Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

The roles of methylprednisolone treatment in patients with COVID-19: A systematic review and meta-analysis

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ABSTRACT

The roles of methylprednisolone in treatment of patients with COVID-19 remain unclear. The aim of this study was to evaluate the efficacy and safety of methylprednisolone in treatment of COVID-19 patients. PubMed, Cochrane and Web of Science were searched for studies comparing methylprednisolone and no glucocorticoids treatment in patients with COVID-19. Statistical pooling was reported as risk ratio (RR) or mean difference (MD) with corresponding 95 % confidence interval (CI). Thirty-three studies were eligible, including 5 randomized trials and 28 observational studies. Meta-analysis showed that compared with no glucocorticoids, methylprednisolone in treatment of COVID-19 patients was associated with reduced short-term mortality (RR 0.73; 95% CI 0.60–0.89), less need for ICU admission (RR 0.77; 95% CI 0.66–0.91) and mechanical ventilation (RR 0.69; 95% CI 0.57–0.84), increased 28-day ventilator-free days (MD 2.81; 95% CI 2.64–2.97), without increasing risk of secondary infections (RR 1.04; 95% CI 0.82–1.32), but could prolong duration of viral shedding (MD 1.03; 95% CI 0.25–1.82). Subgroup analyses revealed that low-dose (≤2mg/kg/day) methylprednisolone treatment for ≤ 7 days in severe COVID-19 patients was associated with relatively better clinical outcomes, without increasing duration of viral shedding. Compared with no glucocorticoids, methylprednisolone treatment in COVID-19 patients is associated with reduced short-term mortality and better clinical outcomes, without increasing secondary infections, but could slightly prolong duration of viral shedding. Patients with severe COVID-19 are more likely to benefit from short-term low-dose methylprednisolone treatment (1–2 mg/kg/day for ≤ 7 days).

1. Introduction

The coronavirus disease 2019 (COVID-19) is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which belongs to the genus Betacoronavirus [1]. As of 6 September 2021, COVID-19 has affected 221 countries and territories, and about 220,563,227 cases have been confirmed around the world, of which 4,565,483 people have died, causing a great threat to human society [2]. Approximately 5% of patients with COVID-19 require transferring to intensive care unit (ICU) for respiratory support and are associated with a high mortality [3,4].

Studies have shown that the rapid clinical deterioration of patients with COVID-19 is closely related to hyper-inflammation (also named cytokine storm). When cytokine storm comes up, T cells, macrophages and natural killer cells rapidly proliferate and hyper-activate, releasing massive inflammatory cytokines, leading to apoptosis of pulmonary epithelium and endothelial cells, destruction of pulmonary microvascular and alveolar epithelial cell barrier, resulting in vascular leakage, alveolar edema and hypoxia, and finally ARDS, which is the primary cause of death in patients with COVID-19 [5–7]. Therefore, aside from active antiviral therapy, inhibiting hyper-inflammatory response and preventing tissue damage is also the focus of COVID-19 treatment.

Glucocorticoids, as the classic anti-inflammatory agents, have been used previously in respiratory diseases such as asthma, chronic obstructive pulmonary disease, severe bacterial pneumonia and ARDS. However, at the start of the COVID-19 pandemic, World Health Organization (WHO) advised against systematic use of corticosteroids in COVID-19 patients [8]. After the publication of RECOVERY trial [9], the WHO changed its original suggestion and recommended the use of

Abbreviations: ARDS, Acute respiratory distress syndrome; CI, Confidence interval; CRP, C-reactive protein; ICU, Intensive care unit; IL, Interleukin; MD, Mean difference; MINORS, Methodological index for non-randomized studies; RCT, Randomized controlled trial; RR, Risk ratio; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; WHO, World Health Organization.

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corticosteroids in patients with severe COVID-19 [10]. In RECOVERY trial, glucocorticoids (dexamethasone) could significantly decrease mortality in cases with severe COVID-19, especially in patients receiving mechanical ventilation support, in comparison with standard care without corticosteroids. Recently, a systematic review analyzed data from 7 randomized controlled trials (RCTs) to evaluate the effectiveness of glucocorticoids in 1703 critically ill patients with COVID-19 [11]. The results demonstrated that administration of systemic corticosteroids was associated with lower 28-day all-cause mortality compared with usual care or placebo.

However, as far as we know in clinical practice, there are a variety of glucocorticoid agents, including dexamethasone, methylprednisolone, prednisolone, prednisone and hydrocortisone. It is still uncertain which agent is preferred. Some scholars suggest that corticosteroids in general are not expected to help as a class of drugs, but rather each steroid should be assessed individually, because different drugs can be associated with a different number of genes [12]. It is well established that the preferred glucocorticoid for the treatment of ARDS in ICU is methylprednisolone rather than dexamethasone. Since the outbreak of epidemic, there have been many studies on methylprednisolone treatment in patients with COVID-19 [13–45], but the results are inconsistent.

The purpose of this study was to conduct a meta-analysis to evaluate the efficacy and safety of methylprednisolone in the treatment of patients with COVID-19 compared with no corticosteroids therapy.

2. Materials and methods

This study was performed in accordance with the Statement of Preferred Reporting Items for Systematic Reviews and Meta-Analyses [46]. Two authors independently conducted literature search, study selection, data extraction and quality assessment. Any disagreements were resolved by discussion.

2.1. Search strategy

The literature search utilized several electronic databases to ensure all available published literature was included in this systematic review. The following electronic databases were searched: PubMed, Cochrane Central Register of Controlled Trials and Web of Science. The following search strategy was used in PubMed and changes depending on the rules of each database: (COVID-19) AND (((corticosteroids) OR ("methylprednisolone"[Mesh])) OR (methylprednisolone)). Because, to our knowledge, the first case of COVID-19 was discovered at the end of 2019, the search was started in 2019. The last search was performed on 25 August 2021. English was set as a language restriction during literature searches. The reference list of retrieved papers was further screened for additional publications.

2.2. Study selection

All published RCTs and non-RCTs comparing methylprednisolone with no glucocorticoids treatment (also named control) for patients with COVID-19 were eligible. When two studies reported on a group of patients at the same institution with an overlapping time period, the article with the longest follow-up period was included to avoid data duplication. Reviews, case reports, non-comparative studies, and comparative studies which presented insufficient data were excluded. Studies comparing methylprednisolone with other corticosteroids therapy for COVID-19 patients were excluded. If methylprednisolone group involved other agents that were not used in control group, the corresponding studies were also excluded.

2.3. Data extraction and quality assessment

The following information was recorded from each eligible study: the first author's name; study design; location; study interval; population characteristics; prescription of methylprednisolone; primary outcome and other study features and data needed for quality assessment. Population characteristics include sample size and mean age of both arms, as well as the disease status of the subjects recruited in each study. For dichotomous variables, the number of events and the total number of participants of each group were extracted. Mean and standard deviation were used for extracting continuous variables. If studies reported continuous data as median and/or range values, the standard deviation was calculated using statistical algorithms by Hozo et al [47]. The quality evaluation of RCT was based on the criteria set by Cochrane Collaboration, which classifies the risk of bias of each trial as low risk, high risk or unclear risk [48]. For non-RCTs, methodological index for non-RCT studies (MINORS) was used for quality assessment [49].

2.4. Primary and secondary outcomes

The primary outcome of our meta-analysis was short-term mortality, which involves in-hospital, 21-day and 28-day mortality corresponding to the definition used in each study. The secondary outcomes were the incidences of ICU admission and mechanical ventilation, 28-day ventilator-free days, hospital stay, duration of viral shedding, and secondary infections rate.

2.5. Statistical analysis

Review Manager, version 5.1.0 was used to perform statistical analysis. As previously described [50], for dichotomous data, the risk ratio (RR) for each study was aggregated to obtain a pooled RR with a corresponding 95% confidence interval (CI). Analysis of continuous variables was done by calculating the mean difference (MD) with the corresponding 95% CI. All results in our analysis were evaluated for clinical and statistical heterogeneity. Given that clinical heterogeneity was unavoidable, subgroup analysis was performed on the basis of different types of study design, the dosage and course of methylprednisolone treatment, and the severity of disease. The low-dose methylprednisolone was defined as ≤ 2 mg/kg/day, the high-dose was > 2 mg/kg/day, and the adult standard body weight was set at 60 kg. The treatment course of methylprednisolone was classified as ≤ 3 days, ≤ 7 days and > 7 days. The severity of patients was categorized as severe and non-severe due to the different definitions in each included study. Statistical heterogeneity between different studies was assessed by use of Cochran's Q test in which $p < 0.1$ is taken to indicate the presence of significant heterogeneity. If statistical heterogeneity was significant, the random effects model would be used and sensitivity analysis would be applied to assess the stability of the results; otherwise, the fixed-effect model would be chosen. Forest plot was generated to graphically assess the statistical heterogeneity by displaying effect estimates and 95 % CI for both individual studies and meta-analyses. Publication bias was evaluated by constructing a funnel plot with visual assessment of asymmetry. The Egger's regression was used to quantitatively test the publication bias (STATA 12.0). A p value<0.05 was considered statistically significant.

3. Results

3.1. Study selection

Initially, we identified 2746 records through the before-mentioned literature search strategy. Among them, 486 were removed as duplicates and 2180 were excluded after screening titles and abstracts. Then, 80 full-text articles were retrieved for detailed evaluation. After reviewing, 47 articles were removed for the following reasons: intervention group involved other agents (n = 16), non-comparative studies (n = 13), data cannot be extracted (n = 11), comparison between different glucocorticoids (n = 4), and duplicate data (n = 3). Finally, 5

RCTs [14,16,26,36,37] and 28 non-RCTs [13,15,17–25,27–35,38–45] met the criteria for inclusion in the meta-analysis. A flow diagram that describes the search process is shown in Fig. 1. A total of 4411 patients with COVID-19 were analyzed, of which 2285 (51.8%) received methylprednisolone and 2126 (48.2%) received no glucocorticoids treatment.

