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.

CHEST

Impact of Corticosteroids in Coronavirus Disease 2019 Outcomes

Systematic Review and Meta-analysis

Edison J. Cano, MD; Xavier Fonseca Fuentes, MD; Cristina Corsini Campioli, MD; John C. O'Horo, MD, MPH; Omar Abu Saleh, MBBS; Yewande Odeyemi, MBBS; Hemang Yadav, MBBS; and Zelalem Temesgen, MD

BACKGROUND: Since its appearance in late 2019, infections caused by severe acute respiratory syndrome coronavirus 2 have created unprecedented challenges for health systems worldwide. Multiple therapeutic options have been explored, including corticosteroids. Preliminary results of corticosteroids in coronavirus disease 2019 (COVID-19) are encouraging; however, the role of corticosteroids remains controversial.

RESEARCH QUESTION: What is the impact of corticosteroids in mortality, ICU admission, mechanical ventilation, and viral shedding in COVID-19 patients?

STUDY DESIGN AND METHODS: We conducted a systematic review of literature on corticosteroids and COVID-19 in major databases (PubMed, MEDLINE, and EMBASE) of published literature through July 22, 2020, that report outcomes of interest in COVID-19 patients receiving corticosteroids with a comparative group.

RESULTS: A total of 73 studies with 21,350 COVID-19 patients were identified. Corticosteroid use was reported widely in mechanically ventilated patients (35.3%), ICU patients (51.3%), and severe COVID-19 patients (40%). Corticosteroids showed mortality benefit in severelly ill COVID-19 patients (OR, 0.65; 95% CI, 0.51-0.83; $P = .0006$); however, no beneficial or harmful effects were noted among high-dose or low-dose corticosteroid regimens. Emerging evidence shows that low-dose corticosteroids do not have a significant impact in the duration of SARS-CoV-2 viral shedding. The analysis was limited by highly heterogeneous literature for high-dose and low-dose corticosteroids regimens.

INTERPRETATION: Our results showed evidence of mortality benefit in severely ill COVID-19 patients treated with corticosteroids. Corticosteroids are used widely in COVID-19 patients worldwide, and a rapidly developing global pandemic warrants further high-quality clinical trials to define the most beneficial timing and dosing for corticosteroids.

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KEY WORDS: coronavirus: corticosteroids; COVID-19; outcomes

ABBREVIATIONS: COVID-19 = coronavirus disease 2019; MERS = Middle Eastern respiratory syndrome; RR = relative risk; SARS = severe acute respiratory syndrome; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

AFFILIATIONS: From the Division of Infectious Disease (E. J. Cano, C. Corsini Campioli, J. C. O'Horo, O. Abu Saleh, and Z. Temesgen) and the Division of Pulmonary and Critical Care Medicine (X. Fonseca Fuentes, J. C. O'Horo, Y. Odeyemi, and H. Yadav), Mayo Clinic, Rochester, MN.

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CORRESPONDENCE TO: Edison J. Cano, MD; e-mail: canocevallos.edison@mayo.edu

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Take-home Points

- Corticosteroids use is reported widely in COVID-19 patients worldwide, although their impact on clinically relevant outcomes in specific populations remains unclear.
- Our study findings show mortality benefit for severely ill COVID-19 patients receiving corticosteroids.
- Low-dose corticosteroids do not seem to have a significant impact in the duration of SARS-CoV-2 viral shedding.
- Patients with severe COVID-19 may benefit from corticosteroids.

In December 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was linked to a cluster of cases of severe acute respiratory syndrome (SARS) in Wuhan, China.[1] By March 11, 2020, the outbreak had affected millions worldwide, and the World Health Organization declared coronavirus disease 2019 (COVID-19) a pandemic.[2,3]

Different interventions have been implemented based on previous experience with other coronavirus diseases, such as SARS caused by severe acute respiratory syndrome coronavirus 1, and Middle Eastern respiratory syndrome (MERS) caused by Middle Eastern respiratory syndrome coronavirus.[4] The literature is evolving rapidly, and newer findings position corticosteroids as a strong candidate for treatment. However, the role of corticosteroids in the management of COVID-19 remains a subject of controversy.

The immune response is a key determinant of SARS-CoV-2 infection.[5] The first phase of illness is characterized by fever, cough, and high viral loads. The next stage, labeled the pulmonary phase, is characterized by persistent lung inflammation despite decreasing viral load, resulting in respiratory failure owing to ARDS (Fig 1). In the last stage, the uncontrolled hyper-inflammatory response results in a syndrome of multiorgan dysfunction with high mortality risk.[6,7]

In asymptomatic patients or those with mild disease, an effective immune response with neutralizing antibodies results in prompt viral clearance and a short-lived inflammatory response.[8] However, the immune response in patients with severe SARS-CoV-2 infection is ineffective and excessive, which often results in progressive pulmonary damage in the form of ARDS or hyper-inflammatory status and subsequent multiorgan dysfunction.[7]

After the invasion of the host cells expressing angiotensin-converting enzyme 2 receptors, active viral replication results in pyroptosis and release of damage-associated molecular patterns, which are recognized by the neighboring cells, including alveolar macrophages. This triggers the release of an array of proinflammatory cytokines and chemokines (including IL-6, interferon γ-induced protein 10, macrophage inflammatory protein 1α, macrophage inflammatory protein 1β, andmonocyte chemoattractant protein 1). Further recruitment of monocytes, macrophages, and T cells to the site infection promotes more inflammation.[9]

Multiple studies showed higher levels of proinflammatory cytokines in patients with severe SARS-CoV-2 compared with patients with mild to moderate illness, both in the serum and in the respiratory specimens. Given the significant role of the immune response in the pathogenesis of SARS-CoV-2, it became clear that immune modulation will be essential in its management. A targeted approach focusing on some of the cytokines involved in the pathogenesis of the hyperinflammatory, status like granulocyte-macrophage colony-stimulating factor, IL-6, or complement, is currently under investigation.

Corticosteroids were the main immunomodulatory agent used for the clinical management of SARS; both benefits and poor outcomes have been reported as a result of their use. Some retrospective studies showed benefits in mortality outcomes.[10,11] Beyond mortality, a study of 107 patients treated with high-dose methylprednisolone (0.5–1 mg/kg prednisolone on day 3, followed by hydrocortisone 100 mg every 8 h plus methylprednisolone pulse 0.5 g intravenously for 3 additional days), 95 (89%) patients recovered from SARS.[12]

Outcomes of COVID-19 patients treated with corticosteroids are starting to emerge mainly in the form of retrospective data. One of the earliest published meta-analyses reviewed 5,270 patients from 15 observational studies of coronavirus diseases caused by SARS-CoV-2, severe acute respiratory syndrome coronavirus 1, and Middle Eastern respiratory syndrome coronavirus with literature available up to March 15, 2020.[13] Of the 5,270 patients, only 179 (3.39%) were COVID-19 patients from two Chinese studies.[14,15] Overall, patients receiving corticosteroids with coronavirus diseases were more likely to be critically ill, had a longer length of hospital

