dose methyl prednisolone in comparison to usual care alone (33). The study by Mareev *et al*, did not report all cause-mortality as an outcome measure (31). Although the study by Liu *et al* reported a total of 2 deaths, the group in which the deaths occurred was not specified (22). Therefore, we included 9 observational studies for estimating the pooled effect in the meta-analysis (23-30,32).

A total of 3110 COVID 19 patients were included in the meta-analysis. Among them, 902 patients received pulse dose methyl prednisolone, 756 patients received low dose systemic corticosteroid (either low dose methyl prednisolone or equivalent dose of dexamethasone) and 1452 patients received usual care without any corticosteroid. Though total 778 patients were included in the study by Bano *et al*, 151 patients were excluded from the quantitative analysis as their study group could not be ascertained and 88 patients receiving only tocilizumab were included in usual care group (24). Similarly, 2 patients from the pulse dose methyl prednisolone group were excluded during the statistical analysis in the study by Cusacovich *et al*, but the reason for exclusion could not be ascertained from the study (29). Four studies had compared the outcome between pulse dose methyl prednisolone and usual care alone (23,26,28,29). Another 4 studies were multiple arm comparative studies reporting the outcome for pulse methyl prednisolone, usual care alone and low dose systemic corticosteroid (24,27,30,32). Only, one study reported the outcome comparing between the pulse methyl prednisolone and low

Table 1. Characteristics of selected studies.

Study name/ year/ country	Study type	Study period	Inclusion criteria	Study groups	Outcome measures	Steroid type/ dose	Duration of therapy	Other treatment received	Follow up period
Liu *et al*, 2020. (22) China	Observational Prospective cohort	Jan 20 to Feb 23, 2020	Laboratory confirmed mild, moderate & severe	High dose vs low dose methyl prednisolone	Outcome of treated patients, Epidemiological character of patients	Methyl prednisolone High dose defined as > 2mg/kg/day	Median IQR is 7 days	Interferon α, Lopinavir/ ritonavir	Variable
Papamanoli *et al*, 2020. (23) USA	Observational Retrospective cohort	March 1 to April 15, 2020	Severe COVID 19 pneumonia with high flow oxygen FIO2≥50	High dose and low dose methyl prednisolone and no steroid group	28 days mortality, 28 days need for ventilation, secondary infections	Methyl prednisolone Median daily dose is 160 mg	Median duration is 5 days	Tocilizumab, HCQS, Remdesivir, Azithromycin	28 days
Bano *et al*, 2020. (24) Spain	Observational Retrospective cohort	Feb 2 to March 31, 2020	COVID 19 with hyper-inflammatory state, 1 clinical & 1 laboratory criteria	No treatment, tocilizumab intermediate high dose steroid, pulse steroid, combination therapy	Intubation or death	Methyl prednisolone Pulse dose > 250 mg/day	NA	Tocilizumab, lopinavir/ ritonavir, HCQS, Remdesivir, Interferon α	21 days
Pinzon *et al*, 2021. (25) Colombia	Observational Ambiseptive cohort	June 11 to September 14, 2020	RT-PCR +ve, oxygen requirement, radiological pneumonia	Dexamethasone vs high dose methyl prednisolone	Mortality, Transfer to ICU, Development of ARDS, Change in laboratory parameter, Recovery time	Dexamethasone- 6mg/day Methyl prednisolone- 250 to 500mg/day for 3 doses followed by 50mg/day orally for 14 days	Dexa- 10 days Methyl pred- 14 days	Colchicine, Antibiotics	30 days
Rubio *et al*, 2020. (26) Spain	Observational Retrospective cohort	NA	RT-PCR +ve, IL-6> 40 pg/ml, ferritin> 300µg/ml/ D-Dimer>1mg/ml/ TG> 300mg/ml	Glucocorticoid pulse, glucocorticoid pulse with tocilizumab, only tocilizumab	Survival, Need for ventilation	Methyl prednisolone Pulse dose ≥ 2mg/kg/day for 3 days	3 days	Tocilizumab	Median 11 days
Cruz *et al* 2020.(27) Spain	Observational retrospective cohort	March 2020	COVID 19 pneumonia with increased inflammation markers	Steroid cohort (pulse & low dose) vs no steroid cohort	In-hospital mortality	Methyl prednisolone Low dose- 1 mg/kg/day Pulse dose 250 mg to 500 mg/ day, a median of 3 days	NA	Tocilizumab, Anakinra	NA