3.2. Study characteristics

The characteristics of the all included studies are summarized in Table 1. The number of single-center and multicenter studies was 23 and 10, respectively. Most studies were conducted in China (n = 16) [18,20,22,24,25,28,36–45], followed by the United States (n = 5) [17,27,30,31,33], Spain (n = 5) [14,15,19,32,35], Italy (n = 3) [21,29,34], the United Arab Emirates (n = 2) [21,29,34], Brazil (n = 1) [26] and Iran (n = 1) [16]. The study interval in each study ranged from 1 January 2020 to 31 July 2020. The mean age of the patients varied between 33.75 years and 85 years across the studies. More than half of the studies recruited patients who suffered from severe or critically ill COVID-19 pneumonia. The prescriptions of methylprednisolone were not consistent across the studies.

3.3. Quality assessment and publication bias

The methodological quality assessments of the RCTs and non-RCTs are briefly showed in Table 1, and summarized in Supplementary Fig. 1 and Supplementary Table 1. Of the 5 RCTs, 3 were classified as low risk of bias and 2 as high risk. Based on the MINORS scoring system for non-RCTs, 12 points for 4 articles, and the scores of other 24 studies ranged from 13 to 22 points. Overall, the included studies were of moderate quality. The funnel plot constructed for publication bias evaluation showed a slight asymmetry (Fig. 2). Nevertheless, the Egger's regression analysis demonstrated that the visual asymmetry was not significant (95% CI of intercept −2.44 to 0.27; $p = 0.11$) (Fig. 3).

3.4. Primary outcome

In our analysis, there were 29 studies [13–17,19,20,22–40,42,43,45]

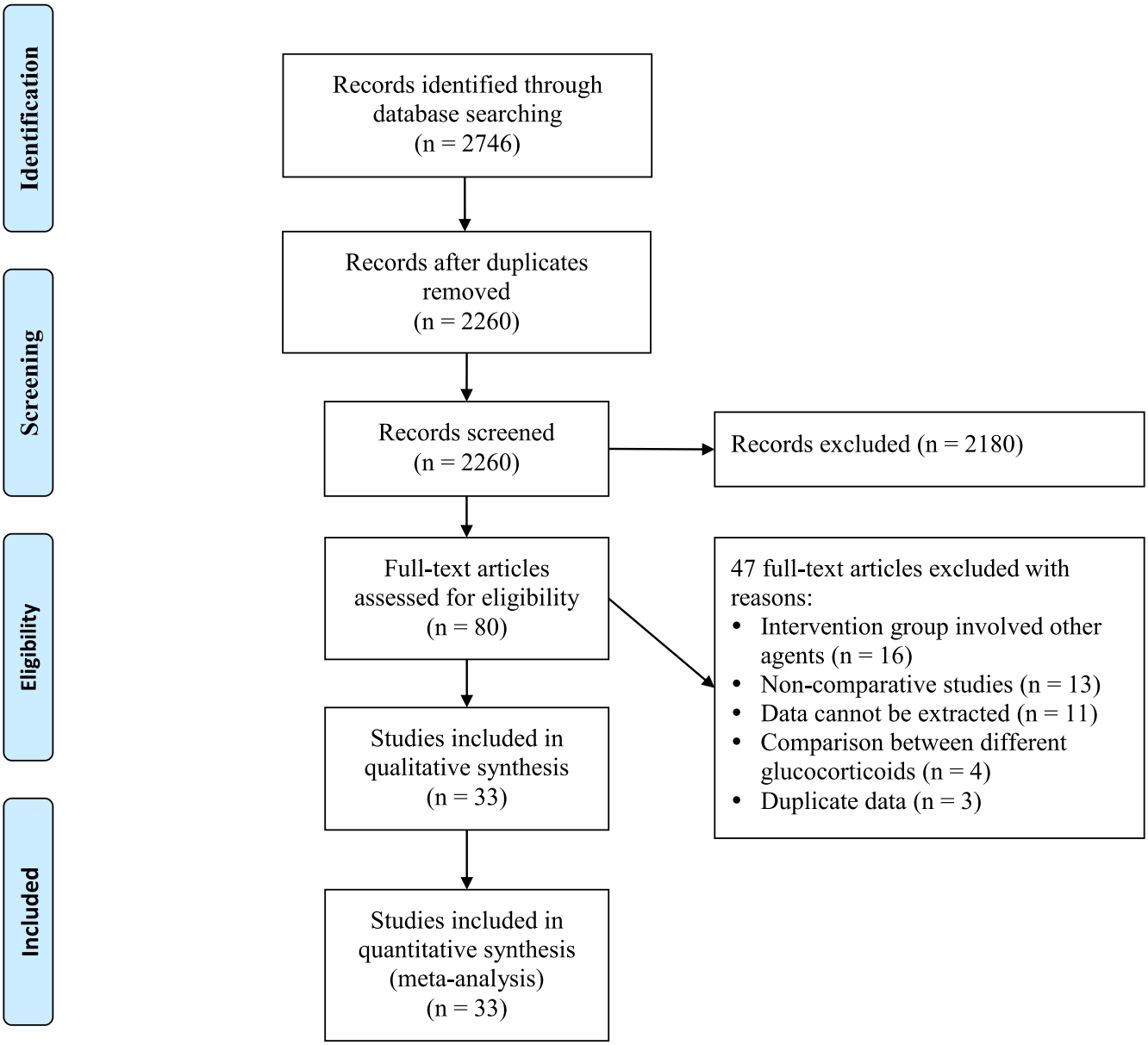

Fig. 1. Study flow diagram chart.

Table 1
The characteristics of the included studies.

Author	Study Design	Location	Study Interval	Sample Size		Mean Age		Subject	Methylprednisolone Prescription	Primary Outcome	Quality Score*
				MG	CG	MG	CG				
Badr M, et al [13]	Single-center, NRCT	Cleveland Clinic Abu Dhabi, United Arab Emirates	1 March 2020 to 29 May 2020	32	45	49	51	COVID-19 patients with ARDS	Median dose, 1 mg/kg/day for 5–7 days	28-day ventilator-free days	16
Corral-Gudino L, et al [14]	Multicenter, RCT	5 hospitals in Spain	April 2020 to July 2020	35	29	73	66	Patients with moderate to severe COVID-19	40 mg twice daily for 3 days followed by 20 mg twice daily for 3 days	A composite of death, ICU admission, or noninvasive ventilation	High risk
Cusacovich I, et al [15]	Multicenter, NRCT	3 teaching hospitals of Castilla y León, Spain	12 March 2020 to 20 May 2020	117	88	75	76	Patients with severe COVID-19	125–500 mg/day for 2–5 days	60-day mortality	17
Edalatifard M, et al [16]	Multicenter, RCT	Imam Khomeini Hospital and Khorshid Hospital, Iran	20 April 2020 to 20 June 2020	34	28	55.8	61.7	Patients with severe COVID-19	250 mg/day for 3 days	Time of clinical improvement and discharge from the hospital or death	Low risk
Fadel R, et al [17]	Multicenter, NRCT	Multicenter health system in Michigan, USA	12 March 2020 to 27 March 2020	132	81	61	64	COVID-19 patients requiring supplemental oxygen or mechanical ventilation	0.5–1 mg/kg/day for 3–7 days.	ICU admission, mechanical ventilation, or in-hospital all-cause mortality.	12
Fang X, et al [18]	Single-center, NRCT	Anhui Provincial Hospital, China	22 January 2020 to 1 March 2020	25	53	General arm: 40.2 Severe arm: 60.6	39.9 54.3	Patients with general or severe COVID-19	General arm: 38 mg/day for 7 days Severe arm: 40 mg/day for 4.5 days	Virus clearance time	16
Fernández-Cruz A, et al [19]	Single-center, NRCT	Hospital Puerta de Hierro-Majadahonda, Spain	During March of 2020	396	67	65.4	68.1	Patients with COVID-19	Low dose:1 mg/kg/day for 3–5 days Pulses: <250 mg/day (20.1%), 250 mg/day (62.5%), and 500 mg/day (17.1%) for 3 pulses.	In-hospital mortality	16
Fu H, et al [20]	Single-center, NRCT	The Third People's Hospital of Kunming, China	26 January 2020 to 2 March 2020	13	20	NA		Patients with mild COVID-19	1 mg/kg/day for 3 days	NA	14
Giacobbe DR, et al [21]	Single-center, NRCT	Ospedale Policlinico San Martino-IRCCS, Italy	20 February 2020 to 10 April 2020	24	54	NA		Critically ill patients with COVID-19	1 mg/kg once daily	NA	16
Gong Y, et al [22]	Single-center, NRCT	Yi Chang Central People's Hospital, China	30 January 2020 to 20 February 2020	18	16	38.22	33.75	COVID-19 patients under 50 years old	1–2 mg/kg/day, gradually halved every 3 days, for 5–10 days	NA	14
Hamed DM, et al [23]	Single-center, NRCT	Rashid Hospital, United Arab Emirates	June 2020	23	27	45.04	47.26	Patients with severe COVID-19	40 mg twice daily for 7 days	All-cause mortality, ICU admission, ICU and hospital stay, and days on ventilators	12
Hu Z, et al [24]	Single-center, NRCT	Second Hospital of Nanjing, China	20 January 2020 to 16 February 2020	28	44	53	38	Patients with non-severe COVID-19	40 mg/day within 1 week	Progression to severe illness	15
Huang R, et al [25]	Multicenter, NRCT	10 hospitals of Jiangsu Province, China	18 January 2020 to 26 February 2020	89	220	48	41	Patients with COVID-19	40–160 mg/day	Virus clearance time	13
Jeronimo CMP, et al [26]	Single-center, RCT	A tertiary care facility in Manaus, Brazil	18 April 2020 to 16 June 2020	194	199	54	57	Patients with suspected COVID-19	0.5 mg/kg, twice daily for 5 days	28-day mortality	Low risk
Ko JJ, et al [27]	Single-center, NRCT	A public teaching hospital in urban Los Angeles, USA	1 March 2020 to 31 July 2020	104	75	56.2	60.5	Patients with COVID-19 admitted to ICU for respiratory failure	1 mg/kg/day for ⩾3 days	All-cause mortality within 50 days of initial treatment	17

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Table 1 (*continued*)

