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The effect of glucocorticoids on mortality in severe COVID-19 patients

Evidence from 13 studies involving 6612 cases

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Abstract

Background: Since the start of the coronavirus disease 2019 (COVID-19) pandemic, there is an urgent need for effective therapies for patients with COVID-19. In this study, we aimed to assess the therapeutic efficacy of glucocorticoids in severe COVID-19.

Methods: A systematic literature search was performed across PubMed, Web of Science, EMBASE, and the Cochrane Library (up to June 26, 2021). The literature investigated the outcomes of interest were mortality and invasive mechanical ventilation.

Results: The search identified 13 studies with 6612 confirmed severe COVID-19 patients. Our meta-analysis found that using glucocorticoids could significantly decrease COVID-19 mortality (hazard ratio (HR) 0.60, 95% confidence interval (CI) 0.45–0.79, $P < .001$), relative to non-use of glucocorticoids. Meanwhile, using glucocorticoids also could significantly decrease the risk of progression to invasive mechanical ventilation for severe COVID-19 patients (HR = 0.69, 95% CI 0.58–0.83, $P < .001$). Compared with using dexamethasone (HR = 0.68, 95% CI 0.50–0.92, $P = .012$), methylprednisolone use had a better therapeutic effect for reducing the mortality of patients (HR = 0.35, 95% CI 0.19–0.64, $P = .001$).

Conclusion: The result of this meta-analysis showed that using glucocorticoids could reduce mortality and risk of progression to invasive mechanical ventilation in severe COVID-19 patients.

Abbreviations: 2019-nCoV = 2019 novel coronavirus, ACE2 = angiotensin-converting enzyme 2, ARDS = acute respiratory distress syndrome, CI = confidence interval, COVID-19 = coronavirus disease 2019, HR = hazard ratio, NOS = Newcastle–Ottawa scale, PRISMA = preferred reporting items for systematic reviews and meta-analyses statement.

Keywords: coronavirus disease 2019, corticosteroids, COVID-19, glucocorticoids, meta-analysis, mortality

1. Introduction

Coronavirus disease 2019 (COVID-19) is a global public health emergency, mainly caused by the 2019 novel coronavirus (2019-nCoV). The spread of this epidemic has affected many countries, which creates unprecedented pressures and challenges in the healthcare system worldwide.[1,2] According to the clinical observation, the severity of COVID-19 disease has a wide range and varies from asymptomatic to critical severe.[3] The 2019-nCoV can cause respiratory and even systemic illness in patients. Critical complications can be caused when the infection of 2019-nCoV further developed.[4] The patients may require long-term intubation and mechanical ventilation. Thus, high efficacy drugs are urgently needed against COVID-19 and prevent the patients from progressing into a severe condition.

Glucocorticoids had beneficial effects in overcoming both hyperinflammation and acute respiratory distress syndrome (ARDS). In the early stage of inflammation, glucocorticoids could inhibit the immune response process included inflammatory cell exudation, leukocyte infiltration, and phagocytosis. In the late stage, glucocorticoids could inhibit the proliferation of fibroblasts and capillaries.[5] The pathophysiology feature of COVID-19 initially was a viral response, followed by the host immune-inflammatory response.[6] Severe COVID-19 was caused by excess pro-inflammatory cytokines which were difficult to control. The disease further deteriorated into immunopathological lung damage, which eventually led the COVID-19 patients to

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death.[7] Therefore, glucocorticoids could be used as an adjunct to treatment in COVID-19.

The efficacy of glucocorticoids in treating patients with severe COVID-19 remained controversial. The therapies of using glucocorticoids for COVID-19 were evaluated to be effective.[8–18] However, there were also studies that found that glucocorticoids could increase mortality in severe COVID-19 cases.[19,20] To figure out the therapy effect of using glucocorticoids for severe COVID-19, we conducted the following meta-analysis.