Table 1 continues…

Irastorza *et al* 2020. (28) Spain	Observational Retrospective cohort	March 1 to April 30, 2020	COVID 19 pneumonia with increased inflammation markers	Pulse glucocorticoid, non-pulse glucocorticoid, no glucocorticoid	Time to death, Time to death or intubation	Methyl prednisolone Pulse dose >125mg/day	3 days	Lopinavir/ Ritonavir, LMWH, HCQS	NA
Cusacovich *et al* 2020. (29) Spain	Observational Retrospective cohort	March 12 to May 20, 2020	COVID 19 pneumonia with PiO2/FiO2< 300	Pulse corticosteroid vs usual care	60 day mortality, 30 day mortality, ICU admission, in-hospital stay, adverse effect	Methyl prednisolone 125mg to 500 mg/day	2 to 5 days	HCQS, Azithromycin, Lopinavr/ Ritonavir,Remdesivir, Colchicine	30 days and 60 days
Zuniga *et al* 2020. (30) Spain	Observational prospective cohort	Feb 4 to April 30, 2020	Confirmed/ suspected COVID 19 patients	High dose vs low dose vs no corticosteroid	Mortality, difference between survivors and non-survivors	Methyl prednisolone High dose> 1.5 mg/kg/day	3 to 5 days	Tocilizumab, plasma therapy, HCQS, Anakinra, lopinavir/ritonavir, Interferon, Anticoagulant	30 days
Mareev *et al* 2020. (31) Russia	Observational Retrospective cohort	NA	Severe COVID 19	Pulse dose vs No steroid group	Clinical status, Change in inflammation markers	Methyl prednisolone 1000mg/day for 3 days, then dexamethasone 8 mg/day for 3 to 5 days	6 to 8 days	NA	NA
Batirel *et al* 2021. (32) Turkey	Observational Retrospective cohort	NA	Confirmed/ suspected COVID 19 patients	Pulse dose vs low dose vs standard care	Mortality, Need for ICU or ventilator, Adverse effect	Methyl prednisolone ≥ 250 mg/day. Dexamethasone 6 mg/day	Median 6 to 7 days	HCQS, Fabipiravir, Remdesivir, LMWH, Lopinavir/ ritonavir, Antibiotics	NA
Edalatifard *et al* 2020.(33) Iran	RCT, single blind, parallel arm	April 20 to June 20, 2020	Severe COVID 19 in early pulmonary phase SpO2< 93%, RR> 18 beats/m	Standard care with methyl prednisolone pulse and standard care alone	Time to clinical improvement, Time to hospital discharge or death, Adverse effect	Methyl prednisolone 250 mg/day	3 days	HCQS, Lopinavir, Naproxen	Death or 1 week after discharge

NA: Not available, HCQS: Hydroxychloroquine, LMWH: Low molecular weight heparin, RT-PCR: Reverse transcriptase polymerase chain reaction

dose systemic corticosteroid (25). The characteristics of patients included in the meta-analysis are summarized in Table 2.

Risk of bias in the included studies

The risk of bias for primary outcome was accessed for all the studies included in the meta-analysis. Across all the included studies, 3 important confounding domains were identified, i.e., non uniformity of COVID 19 patient severity, use of additional treatment modalities and presence of co-morbidities. The study by Zuniga *et al* had overall low risk of bias (30). All other studies had overall moderate to serious risk of bias. The domains like, bias due to confounding**,** bias in selection of participants into the study were identified having moderate to serious risk of bias due to retrospective nature of the included studies (except Zuniga *et al*). The overall predicted direction of bias for the primary outcome (all-cause mortality) was assessed to be unpredictable. The result of the risk of bias assessment of all studies are summarized in Table 3.