Author	Study Design	Location	Study Interval	Sample Size		Mean Age		Subject	Methylprednisolone Prescription	Primary Outcome	Quality Score*
				MG	CG	MG	CG				
Liu J, et al [28]	Single-center, NRCT	The Fifth Affiliated Hospital of Sun Yat-sen University, China	22 January 2020 to 2 March 2020	22	79	NA		Patients with COVID-19	2–8 mg/kg/day, maximum 500 mg/day	NA	15
Mikulska M, et al [29]	Single-center, NRCT	San Martino University Hospital, Italy	NA	45	66	67.5	68.4	Patients with COVID-19	1 mg/kg/day for 5 days, then 0.5 mg/kg/day for 5 days	Failure-free survival	14
Nelson BC, et al [30]	Multicenter, NRCT	A quaternary care medical center in New York, USA	1 March 2020 to 12 April 2020	42	42	60	62	Patients with COVID-19 requiring mechanical ventilation	1 mg/kg/day with a max dose of 80 mg for 5 days	28-day ventilator-free days	17
Papamanoli A, et al [31]	Single-center, NRCT	Stony Brook University Hospital, USA	1 March 2020 to 15 April 2020	153	294	62	61	Patients with severe COVID-19	median dose, 160 mg/day for 5 days	28-day death or mechanical ventilation	18
Piniella-Ruiz E, et al [32]	Single-center, NRCT	Infanta Leonor-Virgen de la Torre University Hospital, Spain	1 March 2020 to 31 May 2020	88	55	85	85	Critically ill patients with COVID-19	125–250 mg/day for 1–3 days, followed by 0.5–1 mg/kg for additional 5 days	In-hospital mortality	13
Saggi SJ, et al [33]	Single-center, NRCT	State University of New York Downstate Medical Centre, USA	1 March 2020 to 30 April 2020	37	38	73	72.5	COVID-19 patients with AKI and ARDS	1–2 mg/kg/day for ⩾3 days	21-day mortality	16
Salton F, et al [34]	Multicenter, NRCT	14 Italian respiratory high-dependency units	27 February 2020 to 24 April 2020	83	90	64.4	67.1	Patients with severe COVID-19	A loading dose of 80 mg + 80 mg/d for ⩾8 days + 16 mg po or 20 mg iv twice daily until CRP < 20% of normal range or PaO_2:FiO_2 > 400 (alternative SpO_2 ⩾95% on room air)	28-day need for ICU referral, intubation, or death	22
Sanz Herrero F, et al [35]	Single-center, NRCT	Consorci Hospital General Universitari, Spain	NA	56	16	67	68.9	Patients with COVID-19	250 mg on day 1 followed by 40 mg every 12 h for 4 more days	In-hospital all-cause mortality	12
Steroids-SARI [36]	Multicenter, RCT	4 hospitals in China	26 January 2020 to 13 April 2020	24	23	67	62	Critically ill patients with COVID-19	40 mg every 12 h for 5 days	Lower lung injury score at day 7 and day 14	High risk
Tang X, et al [37]	Multicenter, RCT	7 tertiary hospitals in Beijing and Hubei province of China	19 February 2020 to 31 March 2020	43	43	57	55	Patients with COVID-19	1 mg/kg/day for 7 days	14-day clinical deterioration rate	Low risk
Wang F, et al [38]	Single-center, NRCT	Tongji Hospital in Wuhan, China	January 2020 to March 2020	55	53	NA		Patients with severe COVID-19	40–80 mg/day for 3–5 days	NA	13
Wang Y, et al [39]	Single-center, NRCT	Union Hospital of Huazhong University of Science and Technology, China	20 January 2020 to 25 February 2020	26	20	54	53	Patients with severe COVID-19	1–2 mg/kg/day for 5–7 days	NA	11
Wu C, et al [40]	Single-center, NRCT	Jin Yin-tan Hospital, China	25 December 2019 to 26 January 2020	62	139	NA		Patients with COVID-19	NA	The development of ARDS and death	15
Xia Q, et al [41]	Single-center, NRCT	The First Affiliated Hospital, Zhejiang University School of Medicine, China	22 January 2020 to 29 February 2020	56	18	NA		Patients with COVID-19	0.75–1.5 mg/kg/day	NA	14
Yang R, et al [42]	Single-center, NRCT	Zhongnan Hospital of Wuhan	1 January 2020 to 7 March 2020	140	35	NA		Patients with severe COVID-19	50–80 mg/day	NA	12

(*continued on next page*)

Table 1 (*continued*)

Author	Study Design	Location	Study Interval	Sample Size MG	Sample Size CG	Mean Age MG	Mean Age CG	Subject	Methylprednisolone Prescription	Primary Outcome	Quality Score*
		University, China									
You X,et al [43]	Single-center, NRCT	Yichang Third People's Hospital, China	1 February 2020 to 31 March 2020	44	44	54.25	56.82	Patients with COVID-19	40 mg once or twice daily for 7 days	Hospital mortality	18
Yuan M, et al [44]	Single-center, NRCT	Central Hospital of Wuhan, China	20 January 2020 to 25 February 2020	35	35	48.1	47.7	Patients with non-severe COVID-19	Median dose, 43.5 mg/day	NA	15
Zha L, et al [45]	Multicenter, NRCT	The Second People's Hospital of Wuhu and Yijishan Hospital, China	24 January 2020 to 24 February 2020	11	20	53	37	Patients with COVID-19	40 mg once or twice daily for 5 days	Virus clearance time	14

MG = methylprednisolone group, CG = control group, NRCT = non-randomized controlled trial, NA = not available, CRP = C-reactive protein
* Methodological index for non-randomized studies (MINORS) was used for quality assessment of non-RCT, risk of bias was used for RCT

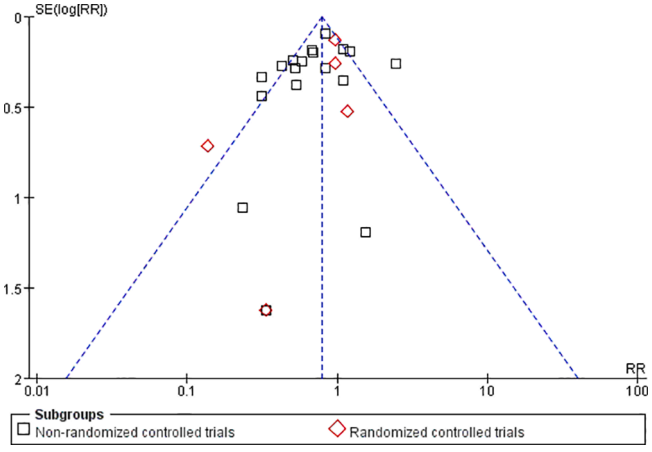

Fig. 2. Funnel plot for publication bias evaluation.

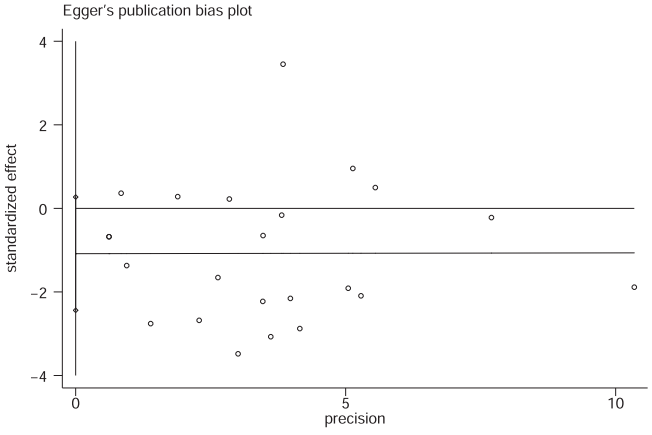

Fig. 3. Egger's regression analysis for publication bias.

providing the information regarding short-term mortality. After pooling data, short-term mortality was seen in 468 (21.8 %) of 2146 patients receiving methylprednisolone and 496 (24.8 %) of 1996 receiving no glucocorticoids treatment. Because statistical heterogeneity across studies was significant ($p < 0.001$), random effects model was used to synthetize the data. The meta-analytic pooling demonstrated a significant reduction of short-term mortality in the methylprednisolone group (RR 0.73; 95% CI 0.60–0.89; $p = 0.002$) (Fig. 4).

3.5. Secondary outcomes

Data of ICU admission were provided by 8 included studies [14,15,17,23,31,34,35,37]. As a whole, 27.2% (175/642) patients were transferred to ICU in methylprednisolone group comparing to 36.7% (245/668) in control group. Fixed-effect model was employed for data synthesis due to the non-significant heterogeneity across studies ($p = 0.28$). Our meta-analysis showed that COVID-19 patients treated with methylprednisolone were less likely to be transferred to ICU than those who did not receive methylprednisolone (RR 0.77; 95% CI 0.66–0.91; $p = 0.001$) (Fig. 5).

Nine included studies [15,17,23,28,31,34,37,39,43] reported the number of patients requiring mechanical ventilation. Overall, the proportion of patients receiving mechanical ventilation in methylprednisolone group and control group were 17.9% (114/636) and 26.5% (205/773), respectively. Meta-analysis on fixed-effect model observed a significantly decreased incidence of mechanical ventilation in methylprednisolone group (RR 0.69; 95% CI 0.57–0.84; $p < 0.001$) (Fig. 6). There was no statistical heterogeneity across studies ($p = 0.18$).

Information about 28-day ventilator-free days was described in three studies [30,31,34]. Owing to no statistical heterogeneity among studies ($p = 0.43$), fixed-effect model was applied. When three studies were pooled in this analysis, the 28-day ventilator-free days was significantly increased in methylprednisolone group than control group by 2.8 days (95% CI 2.64–2.97; $p < 0.001$) (Fig. 7).

There were 15 studies [13,15–17,23–25,32,35,37,39,41,43–45] reporting the date with regard to hospital stay. Due to a significant heterogeneity across studies ($p < 0.001$), random effects model was used. In our meta-analysis, no significant difference in hospital stay between two groups was detected (MD −0.14; 95% CI −2.42–2.14; $p = 0.90$) (Fig. 8).

Duration of viral shedding was mentioned in 13 studies [18,20,22,24,25,28,34,35,37,41,43–45]. Meta-analysis on random effects model revealed that the virus clearance time of patients treated with methylprednisolone was significantly longer than that of patients treated with no glucocorticoids by 1.03 days (95% CI 0.25–1.82; $p = 0.01$) (Fig. 9). Heterogeneity across studies was statistically significant ($p < 0.001$).