2. Methods

2.1. Search strategy

The literature was screened according to the guidelines of the preferred reporting items for systematic reviews and meta-analyses statement (PRISMA).[21] We conducted a comprehensive and systematic search in PubMed, Web of Science, EMBASE, and Cochrane library until June 26, 2021. In each database search, we used the keywords

"corticosteroid," "prednisone," "dexamethasone," "glucocorticoid," "prednisolone," "hydrocortisone," "methylprednisolone," "coronavirus," "nCoV-2019," "2019-nCoV," "COVID-19," and "SARS-CoV-2." The reference list of all included articles was scrutinized to identify additional eligible studies.

2.2. Inclusion/exclusion criteria

Inclusion criteria for studies were as follows: (1) Study population was patients with severe COVID-19. (2) Patients must be divided into the glucocorticoid group and the control group (without glucocorticoid). (3) Studies must report the therapeutic value of glucocorticoid in severe COVID-19 patients. (4) Provide adjusted hazard ratio (HR) with corresponding 95% confidence interval (CI).

Studies were excluded if they met any of the following characteristics: (1) Conference articles, animal studies, review articles, and other irrelevant clinical trials. (2) Trials were excluded if they did not report mortality. (3) Overlapping or duplicate reports. (4) The articles which included non-severe COVID-19 patients were excluded.

2.3. Data extraction and collection

Literature investigation and data extraction were performed independently by the Pairs of reviewers (GQY and ZHJ). A third reviewer (XQQ) had the task of deciding in uncertain situations. Two reviewers (GQY and ZHJ) screening included analyzing the titles and abstracts. "Overlaps" were discarded if they were not relevant to the issues addressed in the review. Finally, potentially eligible articles were submitted to a full-text analysis for verification by qualitative analysis.

2.4. Validity assessment

We assessed the quality of the studies obtained from the literature search by the Newcastle–Ottawa scale (NOS). Results of the validity assessment were discussed until an agreement is reached. A star was assigned if there was a quality feature and scores of 1 to 9 were distributed. Each asterisk denoted 1 point and the NOS score was the sum of the points. Studies with NOS scores of 1 to 3 were defined as poor quality, 4 to 6 intermediate, and 7 to 9 high.[22]

2.5. Ethics

In this study, ethical approval was not necessary because the included data were based on previously published articles, and no original clinical data were collected or utilized.

2.6. Data analysis

The random-effects model was used to calculate pooled HR and the associated 95% CI, and presented in the forms of forest plot figures. The heterogeneity among studies was evaluated using Cochran Q test and the I^2 statistic, whereby $I^2 > 50\%$, $P < .05$ indicated significant heterogeneity.[23] The random-effects model was used to minimize inter-study heterogeneity when there was significant heterogeneity between various studies. Else results were combined using fixed-effect model when $I^2 < 50\%$. All data analysis was performed using the statistical software package Stata version 15.

3. Results

3.1. Literature review

Initially, we identified 3958 potentially relevant pieces of literatures of which 1693 duplicates were removed. The remaining 2265 articles were screened title and abstract, of which 2217 were excluded. The remaining 48 articles were retrieved for more details by reviewing the full text. According to the inclusion criteria, we finally selected 13 studies [8–20] by reviewing the full text. Details of study selection and the flowchart of the literature search were depicted in Figure 1.

The essential characteristics of the included studies were presented in Table 1. All 13 included studies provided data describing the effect of glucocorticoids on severe COVID-19 mortality. Three studies[11,13,18] had calculated the HR of invasive mechanical ventilation in patients with severe COVID-19. Of the 13 studies, 2[10,12] were identified severe COVID-19-based Berlin definition criteria, 2[16,18] were identified according to the World Health Organization definition, 3[17,19,20] were identified by diagnosis and treatment of COVID-19 guidelines, and 6[8,9,11,13–15] were identified as the respiratory failure with the need of supplemental oxygen. The different types of glucocorticoids were used in the articles, which included methylprednisolone,[8–11] dexamethasone,[12–14] and multiple hormones.[15–20] Studies were conducted in Asia,[8,16,17,19,20] Europe,[9,10,13–15,18] and North America.[11,12]

3.2. Meta-analysis

The combined analysis of 13 studies covering 6612 patients described the relationship between using glucocorticoids and mortality of severe COVID-19 patients. The result showed that using glucocorticoids could significantly reduce severe COVID-19 mortality (HR = 0.60, 95% CI 0.45–0.79, $P < .001$, Fig. 2A). The risk of progression to invasive mechanical ventilation was reported in 3 studies.[11,13,18] The estimated effect of glucocorticoids for invasive mechanical ventilation (HR = 0.69, 95% CI 0.58–0.83, $P < .001$, Fig. 2B) also indicated clinical benefits.