Effects of intervention

For all-cause mortality, data form 8 studies were pooled to compare between pulse dose methyl prednisolone group and usual care group and from 5 studies for comparison between pulse dose methyl prednisolone group and low dose corticosteroid group. The pooled effect on secondary outcome was estimated from 5 and 3 studies for comparison between pulse dose methyl prednisolone group vs usual care group and pulse dose methyl prednisolone vs low dose corticosteroid group respectively. The forest plots for the pooled effect are depicted in Figure 2.

All-cause mortality

With the use of random effect model, this meta-analysis indicated that there is a statistically significant mortality benefit with use of pulse dose methyl prednisolone for treatment of COVID 19 patients compared to usual care alone (OR=0.71, 95% CI: 0.51 to 0.97, [P=0.03]).Although, comparison between pulse dose methyl prednisolone group and low dose corticosteroid group indicated overall mortality benefit with pulse dose methyl prednisolone group (OR=0.66, 95% CI: 0.44 to 1.01), it did not reach the threshold of statistical significance (P=0.05). There was no statistically significant heterogeneity among the studies comparing primary outcome between pulse dose methyl prednisolone group vs usual care alone (Chi^2 =8.81, df=7, [P=0.27], I^2= 21%) and between the pulse dose methyl prednisolone group vs low dose corticosteroid group (Chi^2 =5.31, df=4, [P=0.26], I^2= 25%). Sensitivity analysis was not carried out as the test of heterogeneity across the included studies was not significant.

The dose used for pulse dose methyl prednisolone was ≥ 250 mg/day in all the included studies comparing with low dose corticosteroid except in the study by Zuniga *et al*, where the dose was 1.5 mg/kg/day (≥ 125 mg/day).[30] We carried out subgroup analysis for the pooled effect on primary outcome comparing pulse dose methyl prednisolone and low dose corticosteroid by excluding the study Zuniga *et al*. The result remained consistent without any statistically significant difference between the 2 groups (OR=0.72, 95% CI: 0.46 to 1.11, [P=0.13]). The result of subgroup analysis is summarized in Figure 3.

Need for invasive ventilation or intensive care unit (ICU) admission

This outcome was reported in 5 studies comparing pulse dose methyl prednisolone group with usual care group. Similarly, 3 studies reported the number of patients needing for invasive ventilation or intensive care unit (ICU) admission comparing the pulse dose methyl prednisolone and low dose corticosteroid group. The statistically significant benefit persisted for the secondary outcomes (Need for invasive ventilation or intensive care unit (ICU) admission) with the pulse dose methyl prednisolone group in comparison to usual care alone group using random effect model (OR=0.69, 95% CI: 0.53 to 0.91, [P=0.009]). The test of heterogeneity across the studies was not significant (Chi^2= 4.05, df=4, [P=0.40], I^2 = 1%). The overall pooled OR with random effect model for comparison between pulse dose methyl prednisolone group and low dose corticosteroid group was 0.98 (95%CI: 0.63 to 1.52), which was statistically non-significant (p=0.93). Test of heterogeneity revealed statistically significant difference between the studies (Chi^2 =7.58, df=2, [P=0.02], I^2= 74%). Sensitivity analysis by excluding the study by Pinzon *et al* reduced the heterogeneity and was also consistent with the overall result of no statistically significant difference between the 2 groups (OR=1.38, 95% CI: 0.83 to 2.31, [P=0.21]) with I^2 0% (P= 0.36). The result of sensitivity analysis is summarized in Figure 3.

Development of adverse events within the study follow up period

The pooled effect for this secondary outcome was not estimated as different studies reported adverse events in varying manner. There was no uniformity in defining severe or minor adverse effect.

Table 2. Characteristics of patients included in the study.