There were 11 studies [13–17,21,28,30,37,39,44] in our analysis describing the data of secondary infections after both treatments. Overall, 15.5% (86/556) patients experienced secondary infections in methylprednisolone group comparing with 15.1% (80/530) in control group. On the basis of a non-significant heterogeneity among studies (p

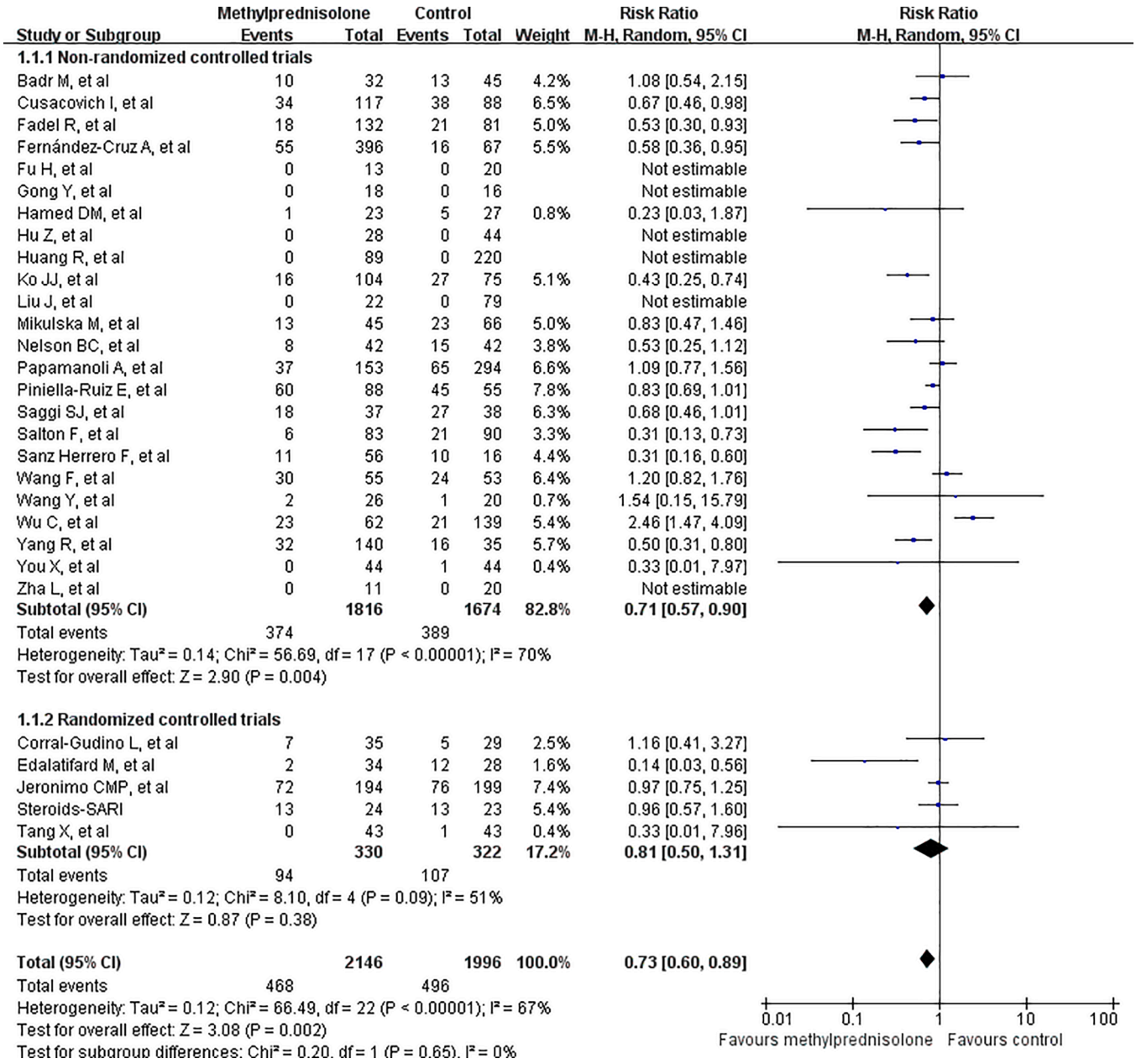

Fig. 4. Forest plot of the short-term mortality in meta-analysis and subgroup analyses of RCTs and Non-RCTs.

= 0.15), fixed-effect model was chosen. The pooling results found that the difference between two groups in secondary infections was not significant (RR 1.04; 95% CI 0.82–1.32; $p = 0.73$) (Fig. 10).

3.6. Subgroup analyses

In the subgroup analysis of non-RCTs, the application of methylprednisolone was associated with a significantly reduced mortality, which was not found in the subgroup analysis of RCTs (Fig. 4). In contrast to high-dose methylprednisolone, low-dose methylprednisolone could significantly lower the risks of admission to ICU (Fig. 5) and mechanical ventilation (Fig. 6), but prolong the duration of viral shedding (Supplementary Fig. 2). Both doses of methylprednisolone could significantly decrease mortality (Supplementary Fig. 3) and increase the 28-day ventilator-free days (Fig. 7), while had no effect on the length of hospital stay (Supplementary Fig. 4) and the incidence of secondary infections (Fig. 10). Methylprednisolone treatment for ≤ 7 days, rather than ≤ 3 days or > 7 days, was associated with a significantly reduced mortality (Supplementary Fig. 5). When performing subgroup analysis for severe COVID-19 patients, methylprednisolone treatment was related with significantly lower mortality (Supplementary Fig. 6) and shorter hospital stay (Supplementary Fig. 7), without increasing the duration of viral shedding (Supplementary Fig. 8) and the risk of secondary infections (Supplementary Fig. 9), as compared to no glucocorticoids treatment. For non-severe patients, methylprednisolone treatment could not shorten the hospital stay (Supplementary Fig. 10), but could prolong the duration of viral shedding (Supplementary Fig. 11).

3.7. Sensitivity analyses

We performed sensitivity analyses on three outcomes including mortality, hospital stay and duration of viral shedding due to the significantly statistical heterogeneity among studies. However, sensitivity analyses did not change the significance of statistical heterogeneity, and had no effect on the results of meta-analysis, suggesting the

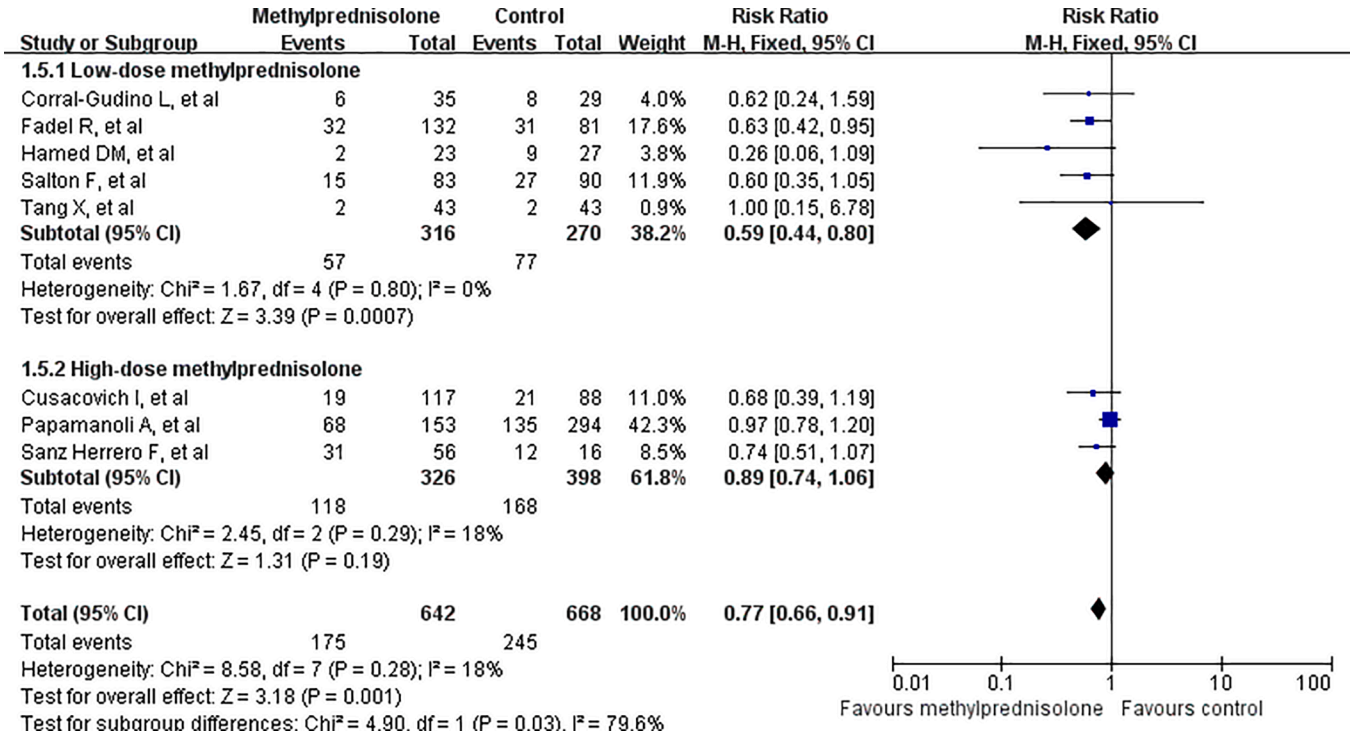

Fig. 5. Forest plot of the ICU admission rate in meta-analysis and subgroup analyses of low- and high-doses of methylprednisolone.