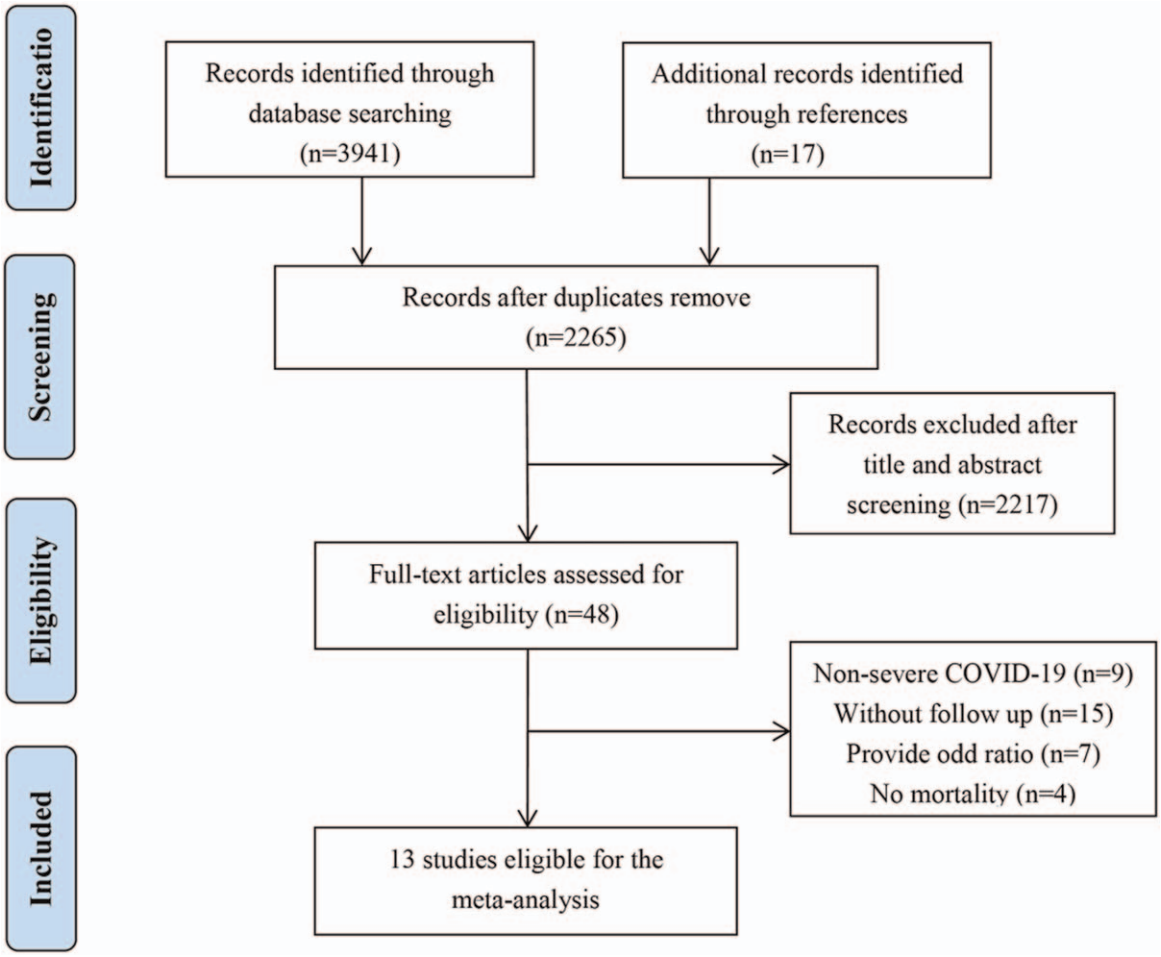

Figure 1. PRISMA flowchart describing literature search and article selection. PRISMA = preferred reporting items for systematic reviews and meta-analyses statement.