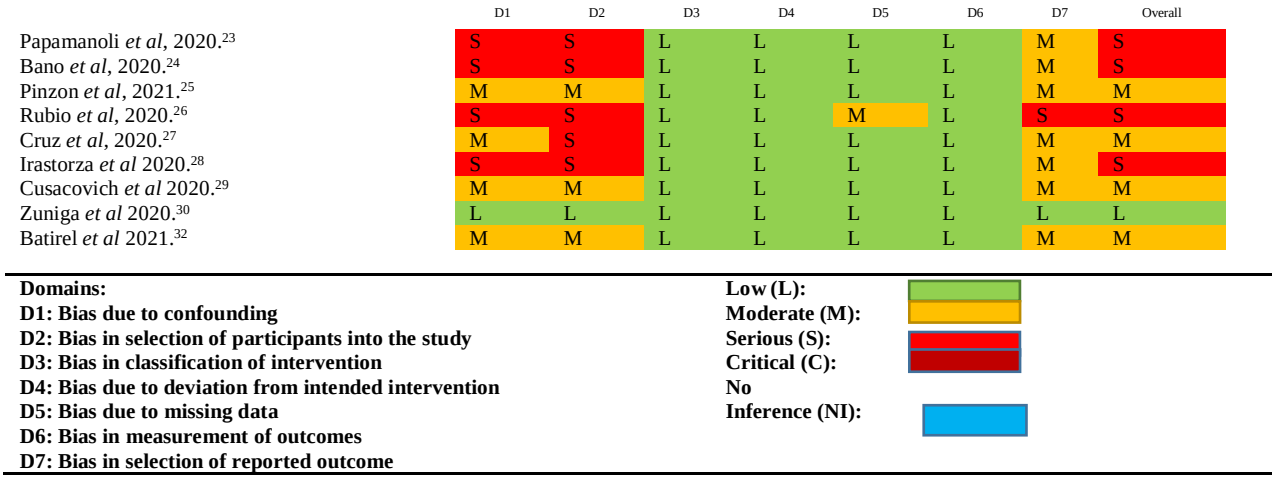
Study name Total sample size (n)		Sample size (n)	Age	Sex	COVID severity	Need for ICU/ Mechanical ventilation (n)	Recovery (n)	Mortality (n)	Adverse events
Liu *et al*, 2020. (22) n (65)	Pulse steroid group	11	NA	NA	Mixed	NA	NA	NA	HTN, Hyperglycaemia, Arrhythmia, Hypokalaemia, GI bleed, Neuropsychiatric symptoms
	Low+ no steroid	20+34	NA	NA	Mixed	NA	NA	NA	HTN, Hyperglycaemia, Arrhythmia, Hypokalaemia, GI bleed, Neuropsychiatric symptoms
Papamanoli *et al*, 2020. (23) n (447)	Pulse steroid group	153	Median 62 (53-72)	M 104 F 49	Severe	50	82	21	(Per 1000 patient days) Bacteraemia 3.8 Nosocomial pneumonia 4.3 GI bleed 2.2
	No steroid	294	Median 61 (48-74)	M 187 F 107	severe	115	148	31	(Per 1000 patient days) Bacteraemia 5.5 Nosocomial pneumonia 9.0 GI bleed 3.6
Bano *et al*, 2020. (24) n (778) 151 excluded	Pulse steroid group	78	Median 71 (62-76)	M 57 F 21	Moderate	5	65	8	GI bleed 1 Bacterial infection 10
	Low dose steroid / No steroid	Low dose (117) No steroid (432)	Median 71 (62-76)	M 84 F 33	Moderate	Low dose (3) No dose (29)	Low dose (92) No dose (360)	Low dose (22) No dose (43)	GI bleed 1 Bacterial infection 8
Pinzon *et al*, 2021. (25) n (216)	Pulse steroid group	105	Median 64 (60–68)	M 67 F 38	Mixed	5	88	12	NA
	Low dose steroid	111	Median 63 (58–69)	M 60 F 51	Mixed	16	62	24	NA
Rubio *et al*, 2020. (26) n (92)	Pulse steroid group	83	NA	NA	Moderate	4	77	6	NA
	No steroid	9	NA	NA	Moderate	1	8	1	NA
Cruz *et al*, 2020. (27) n (463)	Pulse steroid group	86	NA	NA	Mixed	NA	73	13	NA
	Low dose steroid/ No steroid	Low dose (310) No steroid (67)	NA	NA	Mixed	NA	Low dose (268) No steroid (51)	Low dose (42) No steroid (16)	NA
Irastorza *et al*, 2020. (28) n (242)	Pulse steroid group	61	Mean 65.0 (12.1)	M 40 F 21	Moderate	NA	NA	4	NA
	No steroid	181	Mean 64.2 (15.0)	M 110 F 71	Moderate	NA	NA	18	NA
Cusacovich *et al*, 2020. (29) n (257) 2 patients exclude from analysis	Pulse steroid group	122	NA	NA	Moderate to severe	23	NA	37	SAE 17 In hospital infection 29 PE 8
	No steroid	133	NA	NA	Moderate to severe	26	NA	56	SAE 15 In hospital infection 32 PE 19
Zuniga *et al*, 2020. (30) n (318)	Pulse steroid group	64	NA	NA	Moderate to severe	NA	60	4	NA
	Low dose	Low dose (68)	NA	NA	Moderate to severe	NA	Low dose (57)	Low dose (11)	NA