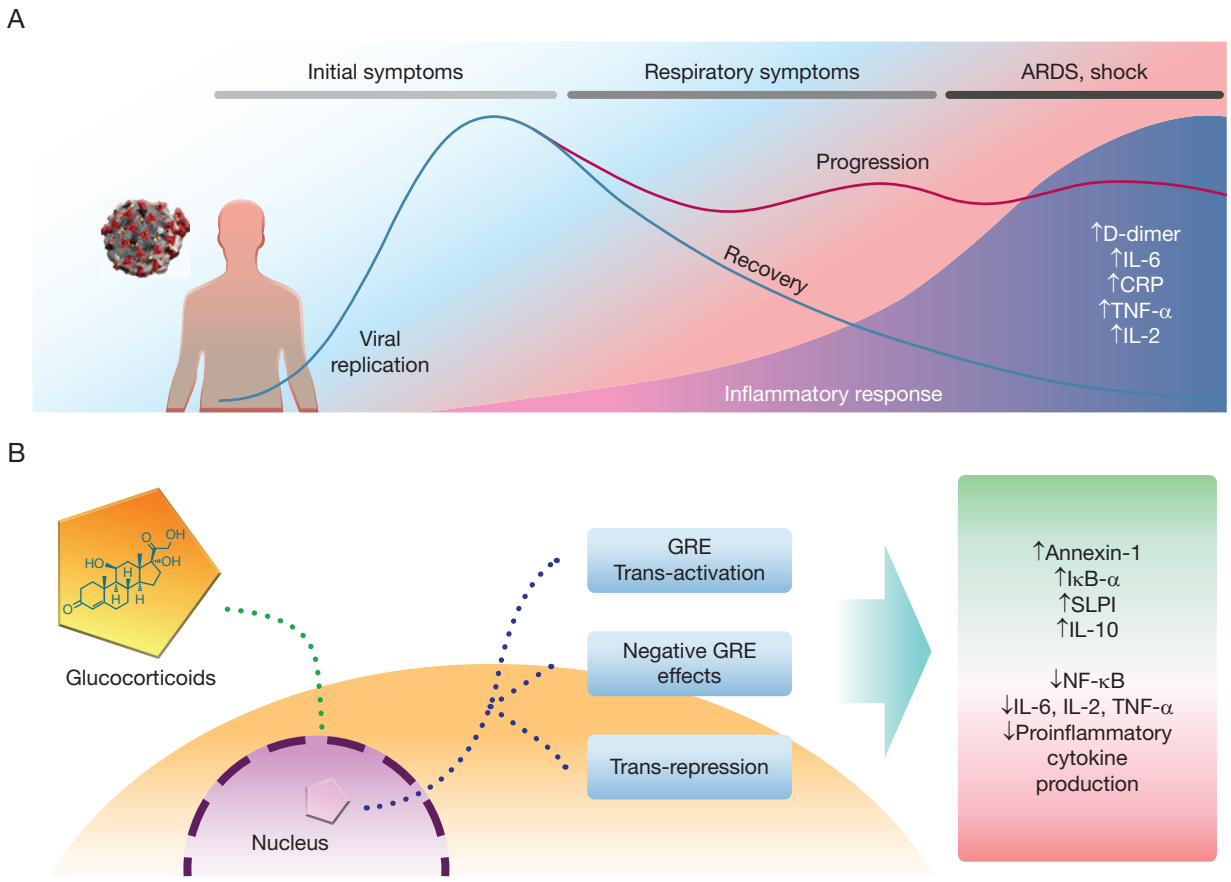

Figure 1 – *A, Diagram showing clinical phases of coronavirus disease 2019. B, Diagram showing immunomodulatory effects of glucocorticoid therapy in the nucleus driven by glucocorticoid response elements (GREs) resulting in increased expression of antiinflammatory molecules (annexin-1; nuclear factor of κ light polypeptide gene enhancer in B-cells inhibitor, α [IκBα]; secretory leukocyte protease inhibitor [SLPI], and IL-10) and decreased production of nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) and proinflammatory cytokines (IL-2, IL-6, and tumor necrosis factor α [TNFα]). CRP = c-reactive protein.*

stay, had higher mortality, had more bacterial infections, and had higher rates of hypokalemia.

A similar meta-analysis addressing the impact of corticosteroids in adults with coronavirus diseases (MERS, SARS, and COVID-19 literature up to March 20, 2020)[16] included four studies available for COVID-19 and showed no mortality benefit or harm with corticosteroid use in coronavirus diseases, although data from three studies[17-19] were generated at the same institution (Jinyintan Hospital in Wuhan, China) without more information about possible overlapping cases.

It is worth emphasizing that COVID-19, SARS, and MERS are phenotypically heterogeneous in terms of contagiousness, fatality rates, and severity, despite their close virus phylogeny,[20] and grouping these diseases to report outcomes may pose significant selection bias, hence the need for literature on COVID-19 specifically. A meta-analysis with mortality outcomes available in four studies for 495 COVID-19 patients (comprising literature up to May 7, 2020) showed no differences in mortality among patients with or without corticosteroid treatment (relative risk [RR], 1.38; 95% CI, 0.87-2.18; $P = .17$).[21] Another meta-analysis with literature until April 25, 2020, showed no benefit of corticosteroids in COVID-19 based on two studies,[22,23] but again, the data were generated at the same hospital with overlapping timelines for both studies.[24]

The impact of corticosteroids in COVID-19 outcomes remains unclear based on early literature mainly comprising retrospective studies with significant population overlap; however, as the pandemic evolves, corticosteroid use in COVID-19 is being reported worldwide. In this study, we sought to determine the mortality impact of corticosteroids vs standard of care in hospitalized COVID-19 patients. Secondary outcomes addressed for qualitative synthesis comprised disease severity, ICU admission, need for mechanical ventilation, viral clearance, and safety.

Methods

We conducted a systematic review and meta-analysis searching for corticosteroids (*methylprednisolone*, *dexamethasone*, *prednisone*, *corticoids*, and *steroids*) and COVID-19 cases in major databases (PubMed, MEDLINE, and EMBASE) for published literature until July 22, 2020. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews and meta-analysis.[25] A detailed search strategy and the PRISMA checklist can be found in e-Appendix 1.

PICO Question

Population: Hospitalized patients with COVID-19.

Intervention: Corticosteroids administered while hospitalized.

Comparisons: Standard of care or investigational therapies.

Outcomes: Mortality (quantitative analysis), severity of COVID-19, ICU admission, need for mechanical ventilation, viral clearance, and safety (qualitative analysis).

Study Selection

The inclusion criteria were (1) peer-reviewed publications on COVID-19 only, (2) retrospective or prospective studies with more than three cases, (3) reporting the outcomes of interest for adult patients receiving corticosteroids in (4) all languages available. We excluded studies (1) without a comparison group to characterize better the effect of corticosteroids, (2) of special populations such as pregnant or pediatric patients because COVID-19 presentation and management are different in these populations, and (3) of organ transplant recipients or inflammatory or rheumatologic patients who reported chronic corticosteroid use.

A total of 945 studies were identified after removing duplicates; 774 were excluded after initial screening. Two investigators (E. J. C., C. C. C.) independently reviewed the identified abstracts and selected articles for full review. Discordances were resolved by a third investigator (X. F.). The excluded studies comprised reviews (n = 275), short communications or letters (n = 229), case reports with fewer than four patients (n = 134), literature on pregnant women or children (n = 49), guidelines or society recommendations (n = 47), studies not reporting outcomes on COVID-19 (n = 27), and preclinical data (n = 13). A total of 171 full-text studies were analyzed for eligibility and 73 peer-reviewed articles were included for qualitative and quantitative analysis (Fig 2).

Data extracted for each study included study design; median or mean age, or both; country, region, or hospital to assess possible population overlap; sample size; patients receiving corticosteroids; corticosteroid dose and duration; other reported therapies; whether they reported outcomes on special populations; and outcomes of interest. Quantitative meta-analysis was performed for mortality outcomes, whereas other clinically relevant end points such as severity of COVID-19, ICU admission, need for mechanical ventilation, viral clearance, and other adverse events were summarized in a qualitative fashion. We labeled as low-dose corticosteroids any reported dose of methylprednisolone ≤ 200 mg daily or ≤ 2 mg/kg/d or equivalent in other corticosteroids.