Table 1

Characteristics of included studies in the meta-analysis.

Author	Mean age	Total	Country	Study design	Follow-up (days)	Outcome	Glucocorticoids type	NOS score
Edalatifard et al[8]	58.5 ± 16.6	68	Iran	RCT	28	Mortality	Methylprednisolone	8
Bozzi et al[9]	63.0 (55.0–76.0)	120	Italy	Cohort study	28	Mortality	Methylprednisolone	8
Salton et al[10]	64.4 ± 10.7	173	Italy	Case-control	28	Mortality	Methylprednisolone	7
Papamanoli et al[11]	62.0 (53.0–72.0)	447	USA	Cohort study	28	Mortality, IMV	Methylprednisolone	8
Tomazini et al[12]	62.7 ± 13.1	299	USA	Case-control	28	Mortality	Dexamethasone	7
Group et al[13]	59.1 ± 11.4	1005	UK	RCT	28	Mortality, IMV	Dexamethasone	9
Hoertel et al[14]	NA	1192	France	Case-control	NA	Mortality	Dexamethasone	7
Piniella-Ruiz et al[15]	85.0 (82.0–89)	143	Spain	Cohort study	28	Mortality	Methylprednisolone, dexamethasone, hydrocortisone, and prednisone	8
Wu et al[16]	60.7 ± 14.1	384	China	Cohort study	60	Mortality	Methylprednisolone, dexamethasone, hydrocortisone, and prednisone	8
Chen et al[17]	65.0 (54.0–72.0)	371	China	Case-control	28	Mortality	Methylprednisolone, dexamethasone, hydrocortisone, and prednisone	7
Comparon et al[18]	67.7 (56.8–75.9)	120	France	Case-control	28	Mortality, IMV	Prednisone,dexamethasone	8
Wu et al[19]	68.0 (58.0–78.0)	1514	China	Cohort study	28	Mortality	Methylprednisolone hydrocortisone, and dexamethasone	7
Liu et al[20]	64.0 (54.0–73.0)	774	China	Cohort study	28	Mortality	Methylprednisolone, dexamethasone, hydrocortisone, and prednisone	8

IMV = invasive mechanical ventilation, NA = not available, NOS = Newcastle–Ottawa scale, RCT = randomized controlled trial.