Table 2. continues…

	steroid/ No steroid	No steroid (186)					No steroid (154)	No steroid (32)	
Mareev *et al*, 2020. (31) n (34)	Pulse steroid group	17	NA	NA	Severe	NA	NA	NA	Thromboembolism 4
	No steroid	17	NA	NA	Severe	NA	NA	NA	NA
Batirel *et al* 2021. (32) n (450)	Pulse steroid group	150	Median 59.5 (48.0-70.7)	M 100 F 50	Mixed	36	136	14	6 adverse events
	Low dose steroid/ No steroid	Low dose (150) no steroid (150)	Median 59.5(49.0-71.2)/ 60.0(48.7-71.0)	M 100 F 50/ M 100 F 50	Mixed	Low dose (30) No steroid (36)	Low dose (134) No steroid (126)	Low dose (16) No steroid (24)	2 adverse events
Edalatifard *et al*, 2020. (33) n (68)	Pulse steroid group	34	Mean 55.8±16.4	M 39 F 23	Moderate	NA	32	2	SAE 2
	No steroid	28 Six patients excluded	Mean 61.7±16.6	M 24 F 10	Moderate	NA	16	12	SAE 2

NA: Not available, HTN: Hypertension, GI: Gastrointestinal, SAE: Serious adverse effect, PE: Pulmonary embolism

Table 3. Risk of bias assessment in included studies (ROBINS I)



The most common adverse events reported across the studies were gastrointestinal bleeding and secondary bacterial infection. But there was no significant difference in terms of reported adverse effects across the compared groups.

Publication bias

Funnel plot suggested the presence of publication bias. The result of funnel plot is depicted in Figure 4.

Grade of evidence

The grade of evidence for primary outcome was of moderate certainty and for secondary outcome was of very low certainty. We calculated the number needed to treat (NNT) for the primary outcome. The calculated NNT for primary outcome while comparing pulse dose methyl prednisolone with usual care was 23.5. Similarly, the calculated NNT for primary outcome while comparing pulse dose methyl prednisolone with low dose corticosteroid was 23.5. The result of grade of evidence is summarized in Table 4.

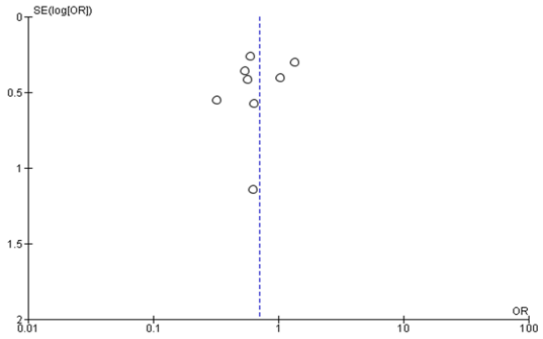
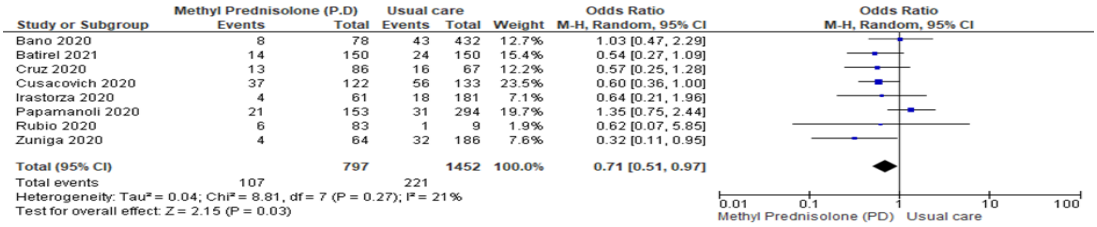


Figure 4. Funnel plot.

a.