Risk of Bias Assessment

Risk of bias was determined using the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool for nonrandomized studies[26] and version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB-2).[27] Studies from the same

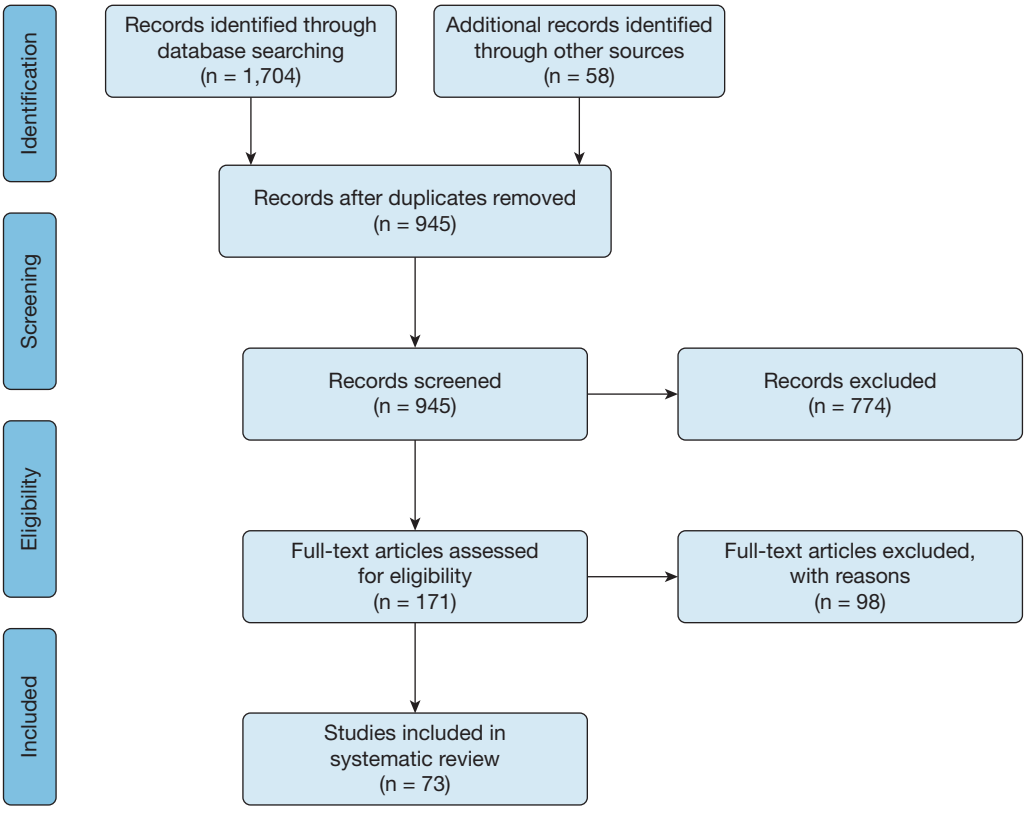

Figure 2 – *PRISMA flow diagram showing study selection.*

hospital or region were noted to perform sensitivity analysis in the likelihood of population overlap.

Statistical Analysis

Summary risk ratios also referred to as relative risk [RR] and their 95% CIs were calculated using the DerSimonian and Laird random-effects model and s fixed-effect model for specific populations as deemed appropriate.[28] Heterogeneity was assessed with an I^2 statistic, where 0% indicates no heterogeneity and 100% indicates the highest level of heterogeneity.[29] Sensitivity and subgroup analyses were performed to analyze sources of heterogeneity. Data analysis was performed using Review Manager (RevMan, version 5.4; The Cochrane Collaboration). This meta-analysis used de-identified publicly available published data and required no ethics committee approval.

Results

A total of 73 peer-reviewed articles were included for qualitative (n = 55) and quantitative (n = 33) analysis. Variables extracted for each publication are listed in Table 1.[17-19,22,23,30-98] All 73 studies included outcomes on COVID-19 patients receiving corticosteroids and a comparison group that did not receive corticosteroids. We were able to find four studies that reported outcomes of propensity score-matched populations[23,40,47,90] and one randomized clinical trial.[50] The remaining studies had limited information about baseline characteristics of their population receiving corticosteroids.

Overall Corticosteroid Use in COVID-19

A total of 21,350 COVID-19 patients were included in the 73 studies; 4,618 (21.6%) patients received corticosteroids. The median or mean age of patients in these studies ranged from 39 years (interquartile range, 32-54 years) to 88 years (interquartile range, 86.6-90 years). The use of corticosteroids across studies was highly variable and ranged from 1% to 97%, with a median corticosteroid use of 35.5% across studies. Most studies were generated in China (n = 55 [75.3%]), followed by the United States (n = 4 [5.4%]) and Spain (n = 4 [5.4%]). The Chinese studies totaled 43% of patients (n = 9,200) included in the meta-analysis, with 2,450 (26.6%) receiving corticosteroids. We identified at least 37 studies from China that shared institutions, locations, and time of chart review that potentially could represent overlapping patients for which sensitivity analysis was performed in the quantitative synthesis. A total of 5,655 patients shared reported institutions or regions; 1,780 (31.4%) of these received corticosteroids.

Dose and Timing of Corticosteroid Use

Thirty-five of 73 studies (47.9%) reported the dose or timing of corticosteroids. From these 35 studies, 26 studies (74.2%) reported using low-dose corticosteroids, four studies reported high-dose or pulse corticosteroid only, two studies (5.6%) reported mixed high-dose and low-dose regimens, and three studies (8.3%) reported a dose of unspecified corticosteroid; thus, we were unable to classify the latter group to either the low-dose or high-dose group. Seventeen studies (47.2%) reported duration of treatment, ranging from 3 to 12 days. Methylprednisolone was the most common corticosteroid reported in 26 studies (35.6%).

Adjunctive therapies reported concomitantly with corticosteroids are reported in Table 1 and include antibiotics, antivirals, tocilizumab, immunomodulators, traditional Chinese medicine, IV immunoglobulin, and convalescent plasma. Limited information was available on medication overlap for most studies, and qualitative synthesis was not performed.

Corticosteroid Use in Severe COVID-19

Nineteen studies (26%) reported corticosteroid use with significant variability ranging from 1% to 100% across studies. Corticosteroid use was reported in 396 of 987 severe COVID-19 patients (40%). These numbers were interpreted as baseline characteristics rather than outcomes because of the lack of information of baseline characteristics across studies (e-Table 1).

Corticosteroid Use in ICU-Admitted Patients

Eighteen studies reported corticosteroid use in 807 of 1,571 COVID-19 patients admitted to the ICU (51.3%). The rate of corticosteroid use in ICU patients ranged from 13.9% to 100% across studies (e-Table 2). Two studies limited their population to patients admitted to the ICU only.[69,98] Four studies from China shared similar institutions and were labeled as possible overlapping populations.

Corticosteroid Use in Mechanically Ventilated Patients

Twelve studies reported corticosteroid use in 230 of 652 mechanically ventilated COVID-19 patients (35.3%), with highly variable corticosteroid use reported (8.5%-100%) across studies (e-Table 3). Two studies from China had possibly overlapping populations (n = 10 and n = 18, respectively),[82,93] but represented a small fraction of mechanically ventilated patients.

TABLE 1] Summary of Evidence of Corticosteroid Use in COVID-19

Study	Design	Age, y	Region, Hospital	Possible Population Overlap	Sample Size	Patients Receiving Corticosteroids	Corticosteroids Dosage	Other Therapies Reported	Special Populations	Outcomes or Characteristics Reported[a]	Risk of Bias
Almazeedi et al[31]	RCS	41 (25-75)	Kuwait	No	1,096	40 (3.64)	. . .	ABX, AVR, HCQ	. . .	1,3	Moderate
Argenziano et al[32]	RCS	63 (50-75)	United States	No	850	178 (20.9)	. . .	ABX, AVR, IVIG, HCQ, TCZB	. . .	1	Serious
Ayerbe et al[33]	Case series	67.57 ± 15.52	Spain	No	2,075	960 (46.2)	. . .	ABX, AVR, HCQ, TCZB	. . .	3	Moderate
Blanco et al[34]	Case series	40 (31-40)	Spain	No	5	1 (20)	. . .	ABX, AVR, HCQ, TCZB	HIV	1	Serious
Callejas-Rubio et al[71]	Case series	63.9 ± 12.9	Spain	No	92	83 (90.2)	MP, 2 mg/kg/3 d, 250 mg/3 d, and 500 mg/3 d	TCZB	. . .	2,3	Moderate
Cao et al[35]	Case series	54 (37-67)	China, Zhongnan Hospital	Yes	102	51 (50)	. . .	AVR, ABX, IVIG, CTM	. . .	3	Moderate
Cao et al[36]	RCS	53 ± 20	China, Beijing YouAn Hospital	Yes	80	19 (23.7)	. . .	AVR, ABX, CTM	. . .	1	Serious
Chen et al[37]	Case series	50.5 (42.5-53.25)	China, Wuhan	No	8	4 (50)	MP, 40 mg/d for 6 d	ABX, AVR	. . .	3	Serious (size)
Chen et al[38]	RCS	54 (20-91)	China, Zhongnan Hospital	Yes	55	34 (61.8)	MP, 40-80 mg/d for 3-5 d	ABX, AVR, IVIG	Age > 65 y	3	Moderate
Chen et al[30]	Cohort study	49 (34-62)	China, Guangzhou 8th People's Hospital	No	267	29 (10.8)	. . .	ABX, AVR, HCQ	. . .	4	Serious
Chen et al[39]	RCS	58.9 ± 13.7	China, Hebei (13 designated hospitals)	No	51	46 (90.1)	MP, 80 mg/d for 5-6 d	ABX, AVR	Critically ill patients	2,3	Moderate
Chroboczek et al[40]	Case series	61 ± 12	France	No	70	21 (30)	. . .	ABX, AVR, HCQ	PSM	2	Low