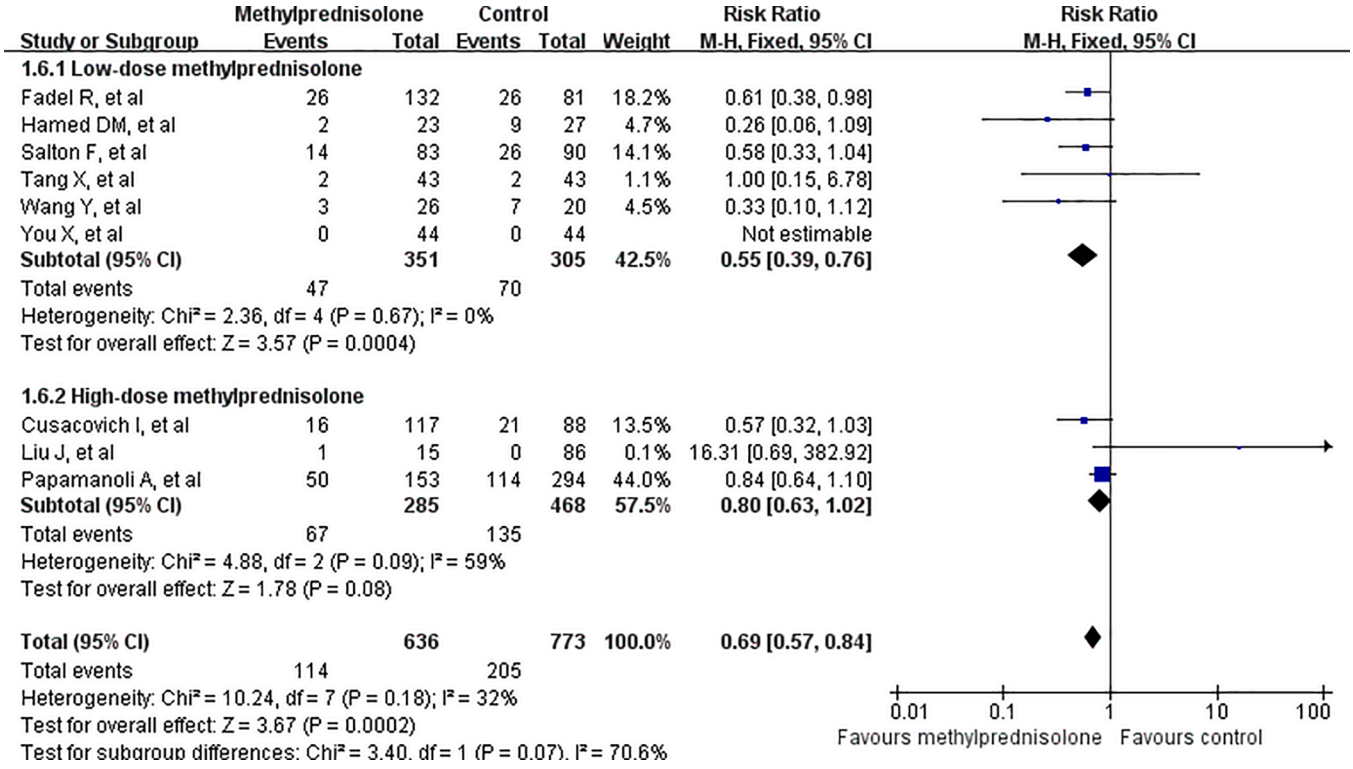

Fig. 6. Forest plot of the need for mechanical ventilation in meta-analysis and subgroup analyses of low- and high-doses of methylprednisolone.

stability of these outcomes.

4. Discussion

Our meta-analysis including 33 studies showed that compared with no glucocorticoids treatment, methylprednisolone in the treatment of COVID-19 patients was related with reduced short-term mortality, less need for ICU admission and mechanical ventilation, increased 28-day ventilator-free days, without increasing the risk of secondary infections, but could slightly prolong the duration of viral shedding. Subgroup analyses revealed that low-dose methylprednisolone treatment for $\leq$ 7 days in severe COVID-19 patients was associated with

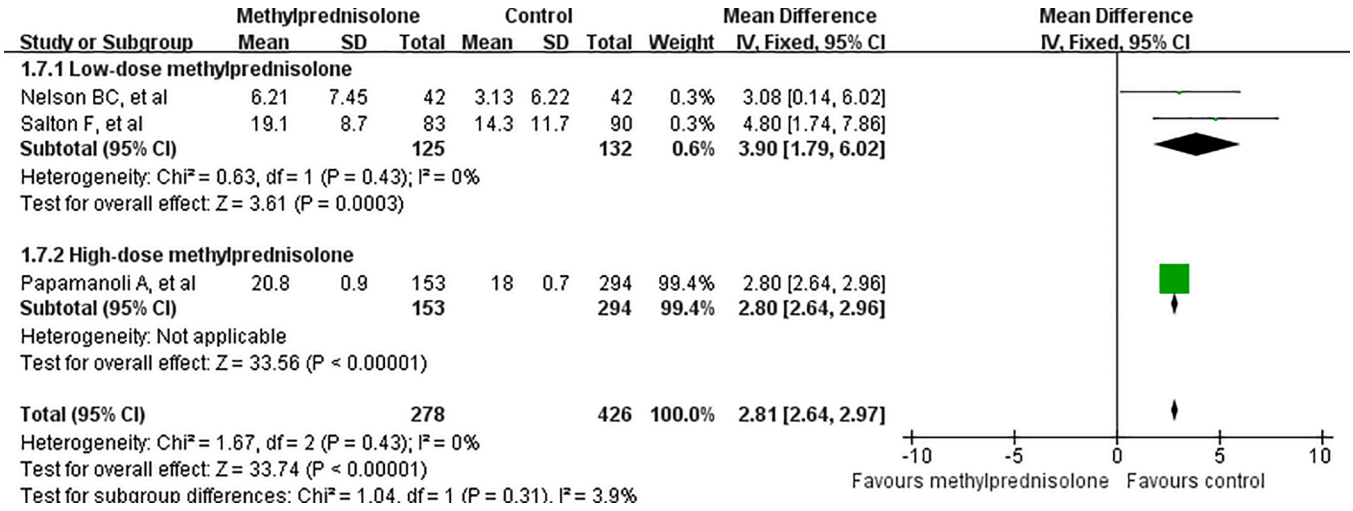

Fig. 7. Forest plot of the 28-day ventilator-free days in meta-analysis and subgroup analyses of low- and high-doses of methylprednisolone.

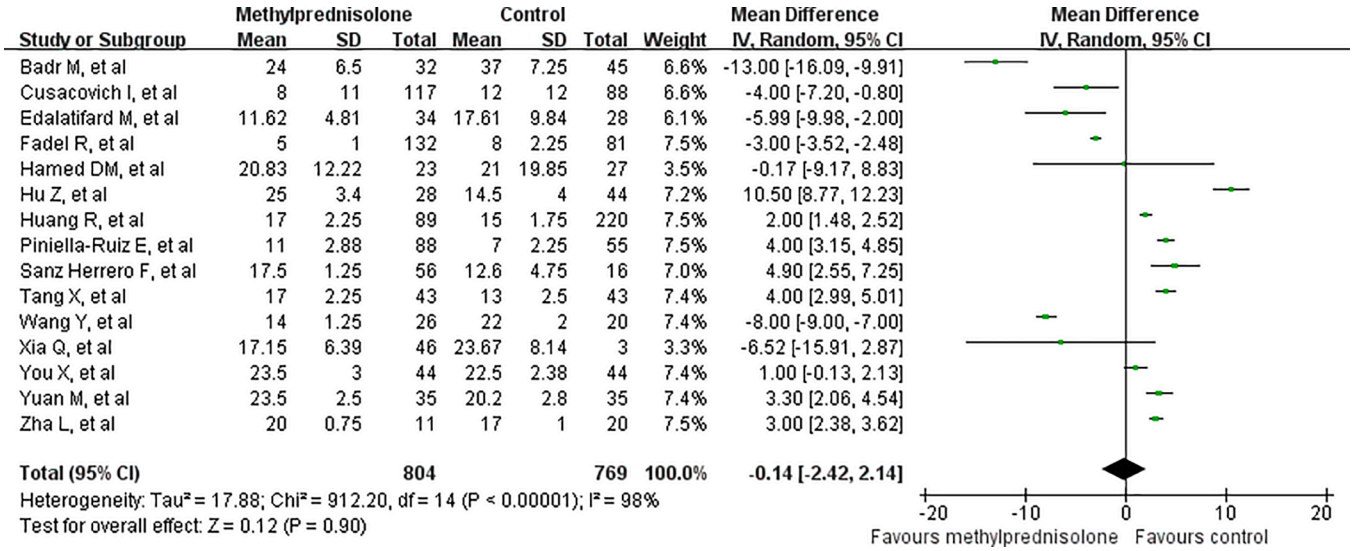

Fig. 8. Forest plot of the hospital stay in meta-analysis.

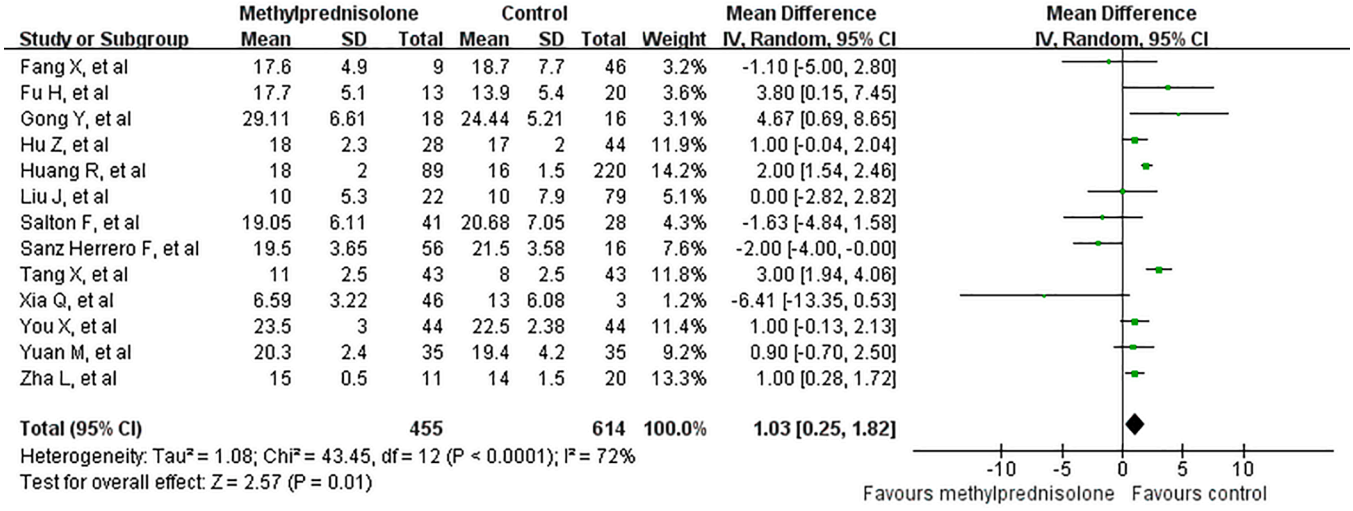

Fig. 9. Forest plot of the duration of viral shedding in meta-analysis.