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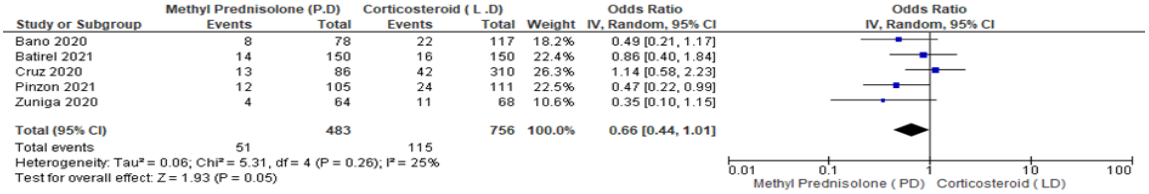

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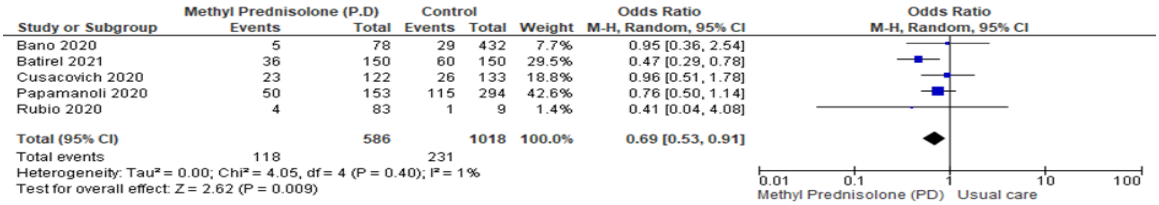

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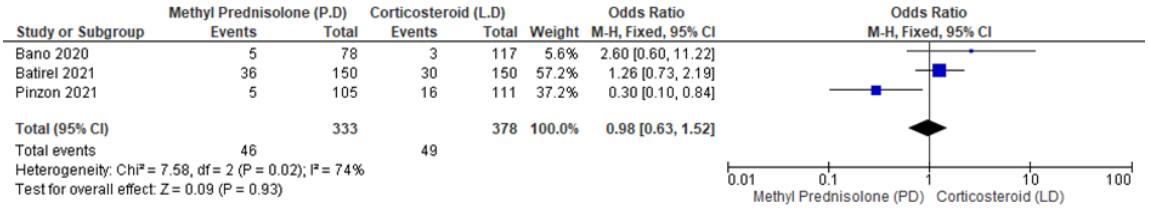
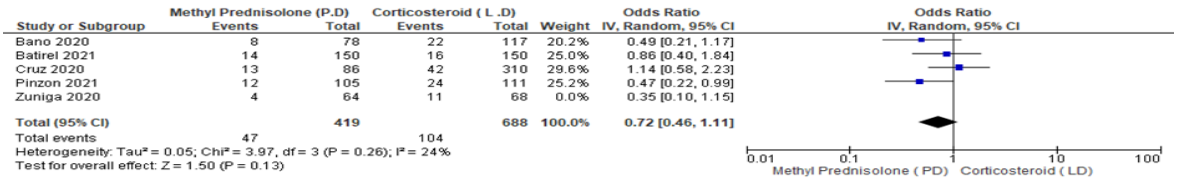


Figure 2. Forest plot. a) All-cause mortality (pulse dose methyl prednisolone vs usual care), b) All-cause mortality (pulse dose methyl prednisolone vs low dose corticosteroid), c) Need for ventilation or ICU admission (pulse dose methyl prednisolone vs usual care), d) Need for ventilation or ICU admission (pulse dose methyl prednisolone vs low dose corticosteroid).

a.



b.