(Continued)

TABLE 1] *(Continued)*

Study	Design	Age, y	Region, Hospital	Possible Population Overlap	Sample Size	Patients Receiving Corticosteroids	Corticosteroids Dosage	Other Therapies Reported	Special Populations	Outcomes or Characteristics Reported[a]	Risk of Bias
Dang et al[41]	RCS	88 (86.6-90)	China, Renmin Hospital	Yes	17	6 (35.2)	. . .	ABX, AVR, IVIG, TCM	. . .	1	Serious
Deng et al[42]	RCS	69 (62-74) in deceased patients vs 40 (33-57) in survivors	China, Tongji, Huazhong and Hankou branch of The Wuhan's Central Hospital	Yes	225	152 (67.5)	. . .	. . .	. . .	3	Moderate
Ding et al[43]	Case series	49 (47-50)	China, Tongji and Huazhong Hospital	Yes	5	3 (60)	. . .	ABX, AVR	Influenza coinfection	1,2,3	Critical (coinfection)
Fadel et al[44]	Quasi-experimental prospective	62 (51-62)	United States	No	213	132 (61.9)	MP, 0.5-1 mg/kg/d for 3 d	. . .	. . .	1,2,3	Low
Fang et al[45]	Case series	40 ± 12.6	China, Anhui Provincial Hospital	Yes	78	25 (32.0)	MP hydrocortisone-equivalent dose, 237.5 mg/d for 7 d in general group, 250.0 mg/d for 4.5 d in severe group	AVR, TCZB	. . .	4	Moderate
Feng et al[46]	RCS	53 (40-64)	China, Jinyintan Hospital, Shanghai Public Health Clinical Center, and Tongling People's Hospital	Yes	476	127 (26.6)	. . .	AVR, ABX	Critical patients	1,3	Moderate

(Continued)

TABLE 1] *(Continued)*

Study	Design	Age, y	Region, Hospital	Possible Population Overlap	Sample Size	Patients Receiving Corticosteroids	Corticosteroids Dosage	Other Therapies Reported	Special Populations	Outcomes or Characteristics Reported[a]	Risk of Bias
Fernandez-Cruz et al[47]	RCS	65.4 ± 12.9 in steroid treated, 68.1 ± 15.7 in steroid free	Spain	No	463	396 (85.5)	Low dose: MP, 1 mg/kg/d for 3-5 d Pulses: 2-4 MP pulses, < 250 mg/d (20.1%), 250 mg/d (62.5%), and 500 mg/d (17.1%)	ABX, AVR, HCQ, TCZB, OIM	PSM	1,3	Moderate
Giacobbe et al[48]	Case series	66 (57-70)	Italy	No	78	24 (30.7)	MP, 1 mg/kg/d	ABX, TCZB	. . .	5	Moderate
Gong et al[49]	RCS	38 ± 8.9	China, First Clinical Medical College of Three Gorges University	No	34	18 (52.9)	MP, 1-2 mg/kg/d gradually halved every 3 d for a total of 5-10 d	. . .	. . .	4	Moderate
Guan et al[51]	RCS	47 (35-58)	China, Jin Yin-tan Hospital	Yes	1,099	204 (18.5)	. . .	ABX, AVR, IVIG	. . .	1,2,3	Moderate
Hong et al[52]	RCS	55.4 ± 17.1	South Korea	No	98	18 (18.3)	. . .	ABX, AVR, HCQ	. . .	1	Serious
Horby et al[50]	Randomized clinical trial	66.1 ± 15.7	United Kingdom	No	6,425	2,104 (32.7)	Dexamethasone 6 mg/d up to 10 d	ABX, AVR, HQC, TCM	. . .	2,3	Low
Hu et al[53]	RCS	46 (33-57)	China, Second Hospital of Nanjing	No	72	28 (38.8)	MP 140 mg/d for 4.54 days	ABX, AVR, IVIG	. . .	3,4	Moderate
Huang et al[54]	RCS	49 (41-58)	China, Jin Yin-tan Hospital	Yes	41	9 (21.9)	MP 40–120 mg/d	ABX, AVR	. . .	1,3,5	Moderate
Huang et al[55]	Case series	45 (34-59)	China, First Hospital of Changsha city	No	238	76 (31.9)	. . .	AVR, HCQ	. . .	1	Serious
Jacobs et al[56]	Case series	52.4 ± 12.5	United States	No	32	5 (15.6)	. . .	AVR, HCQ, OIM	ICU, ECMO	3	Moderate

(Continued)

TABLE 1] *(Continued)*

Study	Design	Age, y	Region, Hospital	Possible Population Overlap	Sample Size	Patients Receiving Corticosteroids	Corticosteroids Dosage	Other Therapies Reported	Special Populations	Outcomes or Characteristics Reported[a]	Risk of Bias
Jiang et al[57]	RCS	41 (12-74)	China, Taizhou Enze Medical Center	No	60	9 (15)	. . .	ABX, AVR, IVIG	. . .	1	Serious
Kato et al[58]	Case series	67 (62-71)	Japan	No	70	2 (2.85)	Steroid pulse therapy	ABX, AVR	. . .	2	Serious
Khamis et al[59]	Case series	48 ± 16	Oman	No	63	15 (23.8)	. . .	ABX, AVR, HCQ, OIM, CPT	. . .	1	Serious
Li et al[60]	RCS	57 (45-70)	China, Tongji Hospital	Yes	128	52 (40.6)	. . .	ABX, AVR, TCM, IVIG	. . .	3	Moderate
Li et al[61]	RCS	. . .	China, Yichang Central People's Hospital	Yes	206	NA	Unspecified corticosteroids 40-80 mg/d	. . .	. . .	4	Critical
Li et al[62]	RCS	47.5 (36-63.5)	China, Beijing YouAn Hospital	Yes	66	17 (25.7)	MP, low-dose group: ≤ 300 mg; high-dose group, > 300 mg	ABX, AVR, TCM	. . .	4	Moderate
Li et al[22]	Case series	56 (44-66)	China, Tongji Hospital	Yes	548	6 (1.1)	Prednisone medium cumulative dose 200 mg for 4 d	ABX, AVR, IVIG	. . .	1	Moderate
Ling et al[63]	RCS	44 (34-62)	China, Shanghai Public Health Clinical Center	Yes	66	5 (7.6)	. . .	. . .	. . .	4	Serious
Liu et al[64]	Case series	42 (34-50)	China, Xixi Hospital	No	10	3 (30)	MP, 80 mg/d	ABX, AVR, IVIG	. . .	1,2	Serious
Liu et al[66]	Case series	45 (30-62)	China, Fifth Affiliated Hospital of Sun Yat-sen University	No	101	15 (14.8)	MP, 2-8 mg/kg/d; maximum 500 mg/d	ABX, AVR		1,2	Moderate

(Continued)