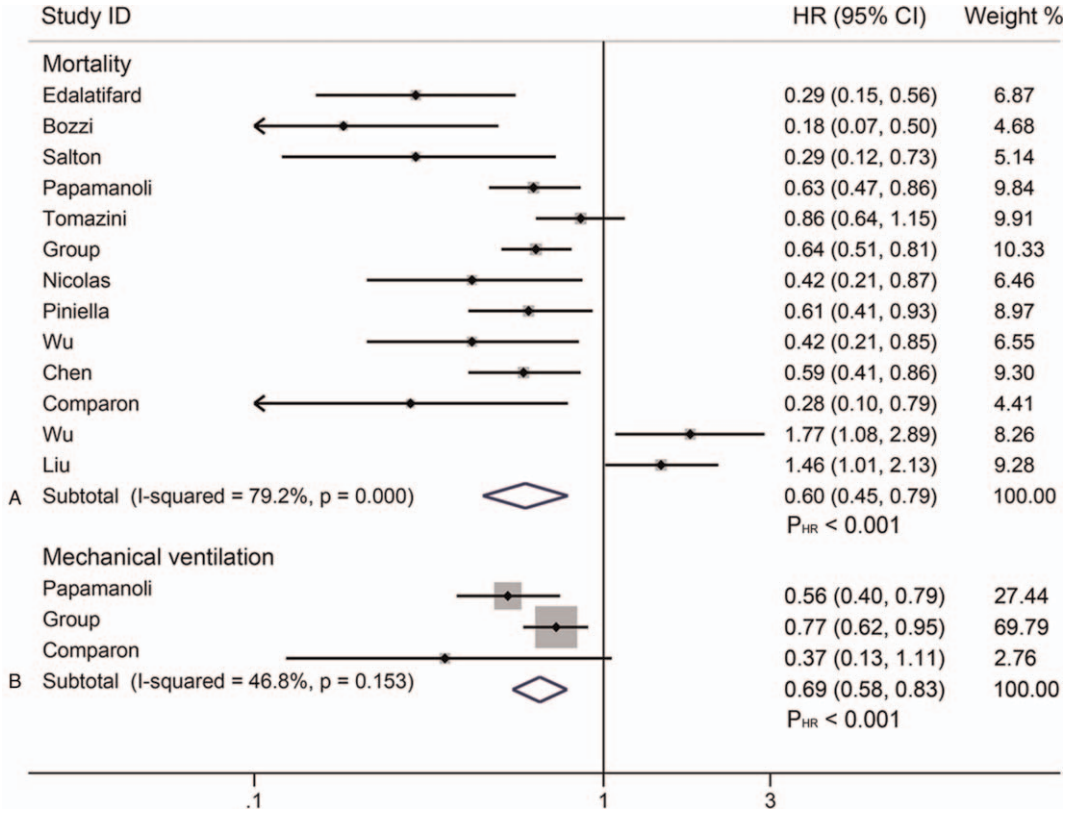

Figure 2. Forest plot of the therapeutic efficacy of glucocorticoids in the severe COVID-19 patients. (a) The efficacy of glucocorticoid therapy for reducing mortality. (b) The efficacy of glucocorticoid therapy for reducing the risk of progression to invasive mechanical ventilation. CI = confidence interval, COVID-19 = coronavirus disease 2019, HR = hazard ratio.

In the subgroup analysis, we grouped the studies by glucocorticoid type. The combined analysis of 4 studies covering 808 patients described the relationship between methylprednisolone and mortality.[8–11] The pooled outcome for the therapy effect of using methylprednisolone was found to be 0.35 (95% CI 0.19–0.64, $P = .001$, Fig. 3A). The combined analysis of 3 studies covering 2498 patients described the relationship between dexamethasone and mortality.[12–14] The result showed that

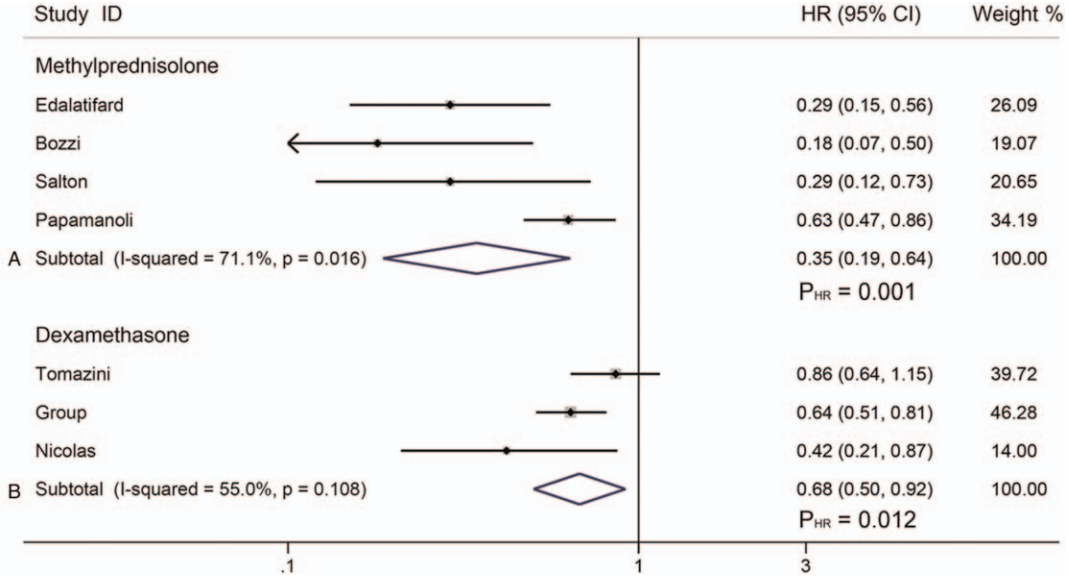

Figure 3. Forest plot of subgroup analysis based on the types of glucocorticoids. (a) Methylprednisolone therapy efficacy for mortality of severe COVID-19. (b) Dexamethasone therapy efficacy for mortality of severe COVID-19. CI = confidence interval, COVID-19 = coronavirus disease 2019, HR = hazard ratio.