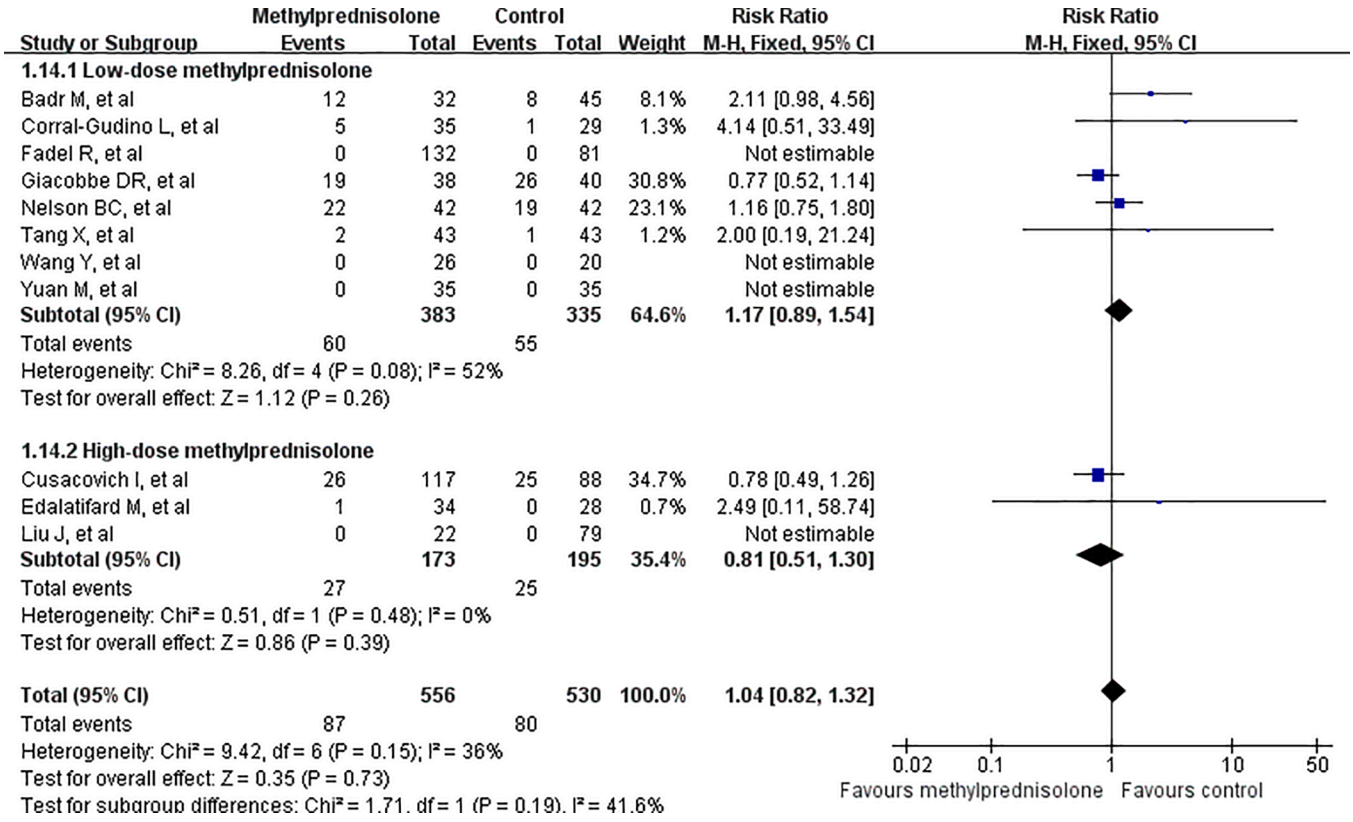

Fig. 10. Forest plot of the secondary infections in meta-analysis and subgroup analyses of low- and high-doses of methylprednisolone.

relatively better clinical outcomes, without increasing the duration of viral shedding, in comparison with standard care without corticosteroids.

Different from the negative therapeutic effect in epidemic of Middle East respiratory syndrome [51], glucocorticoids can play a positive role in the treatment of current COVID-19 pneumonia. The RECOVERY trial [9] cited in the guidelines of WHO just proved the advantages of glucocorticoids in the treatment of severe COVID-19, but the drug used in this study was dexamethasone. However, it was reported that the response of methylprednisolone was higher than that of dexamethasone in vitro [52]. A study by Draghici et al [12] described an initial characterization of the main pro-inflammatory pathways induced by SARS-Cov-2 infection on human lung epithelial cells, and identified methylprednisolone as the most effective agent that targets critical components of the inflammatory pathway responsible for ARDS. Moreover, the results of their study suggested that methylprednisolone would revert the largest number of the gene perturbed by COVID-19, followed by dexamethasone. Furthermore, they demonstrated the efficacy of methylprednisolone in a clinical trial in which 30-day all-cause mortality occurred at a significantly lower rate in the methylprednisolone group compared to conventional therapy group. Fernández-Cruz et al [19] performed a retrospective cohort study and found that the survival of patients with SARS-CoV-2 pneumonia was higher in cases treated with methylprednisolone than in those not treated. Hamed et al [23] reported in their randomized study that patients with severe COVID-19 pneumonia administrated with methylprednisolone were associated with reduced 45-day mortality and lower ICU admission and ventilation rates compared with those who received usual care. Our meta-analysis also showed these advantages of methylprednisolone treatment in patients with COVID-19 pneumonia, especially in severe cases.

Theoretically, glucocorticoids can exert its anti-inflammatory effect through genetic and non-genetic pathways [53]. It can be observed that the plasma inflammatory indicators of COVID-19 patients, such as CRP and IL-6, decreased significantly after methylprednisolone treatment [16]. The reduction of inflammatory response may lead to the rapid improvement of lung injury, easier relief of symptoms and lower risk of requiring ICU admission and mechanical ventilation. This inference is supported by the results of our study, and we believe that the mortality benefit of methylprednisolone observed in this study is a comprehensive reflection of the common improvement of these clinical outcomes.

The optimal prescription of methylprednisolone in the treatment of patients with COVID-19 is inconclusive. Edalatifard et al [16] recruited 68 patients with severe COVID-19 to randomly receive methylprednisolone pulse (250 mg/day for 3 days) or standard care. They observed a significantly higher percentage of improved patients and lower hospital mortality in methylprednisolone pulse group. Nevertheless, the retrospective cohort study conducted by Fernández-Cruz et al [19] declared that hospital mortality was not different between low-dose (1 mg/kg/day) methylprednisolone and pulse treatment. We are aware that the dose of methylprednisolone recommended in the seventh edition of diagnosis and treatment plan for COVID-19 formulated by Chinese National Health Commission [54] was 1–2 mg/kg/day, yet in the eighth edition [55], the recommended dose was changed to 0.5–1 mg/kg/day. We speculate that the reason for adjusting the dose may be due to safety considerations. For example, higher dose of glucocorticoid possibly increases complications and prolongs the virus clearance time. The subgroup analyses of our study showed that low- and high-doses of methylprednisolone had considerable effects on mortality benefit and the occurrence of secondary infections. However, low-dose methylprednisolone (less drug costs) could reduce the risks of ICU admission and mechanical ventilation, although it may increase the virus clearance time by 1 day. This may mean that the savings in drug costs can help patients avoid suffering from mechanical ventilation and additional hospitalization costs due to ICU stay. We believe that the benefits of these clinical outcomes far outweigh the risk of slightly prolonging virus clearance time. Furthermore, our study found that methylprednisolone treatment in severe patients with COVID-19 did not delay the time of virus clearance. With regard to the duration of glucocorticoids

administration, WHO recommends 7–10 days [10], but it refers to dexamethasone rather than methylprednisolone. Our study showed that methylprednisolone therapy within 1 week could benefit patients with COVID-19, which is close to the treatment course (3–5 days) recommended by the guideline from China.

There are several published meta-analyses for glucocorticoids treatment in patients with COVID −19 [36,56–59]. However, the agents analyzed in these studies are not specific. We believe that this evaluation is preliminary but not accurate, because the number of genes affected by different glucocorticoid drugs is not identical, and the clinical effects may be diversified. In contrast, our meta-analysis focused on methylprednisolone, which is often used by clinicians to treat pulmonary inflammatory diseases, making our results closer to clinical practice. Additionally, in some studies included by previous systematic review [56,57], the intervention measure was not limited to methylprednisolone therapy, but also involved other glucocorticoid agents or combined with other treatments, such as tocilizumab, relative to control measure. Such results may overestimate the therapeutic effect of methylprednisolone. In order to reduce the impacts of confounding factors on the results, we only considered studies in which methylprednisolone was designed as the sole intervention agent were eligible for our meta-analysis. We noted a recently published meta-analysis that is similar to our study [60]. However, it included only 5 RCTs with a relatively small sample size and limited outcome (only all-cause mortality). The results made on this basis, which are different from our study, are unstable and inconclusive. By comparison, a total of 31 studies were reviewed in our analysis, with a larger sample size, a lower probability of false negative results and more interested outcomes evaluated, resulting in more reliable conclusions. Therefore, the above mentioned are the strengths of our study.

There are some limitations to the present meta-analysis which deserve to be mentioned. First, like all meta-analytic studies, there is an inevitable clinical heterogeneity across the included studies. Clinical factors such as the inconsistent inclusion criteria and methylprednisolone prescription of each study may have inordinately influenced the results of this systematic analysis. In view of this consideration, we performed subgroup analyses to minimize the interference of these factors. Second, since most of the included studies were carried out in Asia, when calculating the daily dose of methylprednisolone, the standard weight of 60 kg was set according to Asians, and this setting may not be suitable for non-Asians. Third, the majority of reviewed studies were conducted in the first half of 2020, even in the early stage of the epidemic. Due to incomplete knowledge of COVID −19 and lack of treatment experience, the research results of non-RCTs generated in different periods may be biased, which may eventually affect the results of this study. We point out that these results need to be interpreted with caution. With the clearer understanding of the disease and the standardization of treatment, high-quality clinical study is needed to further verify the superiority of methylprednisolone in the treatment of patients with COVID-19.