TABLE 1] *(Continued)*

Study	Design	Age, y	Region, Hospital	Possible Population Overlap	Sample Size	Patients Receiving Corticosteroids	Corticosteroids Dosage	Other Therapies Reported	Special Populations	Outcomes or Characteristics Reported[a]	Risk of Bias
Liu et al[65]	Case series	48 (30-62)	China, Wuhan Union Hospital	Yes	40	8 (20)	MP, 40 mg/d	ABX, AVR		1	Moderate
Liu et al[67]	Case series	38 (28-47)	China, Renmin Hospital	Yes	53	12 (22.6)	. . .	ABX, AVR, IVIG		3	Moderate
Lu et al[23]	Case series	62 (50-71)	China, Tongji Hospital	Yes	62	31 (50)	Median hydrocortisone-equivalent dosage, 200 mg/d (range, 100-800 mg/d) for 4-12 d	ABX, IVIG	ICU, PSM	2,3	Moderate
Luo et al[68]	Case series	73 (62-80)	China, Tongji Hospital	Yes	15	8 (53.3)	MP, 40-160 mg/d	TCZB	. . .	1,3	Moderate
Montastruc et al[69]	Case series	63.4 (20-89)	France	No	96	13 (13.5)	. . .	. . .	ICU	1,2	Moderate
Okoh et al[70]	RCS	62 (49-74)	United States	No	251	35 (13.9)	. . .	ABX, AVR, HCQ, TCZB	. . .	3	Moderate
Shahriarirad et al[72]	RCS	53.8 ± 16.6	Iran	No	113	5 (4.4)	. . .	. . .	. . .	3	Moderate
Shen et al[73]	RCS	51 (36-64)	China, Shanghai Public Health Clinical Center	Yes	325	50 (15.3)	. . .	ABX, AVR, CPT	. . .	4	Critical
Shi et al[74]	RCS	54 (39-64)	China, First Affiliated Hospital of Zhejiang University	Yes	99	77 (77.7)	Unspeficied corticosteroids 60 mg/d	ABX, AVR, IVIG	. . .	4	Moderate
Sun et al[75]	RCS	44 (34-56)	China, Beijing 302 Hospital	No	55	25 (45.4)	Unspecified corticosteroid 40-80 mg/d for 3-5 d	AVR, IVIG	. . .	1	Serious
Vahedi et al[76]	RCS	58.39 ± 13.57	Iran	No	60	30 (50)	Prednisolone 25 mg/d	ABX, AVR	. . .	3	Moderate

(Continued)

TABLE 1] *(Continued)*

Study	Design	Age, y	Region, Hospital	Possible Population Overlap	Sample Size	Patients Receiving Corticosteroids	Corticosteroids Dosage	Other Therapies Reported	Special Populations	Outcomes or Characteristics Reported[a]	Risk of Bias
Wan et al[77]	Case series	47 (36-55)	China, Chongqing Three Gorges Central Hospital	No	135	36 (26.6)	. . .	ABX, AVR, TCM	. . .	1	Moderate
Wang et al[14]	RCS	56 (42-68)	China, Zhongnan Hospital	Yes	138	62 (44.9)	. . .	ABX, AVR	. . .	1	Low
Wang et al[79]	RCS	51 (36-65)	China, Zhongnan Hospital	Yes	107	62 (57.9)	. . .	ABX, AVR	. . .	3	Moderate
Wang et al[80]	Case series	71 ± 10.6	China, Tongji Hospital	Yes	108	55 (50.9)	MP 40-80 mg/d for 3-5 d	ABX, AVR, IVIG	. . .	3	Moderate
Wang et al[81]	RCS	63 ± 14	China, First Affiliated Hospital of Zhejiang University	Yes	104	63 (60.5)	MP 40-80 mg/d	ABX, AVR	. . .	5	Moderate
Wang et al[82]	RCS	54 (48-64)	China, Union Hospital of Huazhong University of Science and Technology	Yes	46	26 (56.5)	MP, 1-2 mg/kg/d for 5-7 d	ABV, AVR	Severe disease	2,3	Moderate
Wu et al[83]	RCS	58.5 (50-69)	China, Jin Yin-tan Hospital	Yes	84	50 (59.5)	. . .	ABX, AVR	ARDS	3	Serious (ARDS)
Wu et al[84]	RCS	61 (50-69)	China, Wuhan Hankou Hospital and No. Six Hospital of Wuhan	No	2,041	1,026 (50.2)	. . .	ABX, AVR	. . .	1	Serious
Xu et al[85]	Case series	52 (43-63)	China, First Affiliated Hospital and the Shenzhen Third People's Hospital	No	113	64 (56.6)	MP, < 1.5 mg/kg/d	AVR	. . .	4	Serious

(Continued)

TABLE 1] *(Continued)*

Study	Design	Age, y	Region, Hospital	Possible Population Overlap	Sample Size	Patients Receiving Corticosteroids	Corticosteroids Dosage	Other Therapies Reported	Special Populations	Outcomes or Characteristics Reported[a]	Risk of Bias
Xu et al[86]	Case series	41 (32-52)	China, multicenter including Wenzhou Central Hospital	Yes	62	16 (25.8)	Unspecified corticosteroid 40-80 mg/d	AVR	. . .	3	Moderate
Yan et al[87]	RCS	64 (49-73)	China, Tongji Hospital	Yes	193	136 (70.4)	. . .	ABX, AVR	Diabetes	3	Serious (diabetes)
Yang et al[88]	Case series	55 ± 17.1	China, Yichang Central People's Hospital	Yes	200	112 (56)	. . .	ABX, AVR	. . .	1	Serious
Yang et al[89]	Case series	56 (44-64)	China, Wuhan Third Hospital	No	136	55 (40.4)	MP, 40 mg/d	ABX, AVR, CTM	. . .	1	Moderate
Yang et al[17]	RCS	59.7 ± 13.3	China, Jin Yin-tan Hospital	Yes	52	30 (57.6)	. . .	ABX, AVR, IVIG	ICU	3	Moderate
Yuan et al[90]	RCS	48.1 (33-64)	China, Central Hospital of Wuhan	No	70	35 (50)	MP, median dose, 44.6 mg/d	ABX	Nonsevere cases, PSM	1,4,5	Moderate
Zha et al[91]	RCS	39 (32-54)	China, Anhui Provincial Hospital	Yes	31	11 (35.4)	MP 40 mg once or twice daily for 5 d	ABX, AVR	. . .	3,4	Moderate
Zhang et al[92]	Case series	55 (39-66)	China, Zhongnan Hospital	Yes	221	115 (52)	MP 1-2 mg/kg/d	ABX, AVR	. . .	1	Moderate
Zhang et al[93]	Case series	38 (32-57)	China, Union Hospital of Huazhong University of Science and Technology	Yes	111	30 (27.0)	. . .	ABX, AVR, IVIG	. . .	1,2	Moderate
Zhang et al[94]	RCS	62 ± 14.2	China, Tongji Hospital	Yes	166	38 (22.8)	MP, 1-2 mg/kg/d for 3-7 d; critically ill patients received MP 240-500 mg pulses/d for 3 d	ABX, AVR, IVIG, TCZB	Diabetes	5	Serious

(Continued)

TABLE 1] *(Continued)*

Study	Design	Age, y	Region, Hospital	Possible Population Overlap	Sample Size	Patients Receiving Corticosteroids	Corticosteroids Dosage	Other Therapies Reported	Special Populations	Outcomes or Characteristics Reported[a]	Risk of Bias
Zhao et al[95]	RCS	56.0 (31.5-66)	China, Henan Provincial People's Hospital	No	29	13 (44.8)	. . .	ABX, AVR, IVIG, TCM	. . .	1	Serious
Zhao et al[96]	RCS	46	China, Jingzhou Central Hospital	No	91	79 (86.8)	. . .	ABX, AVR, IVIG	. . .	1	Moderate
Zheng et al[97]	Case series	59-62 (range)	China, Wuhan Union Hospital	Yes	55	21 (38.1)	MP 0.5-1 mg/kg/d for 5 d	ABX, AVR	. . .	1,2	Moderate
Zheng et al[98]	RCS	66 (58-76)	China, Hangzhou 12 Wenzhou Central Hospital	No	34	33 (97.0)	. . .	ABX, AVR, IVIG	ICU	1,2	Moderate
Zhou et al[18]	RCS	56 (46-67)	China, Jin Yin-tan Hospital	Yes	191	57 (29.8)	. . .	ABX, AVR, IVIG	. . .	3	Moderate

Data are presented as No. (%), mean ± SD, or median (interquartile range), unless otherwise indicated. ABX = antibiotics; AVR = antivirals; COVID-19 = coronavirus disease 2019; CPT = convalescent plasma transfusion; CS = corticosteroids; HCQ = hydroxychloroquine; IVIG = IV immunoglobulin; MP = methylprednisolone; OIM = other immunomodulators; PSM = propensity score matching; RCS = retrospective cohort study; TCM = traditional Chinese medicine; TCZB = tocilizumab.