Table 2

The subgroup analysis of glucocorticoids therapy for severe COVID-19 patients.

Subgroup		Study (No.)	I^2 (%)	P (I^2)	HR	P (HR)
Geographic locations	Asia[8,16,17,19,20]	5	86.4	<.001	0.85 (0.53–1.37)	.505
	Europe[9,10,13–15,18]	6	40.9	.132	0.41 (0.31–0.54)	<.001
	North America[11,12]	2	52.4	.147	0.74 (0.54–1.00)	.051
Study type	RCT[8,13]	2	79.8	.026	0.46 (0.21–0.99)	.046
	Case-control[10,12,14,17,18]	5	63.1	.028	0.52 (0.35–0.79)	.002
	Cohort study[9,11,15,16,19,20]	6	86.2	<.001	0.71 (0.42–1.19)	.196
Sample size	>300[11,13,14,16,17,19,20]	7	82.3	<.001	0.75 (0.53–1.07)	.117
	≤300[8–10,12,15,18]	6	76.0	<.001	0.41 (0.25–0.68)	<.001
Mean Age	>65[15,18,19]	3	43.1	.173	0.50 (0.35–0.71)	<.001
	≤65[8–13,16,17,20]	9	83.4	<.001	0.67 (0.48–0.94)	.018

CI = confidence interval, COVID-19 = coronavirus disease 2019, HR = hazard ratio.

dexamethasone could decrease mortality (HR = 0.68, 95% CI 0.50–0.92, $P = .012$, Fig. 3B). Besides, we performed the subgroup analysis of geographic locations, study type, sample size, and mean age (Table 2). Interestingly, compared with the patients of ≤65 years (HR = 0.67, 95% CI 0.48–0.94, $P = .018$), the glucocorticoid therapy effect was better in the patients of >65 years (HR = 0.50, 95% CI 0.35–0.71, $P < .001$).

4. Discussion

The COVID-19 outbreak was a major global public health emergency. Because of high mortality and paucity of specific effective therapy, clinicians were forced to explore potential therapeutic approaches.[24] Glucocorticoids were widely concerned due to the beneficial effects in overcoming both hyperinflammation and ARDS.[25,26] Previous studies revealed that the use of glucocorticoids could decrease the mortality of COVID-19 patients,[11–13] but the results were inconsistent.[19,20] To assess the therapeutic effect of glucocorticoids in severe COVID-19 patients, we analyzed the data of 6612 severe COVID-19 patients from 13 studies. The main finding of this meta-analysis was that using glucocorticoids could reduce the mortality of severe COVID-19 patients.

Results from a recent study suggested that rapid 2019-nCoV replication could cause inflammation and injury of the lung. Rapid viral replication might cause massive epithelial and endothelial cell apoptosis and vascular leakage, triggering the release of exuberant pro-inflammatory cytokines and chemokines (such as IL-6, IL-8, IL-1α, IL-1β, and TNF-α). [27] The immune cells and mediators were the main cause of severe acute lung injury in COVID-19 patients. The immune mediators (such as IL-6, IL-8, and IL-1β) had been reported to contribute to ARDS.[28] Moreover, 2019-nCoV could hijack angiotensin-converting enzyme 2 (ACE2) enter for cell, and led to loss of pulmonary ACE2 function. ACE2 downregulation could cause dysfunction of the renin-angiotensin system, and further enhance inflammation and cause vascular permeability.[29,30] Glucocorticoid could inhibit the systemic and pulmonary inflammation of COVID-19 patients and improve the ARDS. Based on both anti-inflammatory and immunosuppressant of glucocorticoid, the present study made further research for the correlation between glucocorticoid and severe COVID-19 patients progressed to invasive mechanical ventilation. Our result showed that using glucocorticoids was associated with a reduced risk of progression to invasive mechanical ventilation for severe COVID-19 patients.