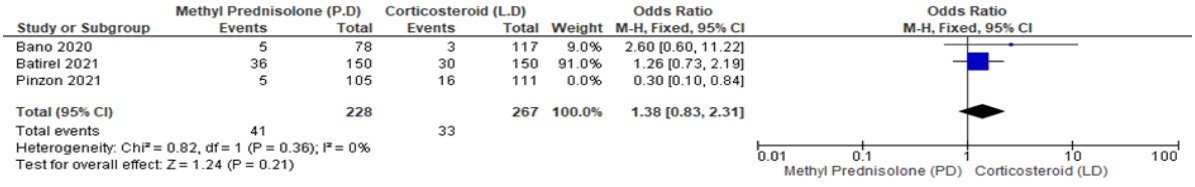


Figure 3. Forest plots for subgroup and sensitivity analysis. a) Subgroup analysis for all-cause mortality (pulse dose methyl prednisolone vs low dose corticosteroid) excluding the study Zuniga *et al.*, b) Sensitivity analysis for Need for ventilation or ICU admission (pulse dose methyl prednisolone vs low dose corticosteroid).

Table 4. Grade of evidence.

Certainty assessment (All-cause mortality)				No. of patients		Effect		Certainty
No. of studies	**Study design**	**Risk of bias**	**Other considerations**	**PD Methyl Prednisolone**	**Usual care**	**Relative (95% CI)**	**Absolute (95% CI)**	
8	observational studies	serious [a]	publication bias [b], All plausible residual confounding would suggest spurious effect, No large effect	107/797 (13.4%)	221/1452 (15.2%)	**OR 0.71** (0.51 to 0.97)	**39 fewer per 1,000** (from 68 fewer to 4 fewer)	⊕⊕⊕◯ MODERATE
No. of studies	**Study design**	**Risk of bias**	**Other considerations**	**PD Methyl Prednisolone**	**Low dose corticosteroid**	**Relative (95% CI)**	**Absolute (95% CI)**	
5	observational studies	serious [a]	publication bias [b], all plausible residual confounding would suggest spurious effect, No large effect	51/483 (10.6%)	115/756 (15.2%)	**OR 0.66** (0.44 to 1.01)	**46 fewer per 1,000** (from 79 fewer to 1 more)	⊕⊕⊕◯ MODERATE
Certainty assessment (Need for mechanical ventilation or ICU)				**No. of patients**		**Effect**		**Certainty**
No. of studies	**Study design**	**Risk of bias**	**Other considerations**	**PD Methyl Prednisolone**	**Usual care**	**Relative (95% CI)**		**Absolute (95% CI)**
5	observational studies	serious [a]	publication bias [b], All plausible residual confounding would suggest spurious effect, No large effect	118/586 (20.1%)	231/1018 (22.7%)	**OR 0.69** (0.53 to 0.91)	**58 fewer per 1,000** (from 92 fewer to 16 fewer)	⊕◯◯◯ VERY LOW
No. of studies	**Study design**	**Risk of bias**	**Other considerations**	**PD Methyl Prednisolone**	**Low dose corticosteroid**	**Relative (95% CI)**	**Absolute (95% CI)**	
3	observational studies	serious [a]	publication bias [a], All plausible residual confounding would suggest spurious effect, No large effect	46/333 (13.8%)	49/378 (13.0%)	**OR 0.98** (0.63 to 1.52)	**2 fewer per 1,000** (from 44 fewer to 55 more)	⊕◯◯◯ VERY LOW

CI: Confidence interval; **OR:** Odds ratio; Explanations. a: Confounding and selection bias, b: Publication bias demonstrated by funnel plot (strongly suspected).

DISCUSSION

In the past, pulse dose corticosteroid therapy has been used in severe SARS or Middle East Respiratory Syndrome (MERS) resistant to usual care alone (13,34). But it has not been accepted in the COVID 19 management guidelines due to lack of definitive and quality evidence. A systematic review and case series by Dolci *et al*, reported that though there was no significant adverse effect with use of pulse dose methyl prednisolone in COVID 19, its indication and effectiveness needed more meticulous exploration (18).