[a]Outcomes: 1 = severity, ICU admission, or both; 2 = mechanical ventilation; 3 = mortality; 4 = viral clearance; and 5 = adverse events.

SARS-CoV-2 Shedding in Corticosteroid Use

Thirteen studies reported viral clearance in 1,482 COVID-19 patients receiving corticosteroids vs no corticosteroids. The nucleic acid test results and timing were not standardized, and the method of reporting viral clearance varied significantly among studies. Three studies that did not report corticosteroid dose concluded that patients treated with corticosteroids might have prolonged viral shedding.[30,63,73]

Seven studies reported low-dose corticosteroids and viral clearance in 604 COVID-19 patients. Findings are summarized in Table 2. Five studies comprising 457 patients showed no evidence for prolonged SARS-CoV-2 viral shedding in low-dose corticosteroid administration. Xu et al[85] reported a higher proportion of COVID-19 patients with prolonged viral shedding receiving low-dose corticosteroids; however, the duration of shedding was not reported by corticosteroids use. Only the study of Gong et al[49] showed a significant delay in viral clearance by an average of 5 days in patients receiving low-dose corticosteroids (29.11 ± 6.61 days vs 24.44 ± 5.21; $P < .05$).

Corticosteroid Safety and Adverse Events

Five studies reported adverse events related to corticosteroid therapy in COVID-19 patients. Unfortunately, details on severity, predisposing risk factors, or other details were not available in these studies. Giacobbe et al[48] reported bloodstream infection in 19 of 24 patients receiving corticosteroids or corticosteroids with tocilizumab vs in 26 of 54 patients who did not receive corticosteroids ($P = .002$). Huang et al[54] reported secondary infection in three of nine patients receiving corticosteroids vs 1 of 32 patients not receiving corticosteroids. Wang et al[81] reported COVID-19-associated pulmonary aspergillosis in 6 of 63 patients (9.5%) receiving corticosteroids vs 2 of 41 patients (4.8%) not receiving corticosteroids. Yuan et al[90] reported no infections in either the group receiving corticosteroids or the group receiving no corticosteroids. Zhang et al[94] reported hyperglycemia in 23 of 38 patients (60%) receiving corticosteroids vs 59 of 128 patients (46%) not receiving corticosteroids.

Quantitative Analysis

Thirty-three of 73 studies reported mortality outcomes in patients receiving corticosteroids with a comparison group not receiving corticosteroids. One study was excluded (Ding et al[43]) owing to a critical risk of bias because it described outcomes in patients with COVID-19 and influenza coinfection.

We identified 32 studies comparing glucocorticoids with not administering glucocorticoids in COVID-19 patients (Fig 3). Heterogeneity was too high ($I^2 = 90\%$) to combine meaningfully for meta-analysis in this set with statistically significant heterogeneity ($P < .00001$; e-Fig 1), with an overall detrimental effect of corticosteroids in mortality of (OR, 2.30; 95% CI, 1.45-3.63; $P = .0004$).

We identified eight studies reporting mortality outcomes exclusively in severely ill COVID-19 patients (ARDS, mechanically ventilated, or critically ill) receiving corticosteroids vs those who did not (Fig 4). Low heterogeneity ($I^2 = 29\%$; heterogeneity $P = .19$; e-Fig 2) was found, with favorable odds of mortality (fixed-effect model) among those receiving corticosteroids, achieving statistical significance (OR, 0.65; 95% CI, 0.51-0.83; $P = .0006$).

We also identified two studies that used high-dose corticosteroid protocols and 15 studies specifying low-dose regimens. Among those studies reporting higher doses (Fig 5), low heterogeneity was found ($I^2 = 0\%$; e-Fig 3), but the odds of mortality (random-effects model) among those receiving high-dose corticosteroids did not achieve statistical significance (OR, 0.57; 95% CI, 0.27-1.23; $P = .16$).

Low-dose corticosteroids were assorted with moderate heterogeneity ($I^2 = 60\%$; e-Fig 4) and also with a nonsignificant odds (random-effects model) for mortality (OR, 1.13; 95% CI, 0.71-1.8; $P = .61$) (Fig 6). Because of concern of possible overlap of some study populations, several iterations of sensitivity analyses were performed, serially removing studies in which the same patient may have been reported more than once. None of these resulted in a meaningful change in heterogeneity metrics, nor in the odds of benefit or harm reaching statistical significance.

Discussion

In this systematic review and meta-analysis, we identified 73 comparative studies describing the experience of corticosteroids in COVID-19, which represents a considerable number of publications for a relatively new disease. Also, significant potential population overlap exists in studies generated in China that should be considered in future syntheses.

Overall, 21.6% of COVID-19 patients received corticosteroids in our analysis, highlighting the wide use

TABLE 2] Studies Reporting Viral Clearance in COVID-19 Patients Receiving Corticosteroids

Study	Age, y	Region, Hospital	Patients Receiving Corticosteroids	Corticosteroid Dosage	Viral Clearance in Corticosteroids vs No Corticosteroids
Fang et al[45]	40 ± 12.6	China, Anhui Provincial Hospital	25/78 (32)	MP hydrocortisone-equivalent dose, 237.5 mg/d for 7 d in general group, 250.0 mg/d for 4.5 d in severe group	Mean viral clearance in nonsevere patients: corticosteroids 17.6 ± 4.9 d vs no corticosteroids 18.7 ± 7.7 d (P = .667) Mean viral clearance in severe patients: corticosteroids 18.8 ± 5.3 d vs no corticosteroids 18.3 ± 4.2 d (P = .84)
Gong et al[49]	38 ± 8.9	China, First Clinical Medical College of Three Gorges University	18/34 (52.9)	MP, 1-2 mg/kg/d gradually halved every 3 d for a total of 5-10 d	Mean time to negative nucleic acid: corticosteroids 29.11 ± 6.61 d vs no corticosteroids 24.44 ± 5.21 d (P < .05)
Hu et al[53]	46 (33-57)	China, Second Hospital of Nanjing	28/72 (38.8)	MP, 140 mg/d for 4.54 d	Median viral clearance: corticosteroids 18 d (IQR, 14.3-23.5 d) vs no corticosteroids 17 d (IQR,12-20 d; P = .252)
Li et al[61]	. . .	China, Yichang Central People's Hospital	NA/206	Unspecified corticosteroids 40-80 mg/d	High-dose corticosteroids (80 mg/d) delayed viral clearance (aHR, 0.67; 95% CI, 0.46-0.96; P = .031), but low-dose corticosteroids (40 mg/d) did not (aHR, 0.72; 95% CI, 0.48-1.08; P = .11)
Xu et al[85]	52 (43-63)	China, First Affiliated Hospital and the Shenzhen Third People's Hospital	64/113 (56.6)	MP, < 1.5 mg/kg/d	Viral shedding > 15 d was seen more frequently in patients receiving corticosteroids, 64.5% vs 40.5% (P = .025)
Yuan et al[90]	48.1 (33-64)	China, Central Hospital of Wuhan	35/70 (50)	MP, median dose 44.6 mg/d	Median viral clearance: corticosteroids 20.3 d (IQR, 15.2-24.8 d) vs no corticosteroids 19.4 d (IQR, 11.5-28.3 d; P = .669)
Zha et al[91]	39 (32-54)	China, Anhui Provincial Hospital	11/31 (35.4)	MP, 40 mg once or twice daily for 5 d	Median viral clearance: corticosteroids 15 d (IQR, 14-16 d) vs no corticosteroids 14 d (IQR, 11-17; P = .87)

Data are presented as No./Total No. (%), mean ± SD, or median (IQR), unless otherwise indicated. aHR = adjusted hazard ratio; COVID-19 = coronavirus disease 2019; IQR = interquartile range; MP = methylprednisolone.