Although methylprednisolone and dexamethasone were both glucocorticoids, there were still many differences between them. In the present study, we performed the subgroup analysis of glucocorticoids types. Compared to those receiving dexamethasone, the severe COVID-19 patients receiving methylprednisolone had lower mortality. In severe COVID-19 patients, the high mortality could be explained by the rapid development of lung injury. This pathology required treatment with "pulse" doses of glucocorticoids.[31] Compared with dexamethasone, methylprednisolone has higher lung penetration.[32] This feature of methylprednisolone could be associated with high doses of glucocorticoids in the lung. Besides, we performed the subgroup analysis of geographic locations, study type, sample size, and mean age. The results found that glucocorticoid therapy might have better benefits for severe COVID-19 of >65 years. There was clear evidence that the T-cell and B-cell function of the elder was significantly impaired with advanced age.[33] Therefore, compared with patients of ≤65 years, glucocorticoid therapies were more likely to require by patients of >65 years. In the subgroup of geographic location, the result found that glucocorticoids treatment could decrease the mortality of the Europe population. But, there was no significant statistical difference in the subgroup of Asia and North America. It indicated that the geographical differences might play roles in the therapy effect of glucocorticoids. There was no evidence to indicate that using glucocorticoids could decrease the mortality of severe COVID-19 patients in the subgroup of case-control, and large sample size researches.

In our meta-analysis, 2 studies [19,20] reported the negative therapy effect of glucocorticoids. The inconsistent finding might be related to glucocorticoids treatment of different practical modalities (ie, glucocorticoids type, different dose, and duration). Because both of the 2 studies were retrospective, the underlying nature of the poorer outcome may be due to sample selection bias.

By now, systemic glucocorticoids have been studied extensively in the treatment of critical complications caused by viral pneumonia. Glucocorticoids could have a beneficial effect by reducing inflammatory storms, but also inhibit immune responses and pathogen clearance.[34] However, the early pathology feature of COVID-19 was the viral response.[6] Glucocorticoid might have not a great therapy effect for patients with mild COVID-19. Theoretically, most severe COVID-19 patients were in the stage of immunopathological elements rather than active virus replication.[35] Patients with severe conditions were more likely

to require glucocorticoids.[36] Our findings showed that using glucocorticoid could reduce the mortality of severe COVID-19 patients.

Our meta-analysis has several limitations. First, most of the studies included in our meta-analysis were retrospective studies. Compared with the randomized controlled trials, the data of retrospective studies may be affected by sample selection bias. Second, very few studies reported the dose and regimen of glucocorticoid in this meta-analysis. The association between the dose of glucocorticoid and mortality has not been estimated. Third, the trials only recruited adults, and the effect of glucocorticoids on children remains unclear.

5. Conclusions

In conclusion, this meta-analysis showed that treating severe COVID-19 patients with glucocorticoids could decrease mortality and the risk of progression to invasive mechanical ventilation. Therefore, glucocorticoids therapy could be a potential therapy for severe COVD-19 patients. In addition, compared with using dexamethasone the use of methylprednisolone had a better therapeutic for decreasing mortality of severe COVID-19. Nevertheless, our conclusion needs to further verify by multicenter clinical trials.

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Author contributions

Guang-Qing Yu and Zhong-Hui Jiang: Design of the study; acquisition and interpretation of data; manuscript preparation and the initial draft; accountable for all aspects of the work. Shi-Qin Jiang and Zhong-Bin Yang: statistical analysis, analysis and interpretation of data; accountable for all aspects of the work. Xiao-Qing Quan: design of the study; critical review of the draft and contribution to the writing of the manuscript; final approval of the version to be published and accountable to the accuracy or integrity of the work.

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