This meta-analysis showed a statistically significant mortality benefit and decreased need for mechanical ventilation or ICU admission with the use of pulse dose methyl prednisolone in comparison to usual care for management of COVID 19 patients. Our result is also in conformity with the result of the RCT by Edalatifard *et al*, which reported significant reduction in mortality with the use of pulse dose methyl prednisolone in comparison to usual care alone (5.9% versus 42.9%; p<0.001) (33). A retrospective study from Japan has also suggested the beneficial effect of pulse/semi-pulse dose methyl prednisolone in shortening the duration of mechanical ventilation for severe COVID 19 patients in comparison to usual care alone (35). However, the use of pulse dose methyl

prednisolone for COVID 19 did not have statistically significant mortality benefit or decreased need for mechanical ventilation or ICU admission in comparison to low dose corticosteroid. Though the study by Pinzon *et al* reported significant improvement in recovery time and need for mechanical ventilation or ICU care with use of pulse dose methyl prednisolone in comparison to low dose dexamethasone, our meta-analysis did not support that observation (25). Also, there was no statistically significant mortality benefit in the subgroup analysis with the use of methyl prednisolone at a higher dose of 250 mg/day (OR=0.72, 95% CI: 0.46 to 1.11, [P=0.13]). Moreover, the mortality benefit in RECOVERY trial was reported with the use of low dose dexamethasone (9). The World Health Organisation (WHO) guideline for management of COVID 19 also recommends low dose dexamethasone or its equivalent dose of other corticosteroid for the management of moderate to severe disease (11).

The certainty of evidence for the pooled result for primary outcome in this meta-analysis is of moderate grade. We calculated the NNT which indicated the clinical desirability of the outcome. For primary outcome, the NNT was 23.5 for pulse dose steroid compared to usual care alone as well as for low dose corticosteroid. This suggests the clinically desirable benefit with use of corticosteroid in moderate to severe COVID 19 patients. But the clinical desirability to use of pulse dose methyl prednisolone over low dose corticosteroid must be interpreted cautiously in view of non-significant p value (P=0.05).

Previous studies have reported increased incidence of hypertension, psychosis, arrhythmia, and hypokalaemia with the use of pulse dose corticosteroid (36,37). But the most common adverse events reported in all included studies were secondary bacterial infection and GI bleeding and there was no significant difference between the groups.

As suggested by previous studies, due to its rapidity and durability of action, pulse steroid has been used in many diseases for treatment and for steroid sparing (38-40). Due to its rapid action, pulse dose steroid downregulates hyper-inflammation early in comparison to low dose steroid, which helps to decrease the duration of steroid therapy. Moreover, gradual dose tapering is not required for stoppage of therapy. But most of the uses are for chronic autoimmune disorders. The evidence for use of pulse dose steroid in the hyper-inflammatory stage of any infectious disease is still lacking. Also, with the increase incidence of COVID 19 associated mucormycosis (CAM), the use of corticosteroid and its dose needs to be planned cautiously.

LIMITATIONS

Most of the included observational studies were retrospective in nature thus impacting bias due to confounding and patient selection into the studies. The disease severity varied across the studies, which would have affected the expected outcome. Lastly, as other antiviral and immunosuppressant drugs were used, their effect would have influenced the overall outcome.

CONCLUSION

This meta-analysis concurs with the previous reports regarding the use of corticosteroid in management of COVID 19 in comparison to usual care. However, for both the primary and secondary outcome, the study did not find any statistically significant difference between the use of pulse dose methyl prednisolone and low dose corticosteroid to treat COVID 19 patients. There was no significant difference in adverse events with use of pulse dose methyl prednisolone. Further RCTs are needed to explore the efficacy and safety of pulse dose methyl prednisolone for management of COVID 19 patients.

AUTHOR CONTRIBUTION. The concept was developed by RRM and BMP. BRM and RRM carried out the search, data extraction, and quality assessment. Any disagreement was resolved by BMP. Statistical analysis and inference were done by BMP and BRM. The manuscript was written by RRM, BRM and BMP. All authors approved the final version for publication.

CONFLICTS OF INTEREST. There are no conflicts of interest.

FINANCIAL DISCLOSURE. None.

GUARANTOR. The corresponding author (along with all authors) is the guarantor of the content of the manuscript, including the data and analysis.

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