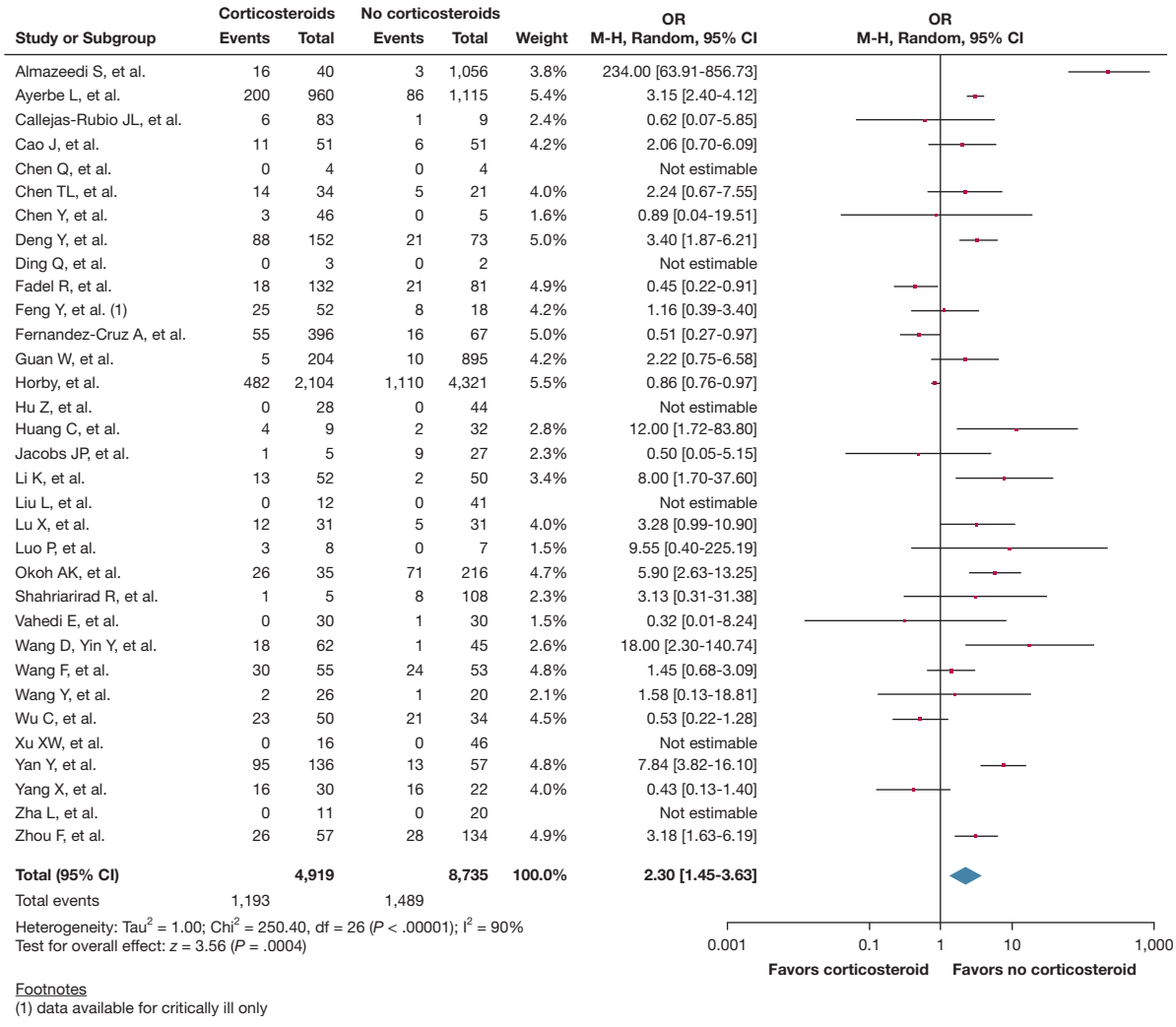

Figure 3 – *Forest plot showing mortality outcomes in coronavirus disease 2019 patients receiving corticosteroids vs those not receiving corticosteroids.*

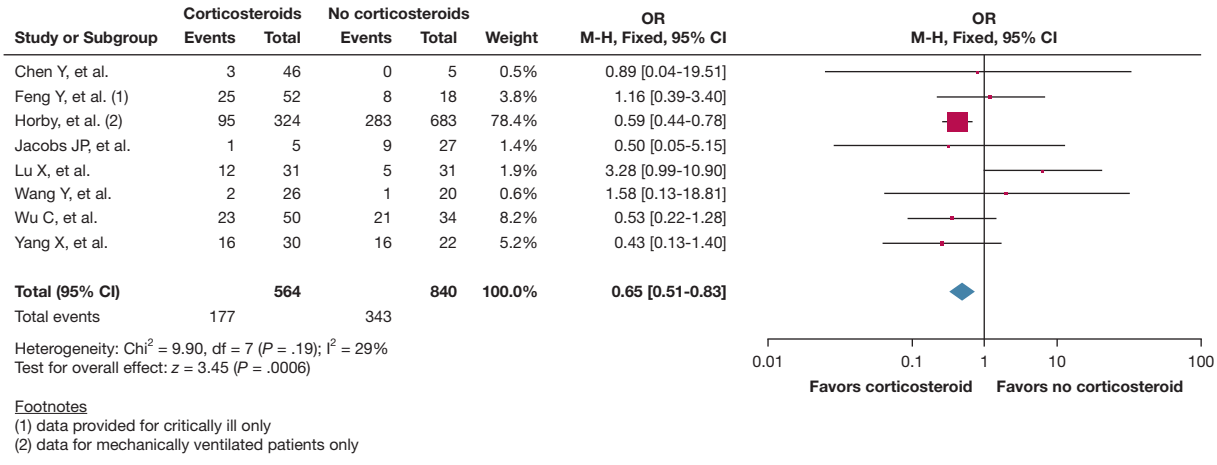

Figure 4 – *Forest plot showing mortality outcomes in severely ill coronavirus disease 2019 patients receiving corticosteroids vs those not receiving corticosteroids.*

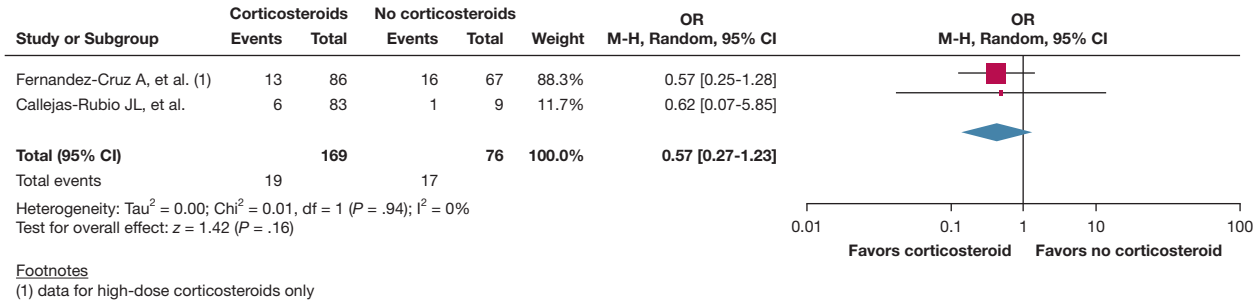

Figure 5 – *Forest plot showing mortality outcomes in coronavirus disease 2019 patients receiving high-dose corticosteroids vs those not receiving corticosteroids.*

of corticosteroids, despite the lack of well-established indications or high-quality studied in favor or against corticosteroids. Almost half of studies reported dose or timing of corticosteroids, with low-dose methylprednisolone being the most common approach. Corticosteroids were used widely in mechanically ventilated patients (35.3%), ICU patients (51.3%), and severe COVID-19 patients (40%), which potentially could reflect a general practice, rather than the impact of corticosteroids in severity of disease, pending high-quality studies. Also, evidence emerged in our synthesis showing that low-dose corticosteroids do not have significant impact in duration of SARS-CoV-2 viral shedding, in contrast with data from SARS and MERS.[16]

Severely ill COVID-19 patients showed a statistically significant mortality benefit from corticosteroids (OR, 0.65; 95% CI, 0.51-0.83; $P = .0006$) in our analysis. No beneficial or harmful effect was noted among high-dose or low-dose corticosteroids recipients. Overall mortality of COVID-19 patients receiving corticosteroids was higher than in patients not receiving corticosteroids, with the caveat that the population studied was too heterogeneous, possibly because of selection bias among studies, with corticosteroids administered to patients with grave prognosis at baseline. The vast majority of studies did not report baseline characteristics of the group receiving corticosteroids.