In conclusion, our meta-analysis suggest that compared with no glucocorticoids treatment, methylprednisolone in the treatment of COVID-19 patients is associated with reduced short-term mortality, less need for ICU admission and mechanical ventilation, increased 28-day ventilator-free days, without increasing the risk of secondary infections, but could slightly prolong the duration of viral shedding. Patients with severe COVID-19 are more likely to benefit from short-term low-dose methylprednisolone treatment (1–2 mg/kg/day for $\leq$ 7 days). Since most of the data in this meta-analysis are from non-RCTs, the findings in our study still need to be further verified by high-quality RCT.

Ethics approval.

Not applicable. The study does not require ethical approval, because the meta-analysis is based on published paper.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.steroids.2022.109022.

References

[1] V. Izda, M.A. Jeffries, A.H. Sawalha, COVID-19: A review of therapeutic strategies and vaccine candidates, Clin. Immunol. 222 (2021) 108634.
[2] World Health Organization. Weekly Operational Update on COVID-19- 6 September 2021. World Health Organization, 2021. https://www.who.int/publications/m/item/weekly-operational-update-on-covid-19—6-september-2021. Accessed 7 September 2021.
[3] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y.i. Hu, L.i. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L.i. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q.i. Jin, J. Wang, B. Cao, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 395 (10223) (2020) 497–506.
[4] W.J. Wiersinga, A. Rhodes, A.C. Cheng, S.J. Peacock, H.C. Prescott, Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review, JAMA. 324 (8) (2020) 782–793.
[5] Z. Xu, L. Shi, Y. Wang, J. Zhang, L. Huang, C. Zhang, S. Liu, P. Zhao, H. Liu, L. i. Zhu, Y. Tai, C. Bai, T. Gao, J. Song, P. Xia, J. Dong, J. Zhao, F.-S. Wang, Pathological findings of COVID-19 associated with acute respiratory distress syndrome, Lancet Respir Med. 8 (4) (2020) 420–422.
[6] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, Y. Qiu, J. Wang, Y. Liu, Y. Wei, J. Xia, T. Yu, X. Zhang, L.i. Zhang, Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet. 395 (10223) (2020) 507–513.
[7] X. Li, M. Geng, Y. Peng, L. Meng, S. Lu, Molecular immune pathogenesis and diagnosis of COVID-19, J Pharm Anal. 10 (2) (2020) 102–108.
[8] World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected: interim guidance, 28 January 2020. World Health Organization, 2020. https://apps.who.int/iris/handle/10665/330893. Accessed 9 March 2020.
[9] P. Horby, W.S. Lim, J.R. Emberson, M. Mafham, J.L. Bell, L. Linsell, et al. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report N Engl J Med. 2020 Accessed 9 September 2020 https://www.nejm.org/doi/10.1056/NEJMoa2021436.
[10] World Health Organization. Corticosteroids for COVID-19. World Health Organization, 2020. https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1. Accessed 9 November 2020.
[11] J.A.C. Sterne, S. Murthy, J.V. Diaz, A.S. Slutsky, J. Villar, D.C. Angus, D. Annane, L. C.P. Azevedo, O. Berwanger, A.B. Cavalcanti, P.-F. Dequin, B. Du, J. Emberson, D. Fisher, B. Giraudeau, A.C. Gordon, A. Granholm, C. Green, R. Haynes, N. Heming, J.P.T. Higgins, P. Horby, P. Jüni, M.J. Landray, A. Le Gouge, M. Leclerc, W.S. Lim, F.R. Machado, C. McArthur, F. Meziani, M.H. Møller, A. Perner, M.W. Petersen, J. Savovic, B. Tomazini, V.C. Veiga, S. Webb, J. C. Marshall, Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis, JAMA. 324 (13) (2020) 1330.
[12] S. Draghici, T.M. Nguyen, L.A. Sonna, C. Ziraldo, R. Vanciu, R. Fadel, et al., COVID-19: disease pathways and gene expression changes predict methylprednisolone can improve outcome in severe cases, Bioinformatics (2021).
[13] M. Badr, B. De Oliveira, K. Abdallah, A. Nadeem, Y. Varghese, D. Munde, S. Salam, B. Abduljawad, K. Saleh, H. Elkambergy, A. Taha, A. Bayrlee, A. Wahla, J. Dibu, R. Haque, F. Hamed, N. Rahman, J. Mallat, Effects of Methylprednisolone on Ventilator-Free Days in Mechanically Ventilated Patients with Acute Respiratory Distress Syndrome and COVID-19: A Retrospective Study, J. Clin. Med. 10 (4) (2021) 760.