Side effects in COVID-19 patients receiving corticosteroids included superinfection, COVID-19-associated pulmonary aspergillosis, and hyperglycemia; however, the literature on side effects is lacking. Well-known corticosteroid side effects such as hyperglycemia and superimposed infections have been reported in coronavirus diseases.[99,100] However, the largest meta-

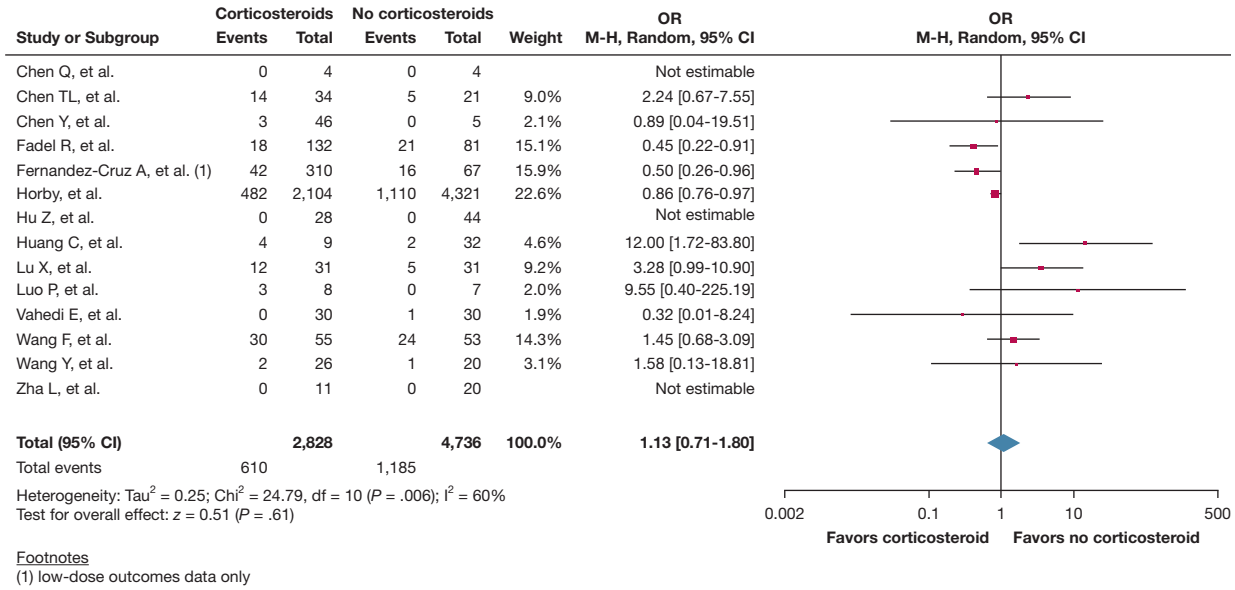

Figure 6 – *Forest plot showing mortality outcomes in coronavirus disease 2019 patients receiving low-dose corticosteroids vs those not receiving corticosteroids.*

TABLE 3] Summary of International Recommendations of Corticosteroid Use in COVID-19

Organization	Date	COVID-19 Population	Recommended Dose	Level of Evidence	Corticosteroid Use Recommendation
Chinese National Health Committee (7th version)	3/4/2020	Progressive deterioration of oxygenation indicators, rapid radiographic progression, and excessive activation of inflammatory response	MP, 1-2 mg/kg/d for 3-5 d	Expert consensus	Favors corticosteroids
The Surviving Sepsis Campaign: Society of Critical Care Medicine/ European Respiratory Society	3/28/2020	Patients on mechanical ventilation and ARDS	Hydrocortisone 200 mg/d	Weak recommendation, low-quality evidence	Favors corticosteroids
Infectious Disease Society of America	9/25/2020	Critically ill patients with severe disease, ie, $SpO_2 \leq 94\%$ on room air, those who require supplemental oxygen, mechanical ventilation, or ECMO	Dexamethasone 6 mg for 10 d (or until discharge if earlier) or equivalent corticosteroids dose	Strong (critically ill)/ conditional (severe disease) recommendation, moderate certainty of evidence	Favors corticosteroids
		Patients without hypoxemia, not requiring supplemental oxygen	. . .	Conditional recommendation, low certainty of evidence	Against corticosteroids
National Institutes of Health	8/27/2020	Patient on mechanical ventilation or requiring oxygen supplementation	Dexamethasone 6 mg/d (or alternative corticosteroids) for up to 10 d or until hospital discharge	AI[a] (mechanically ventilated patients), BI[b] (requiring oxygen)	Favors corticosteroids
		Patients not requiring oxygen supplementation	. . .	AI[a]	Against corticosteroids
World Health Organization[c]	9/2/2020	Patients with severe disease and critically ill	Dexamethasone 6 mg/d or hydrocortisone 50 mg every 8 h for 7-10 d	Strong recommendation, moderate certainty evidence	Favors corticosteroids
American Thoracic Society	4/3/2020	No suggestion	. . .	Expert consensus	Against corticosteroids

ECMO = extracorporeal membrane oxygenation; MP = methylprednisolone; SpO_2 = oxygen saturation.
[a]Grade A, level 1: strong recommendation, high-quality evidence.
[b]Grade B, level 1: strong recommendation, moderate-quality evidence.
[c]World Health Organization is in the process of updating treatment guidelines to include dexamethasone or other corticosteroids.

analysis on low-dose corticosteroid use in patients with sepsis did not show an increased risk of superinfection (n = 5,356; RR, 1.06; 95% CI, 0.95-1.19; $P = .27$) or gastroduodenal bleeding (n = 5,171; RR, 1.07; 95% CI, 0.85-1.35; $P = .55$), although an increased risk of hyperglycemia (RR, 1.20; 95% CI, 1.10-1.31; $P < .0001$), hypernatremia (RR, 1.66; 95% CI, 1.34-2.06; $P < .0001$), and muscle weakness (RR, 1.21; 95% CI, 1.01-1.44; $P = .04$) was found.[101]

Although the role of corticosteroids in COVID-19 remains unclear, evidence suggests benefits of corticosteroids in ARDS. A meta-analysis published in 2018 in patients with ARDS receiving corticosteroids (n = 494 for hydrocortisone and n = 272 for methylprednisolone) showed reduced time to extubation, duration of hospitalization, and mortality, with an increase in ventilation-free days and ICU-free days.[102] The proposed doses for methylprednisolone in this setting are 1 to 2 mg/kg bolus followed by the same daily dose at an infusion rate of 10 mL/h daily with a gradual taper.[103,104] Based on similar information, the Society of Critical Care Medicine/the European Society of Intensive Care Medicine guidelines also recommended the early use of corticosteroids in moderate to severe ARDS.[105] However, the quality of evidence supporting these findings has been questioned.[106]

Study Limitations

Our qualitative synthesis was limited by the detail of reported patients' characteristics among studies. Also, a lack of details in dosing, indication, and timing of corticosteroids was found across studies. Potential for population overlap also was noted in most studies generated in China. Although this was mitigated by sensitivity analysis in the quantitative synthesis, it is difficult to assess the impact of the overlap in the qualitative synthesis. Our qualitative synthesis was limited by the heterogeneity of studies included in high-dose and low-dose corticosteroids.

International Recommendations for Corticosteroids in COVID-19

The international recommendations for corticosteroid use in COVID-19 are summarized in Table 3. The Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment published by the Chinese National Health Committee set the initial recommendations for methylprednisolone in patients with progressive clinical deterioration.[107] Other international societies and organizations are incorporating recommendations for corticosteroids in COVID-19 based on disease severity, including the American Thoracic Society,[108] the Infectious Disease Society of America,[109] the National Institutes of Health of the United States,[110] the Surviving Sepsis Campaign,[111] and the World Health Organization.[112]

Interpretation

The current evidence does not support indiscriminate corticosteroid administration in patients with COVID-19. However, severely ill COVID-19 patients may benefit from corticosteroids based on our findings. The potential role for corticosteroids as an immunomodulatory agent in COVID-19 needs to be explored further in clinical trials. This is particularly important in resource-limited settings where targeted immunomodulators may not be readily available or affordable.

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Additional information: The e-Appendix, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.

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