[14] L. Corral-Gudino, A. Bahamonde, F. Arnaiz-Revillas, J. Gómez-Barquero, J. Abadía-Otero, C. García-Ibarbia, V. Mora, A. Cerezo-Hernández, J.L. Hernández, G. López-Muñíz, F. Hernández-Blanco, J.M. Cifrián, J.M. Olmos, M. Carrascosa, L. Nieto, M. C. Fariñas, J.A. Riancho, Methylprednisolone in adults hospitalized with COVID-19 pneumonia, Wien Klin Wochenschr. 133 (7-8) (2021) 303–311.
[15] I. Cusacovich, Á. Aparisi, M. Marcos, C. Ybarra-Falcón, C. Iglesias-Echevarria, M. Lopez-Veloso, J. Barraza-Vengoechea, C. Dueñas, S.A. Juarros Martínez, B. Rodríguez-Alonso, J.-Á. Martín-Oterino, M. Montero-Baladia, L. Moralejo, D. Andaluz-Ojeda, R. Gonzalez-Fuentes, T.S. Fröde, Corticosteroid Pulses for Hospitalized Patients with COVID-19: Effects on Mortality, Mediators Inflamm. 2021 (2021) 1–10.
[16] M. Edalatifard, M. Akhtari, M. Salehi, Z. Naderi, A. Jamshidi, S. Mostafaei, S. R. Najafizadeh, E. Farhadi, N. Jalili, M. Esfahani, B. Rahimi, H. Kazemzadeh, M. Mahmoodi Aliabadi, T. Ghazanfari, M. Sattarian, H. Ebrahimi Louyeh, S. R. Raeeskarami, S. Jamalimoghadamsiahkali, N. Khajavirad, M. Mahmoudi, A. Rostamian, Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial, Eur Respir J. 56 (6) (2020) 2002808.
[17] R. Fadel, A.R. Morrison, A. Vahia, Z.R. Smith, Z. Chaudhry, P. Bhargava, J. Miller, R.M. Kenney, G. Alangaden, M.S. Ramesh, V. Nauriyal, J. Lakshmikanth, A. Abdul Hamed, O. Nadeem, K. Griebe, J.M. Johnson, P. Bradley, J. Uduman, S. Hegab, J. Swiderek, A. Godfrey, J. Jennings, J. Gardner-Gray, A. Ackerman, J. Lezotte, J. Ruhala, L. Samuel, R.J. Tibbetts, I. Brar, J. McKinnon, G. Suleyman, N. Yared, E. Herc, J. Williams, O.A. Lanfranco, A. Chen, M. Zervos, E. Scher, Early Short-Course Corticosteroids in Hospitalized Patients With COVID-19, Clin Infect Dis. 71 (16) (2020) 2114–2120.
[18] X. Fang, Q. Mei, T. Yang, L. Li, Y. Wang, F. Tong, S. Geng, A. Pan, Low-dose corticosteroid therapy does not delay viral clearance in patients with COVID-19, J Infect. 81 (1) (2020) 147–178.
[19] A. Fernández-Cruz, B. Ruiz-Antorán, A. Muñoz-Gómez, A. Sancho-López, P. Mills-Sánchez, G.A. Centeno-Soto, S. Blanco-Alonso, L. Javaloyes-Garachana, A. Galán-Gómez, Á. Valencia-Alijo, J. Gómez-Irusta, C. Payares-Herrera, I. Morrás-Torre, E. Sánchez-Chica, L. Delgado-Téllez-de-Cepeda, A. Callejas-Díaz, A. Ramos-Martínez, E. Múñez-Rubio, C. Avendaño-Solá, A Retrospective Controlled Cohort Study of the Impact of Glucocorticoid Treatment in SARS-CoV-2 Infection Mortality, Antimicrob Agents Chemother. 64 (9) (2020).
[20] H.-Y. Fu, Y.u. Luo, J.-P. Gao, L. Wang, H.-J. Li, X. Li, L. Xue, X.-Q. Tang, H.-W. Li, Y.-R. Du, Effects of Short-Term Low-Dose Glucocorticoids for Patients with Mild COVID-19, Biomed Res Int. 2020 (2020) 1–10.
[21] D.R. Giacobbe, D. Battaglini, L. Ball, I. Brunetti, B. Bruzzone, G. Codda, F. Crea, A. De Maria, C. Dentone, A. Di Biagio, G. Icardi, L. Magnasco, A. Marchese, M. Mikulska, A. Orsi, N. Patroniti, C. Robba, A. Signori, L. Taramasso, A. Vena, P. Pelosi, M. Bassetti, Bloodstream infections in critically ill patients with COVID-19, Eur J Clin Invest. 50 (10) (2020), e13319.
[22] Y. Gong, L. Guan, Z. Jin, S. Chen, G. Xiang, B. Gao, Effects of methylprednisolone use on viral genomic nucleic acid negative conversion and CT imaging lesion absorption in COVID-19 patients under 50 years old, J Med Virol. 92 (11) (2020) 2551–2555.
[23] D.M. Hamed, K.M. Belhoul, N.A. Al Maazmi, F. Ghayoor, M. Moin, M. Al Suwaidi, M. Narainen, M. Makki, M. AbdulRahman, Intravenous methylprednisolone with or without tocilizumab in patients with severe COVID-19 pneumonia requiring oxygen support: A prospective comparison, J Infect Public Health. 14 (8) (2021) 985–989.
[24] Z. Hu, Y. Lv, C. Xu, W. Sun, W. Chen, Z. Peng, C. Chen, X. Cui, D. Jiao, C. Cheng, Y. Chi, H. Wei, C. Hu, Y.i. Zeng, X. Zhang, Y. Yi, Clinical Use of Short-Course and Low-Dose Corticosteroids in Patients With Non-severe COVID-19 During Pneumonia Progression, Front Public Health. 8 (2020).
[25] R. Huang, C. Zhu, Jian Wang, L. Xue, C. Li, X. Yan, S. Huang, B. Zhang, L.i. Zhu, T. Xu, F. Ming, Y. Zhao, J. Cheng, H. Shao, X.-a. Zhao, D. Sang, H. Zhao, X. Guan, X. Chen, Y. Chen, J. Wei, R. Issa, L. Liu, X. Yan, C. Wu, Corticosteroid therapy is associated with the delay of SARS-CoV-2 clearance in COVID-19 patients, Eur. J. Pharmacol. 889 (2020) 173556.
[26] C.M.P. Jeronimo, M.E.L. Farias, F.F.A. Val, V.S. Sampaio, M.A.A. Alexandre, G. C. Melo, et al., Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With Coronavirus Disease 2019 (COVID-19; Metcovid): A Randomized, Double-blind, Phase IIb, Placebo-controlled Trial, Clin. Infect. Dis. 72 (9) (2021) e373–e381.
[27] J.J. Ko, C. Wu, N. Mehta, N. Wald-Dickler, W. Yang, R. Qiao, A Comparison of Methylprednisolone and Dexamethasone in Intensive Care Patients With COVID-19, J Intensive Care Med. 36 (6) (2021) 673–680.
[28] J. Liu, X. Zheng, Y. Huang, H. Shan, J. Huang, Successful use of methylprednisolone for treating severe COVID-19, J Allergy Clin Immunol. 146 (2) (2020) 325–327.
[29] M. Mikulska, L.A. Nicolini, A. Signori, A. Di Biagio, C. Sepulcri, C. Russo, et al., Tocilizumab and steroid treatment in patients with COVID-19 pneumonia, Plos One. 15 (8) (2020), e237831.
[30] B.C. Nelson, J. Laracy, S. Shoucri, D. Dietz, J. Zucker, N. Patel, et al., Clinical Outcomes Associated With Methylprednisolone in Mechanically Ventilated Patients With COVID-19, Clin. Infect. Dis. 72 (9) (2021) e367–e372.
[31] A. Papamanoli, J. Yoo, P. Grewal, W. Predun, J. Hotelling, R. Jacob, et al., High-dose methylprednisolone in nonintubated patients with severe COVID-19 pneumonia, Eur. J. Clin. Invest. 51 (2) (2021).
[32] E. Piniella-Ruiz, M.T. Bellver-Alvarez, B. Mestre-Gomez, B. Escolano-Fernandez, S. Vinat-Prado, R. Cabezas-Olea, et al., Impact of Systemic Corticosteroids on Mortality in Older Adults With Critical COVID-19 Pneumonia, J. Gerontol. A Biol. Sci. Med. Sci. 76 (8) (2021) e127–e132.
[33] S.J. Saggi, S. Nath, R. Culas, S. Chittalae, A. Burza, M. Srinivasan et al. Early Experience With Methylprednisolone on SARS-CoV-2 Infection in the African American Population, a Retrospective Analysis Clinical Medicine Insights: Circulatory, Respirat. Pulmon. Med. 14 2020 2139719275.
[34] F. Salton, P. Confalonieri, G.U. Meduri, P. Santus, S. Harari, R. Scala, et al., Prolonged Low-Dose Methylprednisolone in Patients With Severe COVID-19 Pneumonia, Open Forum Infect Di. 7 (10) (2020).
[35] F. Sanz Herrero, F. Puchades Gimeno, P. Ortega García, C. Ferrer Gómez, M. D. Ocete Mochón, D.M. García, Methylprednisolone added to tocilizumab reduces mortality in SARS-CoV-2 pneumonia: An observational study, J. Intern. Med. 289 (2) (2021) 259–263.
[36] J. Sterne, S. Murthy, J.V. Diaz, A.S. Slutsky, J. Villar, D.C. Angus, et al., Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis, JAMA. 324 (13) (2020) 1330–1341.
[37] X. Tang, Y. Feng, J. Ni, J. Zhang, L. Liu, K. Hu, et al., Early Use of Corticosteroid May Prolong SARS-CoV-2 Shedding in Non-Intensive Care Unit Patients with COVID-19 Pneumonia: A Multicenter, Single-Blind, Randomized Control Trial, Respiration. (2021) 1–11.
[38] F. Wang, H. Hou, T. Wang, Y. Luo, G. Tang, S. Wu, et al., Establishing a model for predicting the outcome of COVID-19 based on combination of laboratory tests, Travel Med. Infect. Dis. 36 (2020), 101782.
[39] Y. Wang, W. Jiang, Q. He, C. Wang, B. Wang, P. Zhou, et al., A retrospective cohort study of methylprednisolone therapy in severe patients with COVID-19 pneumonia, Signal Transduct Target Ther. 5 (1) (2020) 57.
[40] C. Wu, X. Chen, Y. Cai, J. Xia, X. Zhou, S. Xu, et al., Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. Jama Intern Med. 180 (7) (2020) 934–943.
[41] Q. Xia, W. Dai, K. Xu, Q. Ni, Y. Li, J. Liu, et al., Clinical efficacy of methylprednisolone and the combined use of lopinavir/ritonavir with arbidol in treatment of coronavirus disease 2019, J Med Virol. 93 (7) (2021) 4446–4453.
[42] R. Yang, Y. Xiong, H. Ke, T. Chen, S. Gao, The role of methylprednisolone on preventing disease progression for hospitalized patients with severe COVID-19, Eur J Clin Invest. 50 (11) (2020).
[43] X. You, C. Wu, Y. Fu, Z. He, P. Huang, G. Chen, et al., The use of methylprednisolone in COVID-19 patients: A propensity score matched retrospective cohort study, Plos One. 15 (12) (2020), e244128.
[44] M. Yuan, X. Xu, D. Xia, Z. Tao, W. Yin, W. Tan, et al., Effects of Corticosteroid Treatment for Non-Severe COVID-19 Pneumonia: A Propensity Score-Based Analysis, Shock. 54 (5) (2020) 638–643.
[45] L. Zha, S. Li, L. Pan, B. Tefsen, Y. Li, N. French, et al., Corticosteroid treatment of patients with coronavirus disease 2019 (COVID-19), Med J Aust. 212 (9) (2020) 416–420.
[46] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, J Clin Epidemiol. 62 (10) (2009) 1006–1012.
[47] S.P. Hozo, B. Djulbegovic, I. Hozo, Estimating the mean and variance from the median, range, and the size of a sample, Bmc Med Res Methodol. 5 (2005) 13.
[48] J.P.T. Higgins, S. Green, Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011], The Cochrane Collaboration. 2011. http://handbook.cochrane. org. Accessed 5 May 2013.
[49] K. Slim, E. Nini, D. Forestier, F. Kwiatkowski, Y. Panis, J. Chipponi, Methodological index for non-randomized studies (minors): development and validation of a new instrument, Anz J Surg. 73 (9) (2003) 712–716.
[50] S. Hong, H. Wang, Y. Tian, L. Qiao, The roles of noninvasive mechanical ventilation with helmet in patients with acute respiratory failure: A systematic review and meta-analysis, Plos One. 16 (4) (2021), e250063.
[51] Y.M. Arabi, Y. Mandourah, F. Al-Hameed, A.A. Sindi, G.A. Almekhlafi, M. A. Hussein, et al., Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome, Am. J. Respir. Crit Care Med. 197 (6) (2018) 757–767.
[52] J.D. Croxtall, P.T. van Hal, Q. Choudhury, D.W. Gilroy, R.J. Flower, Different glucocorticoids vary in their genomic and non-genomic mechanism of action in A549 cells, Br J Pharmacol. 135 (2) (2002) 511–519.
[53] C.M. Spies, C. Strehl, M.C. van der Goes, J.W. Bijlsma, F. Buttgereit, Glucocorticoids, Best Pract Res Clin Rheumatol. 25 (6) (2011) 891–900.
[54] National Health Commission of the People's Republic of China. Diagnosis and treatment plan for new coronavirus pneumonia (trial version 7). National Health Commission of the People's Republic of China, 2020. http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml. Accessed 15 March 2020.
[55] National Health Commission of the People's Republic of China. Diagnosis and treatment plan for new coronavirus pneumonia (trial version 8). National Health Commission of the People's Republic of China, 2020. http://www.nhc.gov.cn/yzygj/s7653p/202008/0a7bdf12bd4b46e5bd28ca7f9a7f5e5a.shtml. Accessed 25 August 2020.
[56] E.J. Cano, F.X. Fonseca, C.C. Corsini, J.C. O'Horo, S.O. Abu, Y. Odeyemi, et al., Impact of Corticosteroids in Coronavirus Disease 2019 Outcomes: Systematic Review and Meta-analysis, Chest. 159 (3) (2021) 1019–1040.
[57] Y. Cui, Y. Sun, J. Sun, H. Liang, X. Ding, X. Sun, et al., Efficacy and Safety of Corticosteroid Use in Coronavirus Disease 2019 (COVID-19): A Systematic Review and Meta-Analysis, Infect Dis Ther. (2021).
[58] L. Pei, S. Zhang, L. Huang, X. Geng, L. Ma, W. Jiang, et al., Antiviral agents, glucocorticoids, antibiotics, and intravenous immunoglobulin in 1142 patients

with coronavirus disease 2019: a systematic review and meta-analysis, Pol Arch Intern Med. 130 (9) (2020) 726–733.
[59] J. van Paassen, J.S. Vos, E.M. Hoekstra, K. Neumann, P.C. Boot, S.M. Arbous, Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes, Crit Care. 24 (1) (2020) 696.
[60] S.S. Hasan, C.S. Kow, Z.U. Mustafa, H.A. Merchant, Does methylprednisolone reduce the mortality risk in hospitalized COVID-19 patients? A meta-analysis of randomized control trials, Expert. Rev. Respir. Med. 15 (8) (2021) 1049–1055.